placebo-controlled study with open-label follow-up

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Abstract

Prostacyclins are routinely used to treat vascular features of systemic sclerosis (SSc, scleroderma) but require parenteral infusion or inhalation. This study evaluated the safety and efficacy of oral treprostinil in digital ulcers secondary to SSc.

Methods: This was a randomized (1:1) placebo-controlled, multicenter study in adults with SSc and at least one active digital ulcer at entry. Oral treprostinil was administered twice daily and titrated to maximum tolerated dose with clinical assessments at Weeks 5, 10, 15 and 20. The primary endpoint was change in net digital ulcer burden. Secondary outcomes included ulcer healing and prevention, measures of hand function, quality of life, Raynaud phenomenon and global assessments. Simplified data were gathered during open-label follow up.

Results: Enrolled were 147 patients (109F/38M), mean age 48.8 years with SSc of mean duration 10.5 years. At week 20, mean net ulcer burden was reduced -0.43 ulcers on treprostinil (1.80 vs. 1.37) and -0.10 ulcers on placebo (1.61 vs. 1.51; p = 0.20). There were no effects on ulcer healing or prevention, and small, inconsistent effects on Raynaud phenomenon, global assessment, hand function and quality-of-life measures. In open-label follow-up, there was a continued, small reduction in net ulcer burden (-0.52 month 3, n = 104; -0.64 month 12, n = 36). Common adverse effects were headache, nausea, diarrhea, jaw pain, flushing and other gastrointestinal symptoms.

Conclusions: Administration of oral treprostinil twice daily over 20 weeks was associated with small and statisti- cally insignificant reduction in net ulcer burden in comparison to placebo.

Keywords: Digital ulcers, Oral treprostinil, Scleroderma, Systemic sclerosis

Introduction

Raynaud phenomenon and the related consequence of digital tip ulcers are a serious problem in many patients with systemic sclerosis (SSc, scleroderma) (1). Endoluminal change with intimal hyperplasia and medial/adventitial fibrosis are distinct facets of SSc vasculopathy resulting in impaired affer- ent perfusion as a contributing mechanism (2). Other factors include local platelet activation, leukocyte adherence, micro- vascular distortion and impaired efferent blood flow (1-3).

Digital ulceration occurs in the clinical setting of episodic and reversible vasospasm and is thus thought to be amenable to anti-vasoconstrictive therapy. Prostacyclins have demon- strated efficacy as vasodilators for vascular features of SSc but systemic delivery requires parenteral infusion. Intravenous epoprostenol and iloprost and subcutaneous treprostinil have all been associated with healing of existing digital ulcers (4-6). Treprostinil diolamine is a salt form of the prostacyclin analogue treprostinil developed for oral administration as an extended-release osmotic tablet. Oral treprostinil is a licensed therapy for WHO Group 1 pulmonary arterial hypertension (PAH) including that developing as a complication of SSc (7, 8). A pilot trial in SSc patients with digital ulcers revealed improve- ment in digital perfusion and temperature in relation to plasma concentrations of oral treprostinil (9).

The present study was designed to investigate the effects of oral treprostinil in comparison to placebo as a treatment for digital ulcers secondary to SSc over a 20-week period. The primary objective was change in net ulcer burden at Week 20. Secondary endpoints included patient ratings of pain, physi- cian and patient global assessments, Raynaud symptoms by visual analog scale (VAS), “cardinal” ulcer healing, pre- vention of new ulcers, and measures of hand function and quality of life.

Patients and methods

Study design

This double-blind, randomized, parallel group, placebo- controlled study consisted of a screening period not greater than 28 days and a 20-week treatment period. This study was approved by local ethics committees and conducted in ac- cordance with the ethical principles that have their origins in the Declaration of Helsinki and the International Conference on Harmonization E6 Good Clinical Practice guidance. All patients gave written informed consent.

Setting and participants

Recruitment of 150 patients was planned. Male and fe- male patients with SSc, as defined by preliminary American College of Rheumatology criteria (10) who were at least 18 years of age and had the presence of at least one designated active digital ulcer at baseline were eligible.

A digital ulcer was defined as an area with visually dis- cernable depth and a loss of continuity of epithelial cover- age, which could be denuded or covered by a scab or necrotic tissue. If the area was denuded, the ulcer was designated ac- tive. If denudation could not be judged because of the pres- ence of overlying scab or necrotic tissue, ulcers presenting with features, including underlying pain, based on investiga- tor clinical judgment to be consistent with loss of epitheliali- zation, epidermis, or dermis, and requiring treatment, were designated as active. Otherwise, the ulcer was categorized as indeterminate. These definitions did not include fissures, paronychia, extrusion of calcium, or ulcers over the metacar- pophalangeal joints or elbows. Only digital ulcers distal to the proximal interphalangeal joints, volar to the equator of the finger (inclusive of ulcers located on or crossing the median), and not localized in the proximal or distal interphalangeal creases, painful, possibly triggered by trauma, and without bone infection or subtending calcinosis were assessed. These features identified lesions presumed to be vascular in origin. Patients with known PAH or receiving bosentan were ex- cluded. Conventional therapy for SSc, Raynaud phenomenon and digital ulcers, if applicable and not otherwise prohibited by the entry criteria or explicitly prohibited by the protocol, was permitted to be continued without changes unless medi- cally warranted over the course of the study for all patients. Initially prohibited, the protocol was amended during the study to allow background phosphodiesterase-type 5 inhibi- tor (PDE5I) therapy, provided such treatment had been start- ed at least six months prior to baseline assessments (except for intermittent treatment of male erectile dysfunction) and continued throughout the study. The rationale was that the development of an active digital ulcer in the face of conventional therapy represented treatment failure.

Other exclusion criteria included body weight <40 kg; his- tory of postural hypotension, unexplained syncope, a systolic blood pressure <90 mmHg; hemoglobin concentration <75% of the lower limit of the normal range; moderate to severe he- patic impairment, intractable diarrhea, or severe malabsorp- tion, defined >15% unintentional loss of bodyweight in the last 6 months prior to screening; any severe organ failure (e.g.,lung, kidney), bleeding diathesis or platelet disorder, or any life-threatening condition; pregnancy or breast-feeding; clinical diagnosis of SSc in overlap with another connective tissue dis- ease. Exclusions relevant to assessment of digital ulcer status included sympathectomy of the upper limb, including involv- ing the hand, performed within 12 months of baseline; receipt of prostanoid treatment (epoprostenol, treprostinil sodium, or other prostacyclin analogue) within the previous 3 months of baseline for conditions including Raynaud phenomenon, rest pain and/or digital ulcers; requirement for systemic antibiotics for infected digital ulcers within 2 weeks of screening; local injection of botulinum toxin in an affected finger or treatment with endothelin receptor antagonists within 1 month prior to baseline; treatment with statin within 1 month prior to screen- ing, unless for management of hyperlipidemia; and tobacco or nicotine use at any level within the past 6 months prior to screening.

Randomization and interventions

Patients were randomized in a 1:1 ratio (active and place- bo) according to a centrally administered stratified permuted block randomization, stratified by number of active ulcers at baseline (≤2 ulcers and >2 ulcers). Background PDE5I therapy use was added as a stratum following protocol amendment.

Patients were instructed to take study drug twice daily (BID; approximately every 12 ± 1 hours) with a meal containing approximately 500 calories. Dosing was initiated at

0.25 mg BID and titrated gradually in stepwise 0.25 mg BID increments approximately every 48-72 hours to a maximum dose of 16 mg BID. Upon reaching a dose of 5 mg BID, the dose titration increment could be increased to 0.5 mg BID every 48-72 hours at the investigator's discretion. Dose esca- lation was suspended or the titration slowed at the investiga- tor's discretion based upon individual patient tolerability.

Outcomes

The primary objective of this study was to assess the effi- cacy of oral treprostinil in reducing net ulcer burden. Second- ary endpoints included development of new ischemic digital ulcers, healing of a designated cardinal ulcer, assessment of digital ulcer-related pain, measures of patient and hand function (as Scleroderma Health Assessment Questionnaire [SHAQ]) and Cochin Hand Function Score (CHFS) (11), quality of life (via SF-36), patient and physician global assessment of digital ulcers measured via VAS. Patient impression of change (PIC) questionnaire and skin thickening assessed via the mod- ified Rodnan skin score (mRSS). Patients were assessed at baseline and at weeks 5, 10, 15, and 20.

One digital ulcer was identified and designated by the in- vestigator as the cardinal ulcer at baseline. The cardinal ulcer must have met the qualifications for designation as an ac- tive ulcer. If only one active ulcer was present at entry, it was designated as the cardinal ulcer. If several digital ulcers quali- fied, the cardinal ulcer could be either the largest or the most painful ulcer, or the ulcer that disturbed the patient the most. At each subsequent visit, the status of each digital lesion was rated as 'active', 'healed', or 'indeterminate'. New digital ul- cers were recorded at each visit as well.

Statistical methods

The primary efficacy analysis compared change from baseline in net ulcer burden at Week 20 between treat- ment groups in the intention to treat (ITT) population using nonparametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test. Net ulcer burden was calculated as all baseline "active" ulcers (unless graded "healed") + all new ulcers (unless graded "healed"). Indeterminate" ulcers at baseline were not counted unless they became "active" during the study. Specifically, a Cochran-Mantel Haenszel mean score test was used on the standardized reverse mid-ranks (i.e., overall reverse ranks divided by the number of ranks + 1, or "modified ridit" scores; thus, largely negative changes had ranks near 1 and largely positive changes had ranks near 0) of the residuals from an ordinary least-squares regression with change in net ulcer burden at Week 20 as a linear function of baseline PD5EI or prostacyclin use (as a binary variable: Yes or No) and net ulcer burden at baseline (as a continuous variable). The magnitude of the treatment effect was assessed with the median difference between treatment groups as determined by the Hodges-Lehmann (H-L) estimate. For missing primary efficacy data and parametric analyses, missing values were imputed using a value corresponding to the mean of the changes in all observed values from their respective baseline across all observed values in the placebo group for that assessment. For all nonparametric analyses, patients who did not meet the criteria for being assigned the lowest rank had their standardized rank imputed using the mean placebo rank (i.e., arithmetic mean of all observed ranks in the placebo group for that assessment).

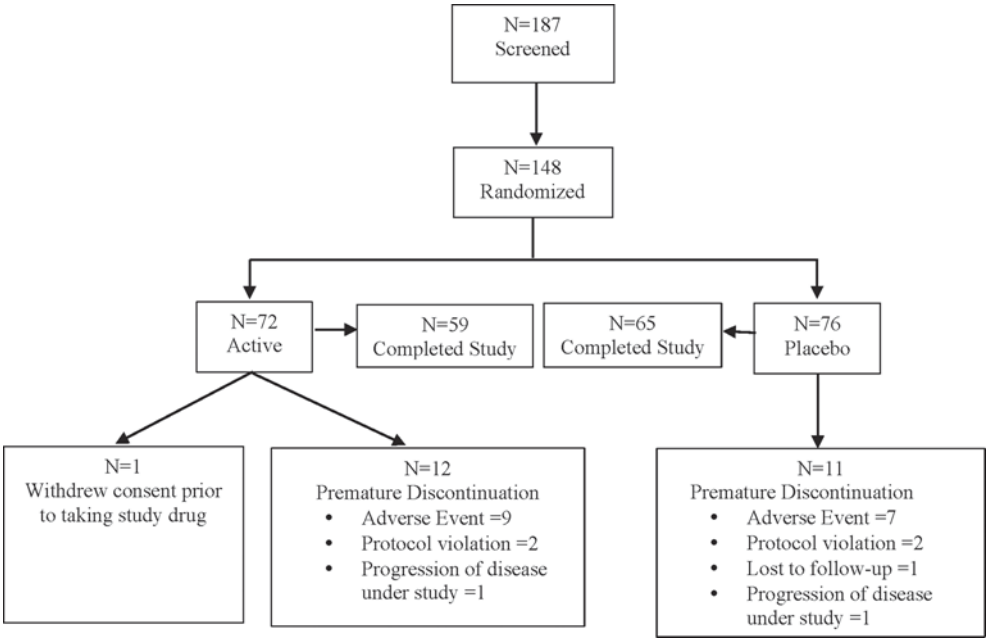
Measures of ulcer healing were included as secondary outcomes. A patient's cardinal ulcer was considered completely healed at the earliest assessment for which it was designated as "healed". A patient was counted as having all ulcers completely healed at the earliest assessment for which all ulcers were designated as "healed" and after which no new ulcers were recorded for the remainder of the trial. The time to complete healing of the cardinal

ulcer and all ulcers was calculated as the number of days from randomiza- tion to the date of these respective assessments, provided that complete healing was achieved during the study. Actual healing times, censoring times, and disease progression and mortality information was incorporated into a single ranked response score for each patient for both the cardinal ulcer and all ulcers as specified in the statistical analysis plan. Stan- dardized mid-ranks (or "modified ridit" scores) of the time to healing rank scores were calculated. The standardized mid-ranks were compared between treatment groups using log-rank test. The number and percentage of patients who developed new ulcers during the study were summarized and rates between treatment groups were compared using the Fisher's exact test.

The digital ulcer VAS-pain assessment was captured in millimeters, with possible values ranging from 0 to 100. The recorded value was divided by 10, with values ranging from

0.0 (no pain) to 10.0 (unbearable pain), expressed to one dec- imal point. The patient and physician VAS-global assessments were recorded in centimeters, with possible values ranging

Fig. 1 - Study subject disposition.



from 0.0 to 15.0. The recorded value was divided by 15, then multiplied by 100 to convert it to the VAS-global scale, with values ranging from 0 (no disease activity) to 100 (very severe disease). The difference between treatment groups for the change from baseline VAS at each assessment was tested us- ing the Wilcoxon rank-sum test.

Component, domain and aggregate scores were calculat- ed according to the designated scoring tools for the SF-MPQ, CHFS, SHAQ and SF-36 (SF-36v2 scoring manual) question- naires and the difference between treatment groups for the change from baseline for each component at each assess- ment was tested using the Wilcoxon rank-sum test.

The PIC assessments (for digital ulcers, Raynaud symp- toms, and overall) have possible integer values ranging from

-3 (very much worse) to +3 (very much improved). The differ- ence between treatment groups for the change from baseline at each assessment was tested using the Wilcoxon rank-sum test. Assessment of Raynaud phenomenon was, by design, limited in this study. Impact of treatment on Raynaud phemomenon was assessed via the Scleroderma Specific Rayn- aud Visual Analogue Scale subcomponent of the SHAQ. The difference between

treatment groups for the change from baseline at each assessment was tested using the Wilcoxon rank-sum test. The difference between treatment groups for the change from baseline and at Week 20 in the mRSS was tested using the Wilcoxon rank-sum test.

Sample size calculations were based on the RAPIDS-2 trial (12) during which the background rate in overall mean change in digital ulcers was approximately -1.5 (standard deviation [SD] = 3) at 5 months. Using an allocation ratio of 1:1 between oral treprostinil and placebo, a fixed sample size of 128 patients provided 80% power to detect a between-treatment difference at a significance level of 0.05 (two-sided hypothesis) assuming the active group leads to a change of -3 digital ulcers. Drop-out rate was estimated to be 10%-15%; therefore, enrollment of approximately 150 patients was planned to account for additional variability from imputation.

Results

Patient characteristics and disposition

One hundred and forty-eight patients were enrolled and randomized with 147 patients (71 active/76 placebo) receiv- ing at least one dose of study drug; one patient withdrew consent after randomization prior to taking any study medi- cation. The disposition of patients is illustrated in Figure 1.

Patient demographics and disease characteristics were typical for recent studies of SSc-related Raynaud phenomenon or digital ulcers, dominantly female with limited cutane- ous SSc of long duration (mean 10 years). The two treatment groups were well matched for the number of active ulcers and total ulcers at study entry (Tab. I).

The mean ±SD maximum dose of oral treprostinil at Week 20 was 3.25 ± 2.8 mg BID (range, 0-13 mg) compared with 8.13 ± 4.9 mg BID (range, 0-16 mg) in the placebo group. Doses of treprostinil versus placebo reached at Week 5, 10 and 15 were 2.27 ± 0.96 mg versus 2.70 ± 1.04 mg; 3.35 ±

2.25 mg versus 5.24 ± 2 mg; and 3.49 ± 2.80 mg versus 7.79 ±

3.46 mg, respectively.

Primary outcome – net ulcer burden

The primary hypothesis of this trial was that oral trepro- stinil would reduce the net ulcer burden in comparison to placebo at Week 20 in patients with SSc. Table II summa- rizes the mean net ulcer burden and change from baseline for each visit in the ITT primary analysis population. Whereas the reduction of -0.37 ulcers after 15 weeks of oral trepro- stinil versus an increase of 0.07 net ulcers on placebo was statistically significant (p = 0.05), results at 20 weeks were not ulcer burden (e.g., 20%, 30%, 40% and 50%). There was no relationship of response to background therapy including use of PDE5Is, SSc disease classification and autoantibody status. Only 13% of patients in the study population had greater than two active ulcers documented at the time of baseline limiting evaluation of a treatment effect based on disease severity. Treatment effect was not associated with increasing exposure (dose) to oral treprostinil therapy. However, dose response was not a planned endpoint in this study; therefore, formal dose-response analyses were not planned. Utilization of a ti- trated dosing regimen, based on patient tolerability, provides non-random dose cohorts and makes it difficult to interpret

Net ulcer burden would be influenced by healing of exist- ing ulcers and by prevention of the occurrence of new digital ulcers. There was no difference in proportion of patients re- porting complete healing of the cardinal ulcer, all ulcers, or in time to healing observed between treatment groups. The proportion of patients with no new digital ulcers up to Week 20 was similar with oral treprostinil and placebo (Tab. III). The maximum number of new digital ulcers per patient was six for both treatment groups.

Other outcomes

Statically significant reductions in digital ulcer pain VAS were reported at Week 10 and 15; however, while a clini- cally relevant reduction was observed on active treatment at Week 20 (median change -1.45 on treprostinil; -0.40 on placebo), the between treatment differences were not sig- nificant (H-L treatment effect estimate = -0.4 [95% CI -1.40, 0.40]; p = 0.31). Digital ulcer pain was also assessed using the Short-Form McGill Pain questionnaire and there was no observed treatment effect on any of the component scores.

Safety and tolerability

Seventy-one patients (100%) in the active treatment group and 74 patients (97%) in the placebo treatment group report- ed at least one adverse effect (AE), regardless of relationship during the course of the study. Overall, the most commonly reported AEs considered probably or possibly related to oral treprostinil that occurred more frequently in the active group were headache (73%), nausea (56%), diarrhea (52%), flush- ing (24%), pain in jaw (23%) and vomiting (17%); these same events occurred in 37%, 14%, 16%, 3%, 5% and 1% of placebo patients, respectively. The majority of AEs in the two groups were reported to be either mild or moderate in intensity. Headache was the most frequent AE attributed to study drug and was rated as severe in 10% of active patients compared to 1% of placebo patients. These are expected effects of sys- temic prostacyclin therapy. Overall, there was no difference in the number of patients in the active (11 patients) or placebo (eight patients) treatment groups who reported permanently discontinuing the study drug due to AEs.

A total of 27 serious adverse events were reported by thirteen patients (active: 9 patients, 22 events; placebo: 4 patients, 5 events) during the study. Six events in the ac- tive treatment group were considered probably or possibly attributable to study drug. There were no deaths during this trial.

Open-label follow-up

Patients completing the full 20 weeks of the randomized phase of trial were offered open-label treatment with oral treprostinil according to the same titration schedule. This continued until the randomized phase of study was complet- ed with analysis of results. Study visits were at one month, then every three months and included 115 patients.

A decrease in net ulcer burden and total ulcer number was observed and persisted over the duration of the study (Tab. V). No new ulcer formation was reported in 48 (42%) pa- tients; with 63 (55%) reporting at least one new ulcer during the duration of the study. An average of 1.52 new ulcers per patient-year of follow-up developed during the study.

Discussion

This randomized, placebo-controlled trial failed to achieve the a priori specified primary endpoint of a reduction in net ulcer burden at 20 Weeks. Post hoc analysis evaluating change in total ulcers was also not significant. Additionally, no sig- nificant treatment effect was observed at Week 20 in several secondary outcomes, including

ulcer healing, ulcer pain, pa- tient rating of disease severity, CHFS and SF-36 questionnaire. Interestingly, at 15 Weeks, there was a statistically significant reduction in net ulcer burden, as well as, improvement in the Grip and Hand Function components of the SHAQ, pa- tient and physician global assessment, ulcer pain and patient ratings of Raynaud phenomenon. Physician-rated digital ul- cer disease severity VAS-global scores remained significant at Week 20, but were discordant with the net ulcer burden outcome and patient VAS scores for pain and digital ulcer se- verity. There were significant differences in patient percep- tion with positive improvements in Raynaud phenomenon symptoms ($p = 0.00004$) and how they felt overall ($p = 0.02$) between treatment groups on the PIC questionnaire at Week

20. The open-label extension showed a similar small effect of continuing therapy with a reduction in net ulcer burden at 9 months of -0.52 ulcers.

We had hypothesized that the approach of a maximally tolerated dosing scheme would permit full realization of po- tential therapeutic effects of systemic prostanoids. A previous trial with a fixed low dose of oral iloprost for Raynaud phe- nomenon secondary to SSc had failed to demonstrate ben- efit (13) in contrast to effects seen with maximum tolerated dosing by intravenous administration (14). Dose response in prostacyclin therapy is inherent in the clinical use in PAH (4, 7, 8, 15). It is possible that our dosing schedule was inappropri- ate. Although the trials supporting registration of oral trepro- stinil for PAH were also conducted on a BID dosing schedule (7, 8), three times a day (TID) dosing has been shown to pro- vide a sustained plasma exposure at steady state in normal volunteers (16). Limited study of TID dosing in patients with PAH has demonstrated improved efficacy and tolerability as well as a reduced peak:trough ratio of plasma treprostinil levels (17). It is possible that TID dosing in patients with digi- tal ulcers secondary to SSc might lead to a larger clinical ef- fect. It is also possible that longer duration of therapy would make a difference; particularly given the significant structural vascular disease present in scleroderma. While not achiev- ing statistical significance, we note a trend of continuous im- provement in net ulcer burden whilst on oral treprostinil both during the controlled and open-label phases of this study.

Accepting this trial as offering no evidence of therapeutic effect does not exclude consideration of other potential rea- sons for failure. The vascular damage in the fingers of patients with SSc is notable for its irregular distribution. Studies by high-resolution magnetic resonance angiography have sug- gested that the digits in which ulcerations develop have more severe vascular attenuation (18). Improving proximal blood flow may not be sufficient to address the biology of critical tissue ischemia in this clinical setting. These conclusions are similar to those seen in studies of peripheral vascular disease of the lower extremity wherein gains seen in intermittent claudication are not paralleled by reduction in need for surgi- cal amputation (19). Effective vasodilatation may represent an inadequate treatment for this common clinical problem.

Two randomized controlled trials with bosentan demon- strated an effect in reducing the occurrence of new digital ulcers with effects most easily demonstrated in patients with higher numbers of ulcers at trial outset (12, 20). Neither trial demonstrated effects on ulcer healing or on overall net ulcer burden and was thus not associated with improved patient hand function. Treatment effects were not seen in Raynaud phenomenon. These trials suggest a more subtle effect on peripheral vascular integrity or angiogenesis. High levels of pla- cental growth factor and low circulating endothelial progeni- tor cells have been associated with the occurrence of digital ulcers in SSc (21). Emerging data suggest benefits of bone- marrow-derived mononuclear cell implantation in the treat- ment of SSc patients with ischemic ulcers of the digits (22).

The primary endpoint of this trial required investigator clinical judgment as to whether or not a digital lesion was in fact an ulcer and furthermore required serial judgment as to “active” versus “indeterminant” versus “healed”. One web-based study of photographs of SSc-related digital le- sions suggested that intra-observer reliability was quite high (kappa value of 0.81), but that inter-observer consistency was strikingly weak (kappa = 0.46) (23). We utilized iterative pho- tographic examples in investigator training sessions, but did not have a mechanism to test-retest investigator consistency during the period of trial performance. It remains possible that clinical inconsistency in scoring digital lesions was a fac- tor in diminishing the capability to judge therapeutic effect. However, the lack of other validated measures of outcome in paralleling ulcer counts suggests that this was not an impor- tant factor.

In summary, this placebo-controlled trial of oral treprosti- nil, using a maximum-tolerated BID dose schedule, failed to demonstrate benefit in patients with digital ulcers secondary to systemic sclerosis.

Disclosures

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TABLE I - Summary of baseline demographics and characteristics

Characteristic	Oral treprostinil n = 71	Placebo n = 76
Age in years, mean (range)	49.8 (19-82)	47.8 (20-74)
Gender, male/female, n	17/54	21/55
Race, n		
Asian	4	3
Caucasian	59	62
African-American	7	10
Native Hawaiian/Pacific Islander	1	0
Not provided	1	1
SSc characteristics		
Limited/diffuse, n	40/31	55/21
Years since SSc diagnosis, mean (range)	10.3 (0-35)	10.7 (0-30)
Ulcer characteristics		
Active ulcers at baseline (mean, range)	1.8 (1-6)	1.6 (1-5)
Total ulcers at baseline (mean, range)	2.7 (1-10)	2.4 (1-7)
Active ulcers at baseline, n (%)		
1	35 (49%)	44 (58%)
2	26 (37%)	22 (29%)
3	4 (6%)	7 (9%)
4	3 (4%)	2 (3%)
5	1 (1%)	1 (1%)
6	2 (3%)	0
Autoantibody status, n		
Anti-centromere		
Positive/negative/unknown	19/40/12	29/34/13
Anti-topoisomerase		
Positive/negative/unknown	27/32/12	22/38/16
Background PDE5I use, n	12	13

SSc = systemic scleroderma; PDE5I = phosphodiesterase-type 5 inhibitor.

taBle ii - Summary of mean net ulcer burden and mean change from baseline in ITT population

time period	net ulcer burden			
	Oral treprostinil n = 71		Placebo n = 76	
	Mean ± sD	Mean change from baseline	Mean ± sD	Mean change from baseline
Baseline	1.80 ± 1.13		1.61 ± 0.87	
Week 5	1.80 ± 1.23	-0.00 ± 1.10	1.56 ± 0.97	-0.04 ± 0.87
Week 10	1.53 ± 1.50	-0.27 ± 1.55	1.48 ± 1.17	-0.12 ± 1.15
Week 15	1.44 ± 1.83	-0.37 ± 1.72	1.67 ± 1.65	0.07 ± 1.65
Week 20	1.37 ± 1.85	-0.43 ± 1.83	1.51 ± 1.79	-0.10 ± 1.81

ITT = intention to treat.

taBle iV - Summary of magnitude of effect from baseline to week 20 in SHAQ domain scores

component	shaQ component score Median				Hodges-Lehmann estimate of treatment effect (95% CI)	p value[§]
	Oral treprostinil n = 71		Placebo n = 76			
	Baseline	Week 20	Baseline	Week 20		
Dressing and grooming	1.00	0.50	0.50	0.50	0.00 (0.00, 0.00)	0.11
Arising	0.00	0.00	0.00	0.00	0.00 (0.00, 0.00)	0.71
Eating	0.67	0.67	0.67	0.67	0.00 (-0.33, 0.00)	0.15
Walking	0.00	0.00	0.00	0.00	0.00 (0.00, 0.00)	0.35
Hygiene[a]	0.33	0.33	0.00	0.00	0.00 (0.00, 0.00)	0.80
Reach[a]	0.50	0.50	0.00	0.50	0.00 (0.00, 0.00)	0.76
Grip[a]	0.33	0.33	0.33	0.33	0.00 (-0.33, 0.00)	0.05
Activity[a]	0.67	0.33	0.33	0.33	0.00 (0.00, 0.00)	0.37
HAQ aggregate score[a]	0.53	0.48	0.34	0.43	-0.06 (-0.13, 0.00)	0.06
Hand function aggregate score[a]	0.57	0.50	0.39	0.42	-0.11 (-0.17, 0.00)	0.05
Intestinal problems VAS[b]	0.11	0.47	0.20	0.30	0.10 (0.00, 0.30)	0.06
RP VAS[c]	0.18	0.14	0.12	0.14	0.00 (-0.06, 0.06)	0.81
Digital ulcer VAS	1.50	0.50	1.43	0.77	-0.18 (-0.50, 0.06)	0.13
Breathing problems VAS	2.16*	0.34	1.54*	0.78	-0.42 (-0.76, -0.10)	0.01
Pain VAS[d]	1.54	0.54	1.27	0.75	-0.24 (-0.52, 0.02)	0.07
Overall disease VAS	1.52	1.06	1.22	0.87	-0.12 (-0.38, 0.14)	0.39

[§] Wilcoxon sum-rank test.
* $p<0.05$.
[a] Treprostinil n = 68/placebo, n = 76.
[b] Treprostinil, n = 70/placebo, n = 75.
[c] Treprostinil, n = 71/placebo, n = 75.
[d] Treprostinil, n = 69/placebo, n = 76.
SHAQ = Scleroderma Health Assessment Questionnaire; VAS = visual analog scale; HAQ = Health Assessment Questionnaire; RP = Raynaud phenomenon.

TABLE III - Summary of ulcer healing status and new ulcer formation outcomes

	Oral treprostinil n = 71	Placebo n = 76
Cardinal ulcer healed (n, %)	44 (62%)	46 (61%)
Time to cardinal ulcer healing (mean ± SD days)	76.3 ± 35	83.2 ± 37.9
All ulcers healed (n, %)	35 (49%)	31 (41%)
Time to all ulcers healed (mean ± SD days)	90.2 ± 35.6	96.7 ± 39.7
Any new ulcers formed during study (n, %)	24 (34%)	22 (29%)
No new[§a]	39 (55%)	44 (58%)
At least one new indeterminate/ missing data	8 (11%)	10 (13%)
Any new ulcers formed after Week 5 (n, %)	30 (42%)	26 (24%)
No new[§b]	27 (38%)	39 (51%)
At least one new indeterminate/ missing data	14 (20%)	11 (14%)

[§] Fisher's exact test.
[a] $p = 0.59$.
[b] $p = 0.40$.