Original Investigation

Effect of Macitentan on the Development of New Ischemic Digital Ulcers in Patients With Systemic Sclerosis
DUAL-1 and DUAL-2 Randomized Clinical Trials

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IMPORTANCE Digital ulcers in patients with systemic sclerosis are associated with pain and poor quality of life. Endothelin-1 promotes vasculopathy in systemic sclerosis after macitentan, an endothelin-1 blocker.

OBJECTIVE To evaluate the efficacy of macitentan in reducing the number of new digital ulcers in patients with systemic sclerosis.

DESIGN, SETTING, AND PARTICIPANTS Two international, randomized, double-blind, placebo-controlled trials (DUAL-1, DUAL-2) were conducted between January 2012 and February 2014. Participants were patients with systemic sclerosis and active digital ulcers at baseline. Target enrollment for each study was 285 patients.

INTERVENTIONS Patients were randomized (1:1:1) to receive oral doses of 3 mg of macitentan, 10 mg of macitentan, or placebo once daily and stratified according to number of digital ulcers at baseline (≤3 or >3).

MAIN OUTCOMES AND MEASURES The primary outcome for each trial was the cumulative number of new digital ulcers from baseline to week 16. Treatment effect was expressed as the ratio between treatment groups.

RESULTS In DUAL-1, among 289 randomized patients (mean age 51.2 years; 85.8% women), 226 completed the study. The adjusted mean number of new digital ulcers per patient over 16 weeks was 0.94 in the 3-mg macitentan group (n = 95) and 1.08 in the 10-mg macitentan group (n = 97) compared with 0.85 in the placebo group (n = 97) (absolute difference, 0.09 [95% CI, −0.37 to 0.54] for 3 mg of macitentan vs placebo and 0.23 [−0.27 to 0.72] for 10 mg of macitentan vs placebo). Among 265 patients randomized in DUAL-2 (mean age 49.6 years; 81.9% women), 216 completed the study. In DUAL-2, the adjusted mean number of new digital ulcers was 1.44 in the 3-mg macitentan group (n = 88) and 1.46 in the 10-mg macitentan group (n = 88) compared with 1.21 in the placebo group (n = 89) (absolute difference, 0.23 [95% CI, −0.35 to 0.82] for 3 mg of macitentan vs placebo and 0.25 [95% CI, −0.34 to 0.84] for 10 mg of macitentan vs placebo). Adverse events more frequently associated with macitentan than with placebo were headache, peripheral edema, skin ulcer, anemia, upper respiratory tract infection, diarrhea, and nasopharyngitis.

CONCLUSIONS AND RELEVANCE Among patients with systemic sclerosis and active ischemic digital ulcers, treatment with macitentan did not reduce new digital ulcers over 16 weeks. These results do not support the use of macitentan for the treatment of digital ulcers in this patient population.

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Systemic sclerosis is a chronic multisystem autoimmune disease characterized by systemic vascular dysfunction and fibroblast dysregulation.[1] Microvascular involvement contributes to the pathogenesis of the hallmark manifestations in systemic sclerosis, including pulmonary arterial hypertension, scleroderma renal crisis, Raynaud phenomenon, and digital ischemia.[1] Digital ulcers are a clinical manifestation of digital ischemia that occur in 35% to 68% of patients with systemic sclerosis[2-5] and are associated with pain, disfigurement, poor quality of life, and disability.[2,6]

Systemic sclerosis–related vasculopathy is associated with the initiation and progression of systemic sclerosis and the development of digital ulcers.[7] Endothelin-1 (ET-1) is a mediator of vascular hypertrophy, proliferation, inflammation, and fibrosis.[8] ET-1 is overexpressed in plasma in patients with systemic sclerosis, especially those with digital ulcers.[9] ET receptors are upregulated in microvessels of skin in systemic sclerosis.[10] The dual ET-receptor antagonist (ERA) bosentan significantly reduced the number of new digital ulcers in 2 randomized clinical trials (RCTs) of patients with systemic sclerosis with digital ulcers.[11,12] Macitentan is a novel dual ERA[13,14] approved for long-term treatment of pulmonary arterial hypertension.

DUAL-1 and DUAL-2 are 2 RCTs that evaluated whether macitentan reduces the number of new digital ulcers and their associated disability in patients with systemic sclerosis and active ischemic digital ulcers. DUAL-1 and DUAL-2 also evaluated the safety and tolerability of macitentan in this patient population.

Methods

Study Design

DUAL-1 and DUAL-2 were phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group trials, designed to fulfill the regulatory requirement for providing substantial evidence of effectiveness. Patients were enrolled in DUAL-1 at 70 centers in 17 countries from January 2012 to November 2013 and in DUAL-2 at 73 centers in 20 countries from February 2012 to February 2014. Investigational sites were specific to each study; although, 6 countries were involved in both trials (eFigure in Supplement 1). The trial protocols (Supplement 2 and Supplement 3) were approved by ethics committees at each center and the studies were performed in accordance with the principles of the Declaration of Helsinki and within the regulations of each country. Written informed consent was obtained from all patients. An independent data monitoring committee regularly reviewed unblinded efficacy and safety data, and an international liver safety board assessed all hepatic events (eTable 1 in Supplement 1).

Participant Selection

Inclusion criteria were age of at least 18 years; physician diagnosis of systemic sclerosis according to the 1980 American College of Rheumatology classification criteria[15] with limited or diffuse cutaneous systemic sclerosis[16]; at least 1 visible, active ischemic digital ulcer located at or distal to the proximal interphalangeal joint that developed or worsened within 8 weeks prior

to screening; and a history of additional active digital ulcers prior to screening (≥1 within 6 months or ≥2 within 12 months). An active digital ulcer was defined as a finger lesion with visually discernible depth and a loss of continuity of epithelial coverage associated with pain not attributable to other etiologies.

Patients were excluded if they had digital ulcers not due to systemic sclerosis, or if they had comorbidities that could affect assessment of hand function. Other exclusion criteria included any severe organ failure or life-threatening condition; tobacco use within 6 months before screening; treatment with phosphodiesterase type 5 inhibitors; treatment with prostanoids or ERAs within 3 months prior to screening or any investigational drug within 1 month prior to screening; and disease-modifying agents given for less than 3 months or at a nonstable dose for at least 1 month prior to screening.

Study Procedures

In each study, patients were randomly assigned (1:1:1) to receive 3 mg of macitentan, 10 mg of macitentan, or matching oral placebo once daily. Treatment allocation was stratified by number of digital ulcers at randomization (≤3 and >3) with a block size of 6. Each patient was randomized via a centralized Interactive Response System (ICON) and received a unique randomization number. The patients, investigators, and study sponsor remained blinded to treatment until database lock.

Patients were assessed at randomization and every 4 weeks up to week 16 (period 1). Between week 16 and the end of the study they were assessed every 3 months (period 2) (eTable 2 in Supplement 1). Patients continued double-blind treatment until the end of study, which occurred for all patients when the last patient completed the week-16 visit. Within 7 days of the end of the study, patients completed the end of treatment visit. Within 30 days of the end of the study, patients underwent their end-of-study visit. Patients who prematurely discontinued the study drug in period 1 or 2 completed the end of treatment visit within 7 days of the last administered dose. These patients underwent follow-up every 3 months until the end of the study. Adverse events (AEs) were monitored throughout the study.

Outcome Measures

The primary efficacy end point was the cumulative number of new digital ulcers from baseline to week 16. Digital ulcers that occurred and healed between visits were not recorded as new. Complete healing was defined as complete epithelialization of the ischemic digital ulcer, regardless of residual pain. Since there is low interrater reliability in assessing digital ulcers,[17] each patient was assessed for digital ulcers by the same investigator throughout the study. All investigators were trained to visualize and score the stages and types of digital ulcers in face-to-face meetings and were provided with a reference document to use during the study.

Other prespecified end points included the evaluation of hand function (assessed by the change between baseline and week 16 in Health Assessment Questionnaire-Disability Index [HAQ-DI][18] and Hand Disability in Systemic Sclerosis-Digital Ulcers [HDISS-DU] scores [eMethod in Supplement 1]); the evaluation of digital ulcer burden (assessed by the proportion of patients with or without multiple new digital ulcers at

week 16 and by the change from baseline to week 16 in the total number of digital ulcers); the change from baseline to week 16 in the patient- and physician-reported global assessment of digital ulcer activity (severity of illness and global improvement; score range, 1-7); the proportion of patients with complete healing of all digital ulcers at week 16; the change from baseline to week 16 in overall hand pain related to digital ulcers (score range, 1-10); the change from baseline to week 16 in the Scleroderma Health Assessment Questionnaire visual analog scales (SHAQ-VAS; score range, 1-3) for overall global assessment of disease and for activity limitation due to digital ulcers and to Raynaud phenomenon[19]; and the evaluation of digital ulcer complications (assessed by the proportion of patients with digital ulcer complications at the end of treatment and the time from randomization to first digital ulcer complication up to the end of treatment).

Statistical Analyses

For the primary end point, the null hypotheses were that the mean cumulative number of new digital ulcers per patient up to week 16 was the same between placebo vs 10-mg macitentan groups and between placebo vs 3-mg macitentan groups. A sample size of 95 patients per treatment group (285 patients in total) was calculated by statistical simulations on the basis of a 2-sided comparison at the 5% significance level using an unstratified Pitman permutation test, 90% power, an overdispersion of 0.76, and an estimated 45% reduction in new digital ulcers at week 16 (based on an RCT comparing bosentan vs placebo, in which the mean number of new digital ulcers up to week 24 was 4.4 for placebo and 2.4 for bosentan).[12] The use of a binomial-2 regression (NB-2) model[20] adjusted for the number of digital ulcers at randomization (≤3 or >3) was introduced before study start. With the same sample size, it was estimated that a significant difference between the active and the placebo groups could be determined with greater than 97% power. The treatment effect was expressed as the ratio of incidence rates of new digital ulcers over 16 weeks between each of the macitentan dose groups and the placebo group, and presented with corresponding 95% CIs. The incidence rates were calculated as the cumulative number of new digital ulcers observed up to week 16 and were standardized to 16 weeks to account for different exposure times among patients. The main imputation rules for missing values for the primary end point are explained in eTable 3 in Supplement 1. This imputation method relies on the assumption of a constant rate of new digital ulcers occurring over time, as observed in previous studies[11,12] and verified post hoc for these analyses.

A post hoc sensitivity analysis was performed using multiple imputation by fully conditional specification.[21] Variables used for imputation were treatment group, number of digital ulcers at randomization, and the count of new digital ulcers at each visit up to week 16 (eTable 4 in Supplement 1). Additional predefined sensitivity analyses of the primary end point were performed, as detailed in eTable 4 (Supplement 1). A prespecified subgroup analysis evaluated the primary end point by number of digital ulcers at randomization (≤3 or >3).

For other efficacy end points evaluating a change from baseline to week 16, treatment differences were analyzed using analysis of covariance. Treatment differences for binary efficacy end points were expressed as odds ratios (ORs) calculated using logistic regression. Treatment differences were adjusted for baseline values. Missing data at week 16 were imputed using the last observation carried forward, and for HAQ-DI, the standard scoring was used.[19] For time-to-event analyses, Kaplan-Meier estimates were calculated and proportional hazard models were used to compute hazard ratios (HRs) and 95% CIs. All analyses were adjusted for the number of digital ulcers at randomization (≤3 or >3). Safety data were summarized descriptively.

The primary end point analysis was performed in the intention-to-treat population, whereas all other efficacy end point analyses were performed in the modified intention-to-treat population (defined as all randomized patients who received ≥1 dose of study treatment and had ≥1 post-baseline primary efficacy assessment). The safety analysis included all randomized patients who received at least 1 dose of study treatment. The studies were planned to be reported separately. All analyses were conducted using SAS version 9.3 (SAS Institute Inc), using a significance threshold of 5% with 2-sided P values.

Results

Patient Characteristics

In the DUAL-1 study, 289 patients were randomized to receive 3 mg of macitentan (n = 95), 10 mg of macitentan (n = 97), or placebo (n = 97) (Figure 1). In the DUAL-2 study, 265 patients were randomized to receive 3 mg of macitentan (n = 88), 10 mg of macitentan (n = 88), or placebo (n = 89) (Figure 2). In each study, groups were balanced with respect to patient demographics, disease characteristics, and concomitant medications (Table 1). In DUAL-1, the number of digital ulcers at baseline ranged from 1 to 13 (mean, 3.4), and 201 patients (69.6%) presented with 3 or fewer digital ulcers. In DUAL-2, the number of digital ulcers at baseline ranged from 1 to 18 (mean, 3.5), and 180 patients (67.9%) presented with 3 or fewer digital ulcers. DUAL-2 was terminated prematurely based on recommendations by the independent data monitoring committee, which had overall responsibility for safeguarding the interests of the study participants by monitoring safety and efficacy data. Although formal interim analyses were not predefined, the committee concluded, after reviewing unblinded data during a routine safety monitoring meeting (November 2013), that while risks of macitentan appeared modest, the possibility of any benefit was small and additional data were not expected to result in a positive primary outcome. The committee recommended that DUAL-2 be halted and study treatment was discontinued in all patients (93.0% of planned patients had been enrolled and 74.7% of those underwent ≥16 weeks of treatment).

Development of New Digital Ulcers

The 2 trials did not achieve the primary end point of a reduction of cumulative number of new digital ulcers over 16 weeks (Table 2). In DUAL-1, the adjusted mean numbers of new digital ulcers per patient over 16 weeks were 0.94 in the 3 mg of macitentan group, 1.08 in the 10 mg of macitentan group, and 0.85 in the placebo group, and observations were similar in DUAL-2

Figure 1. Flow of Study Participants for DUAL-1
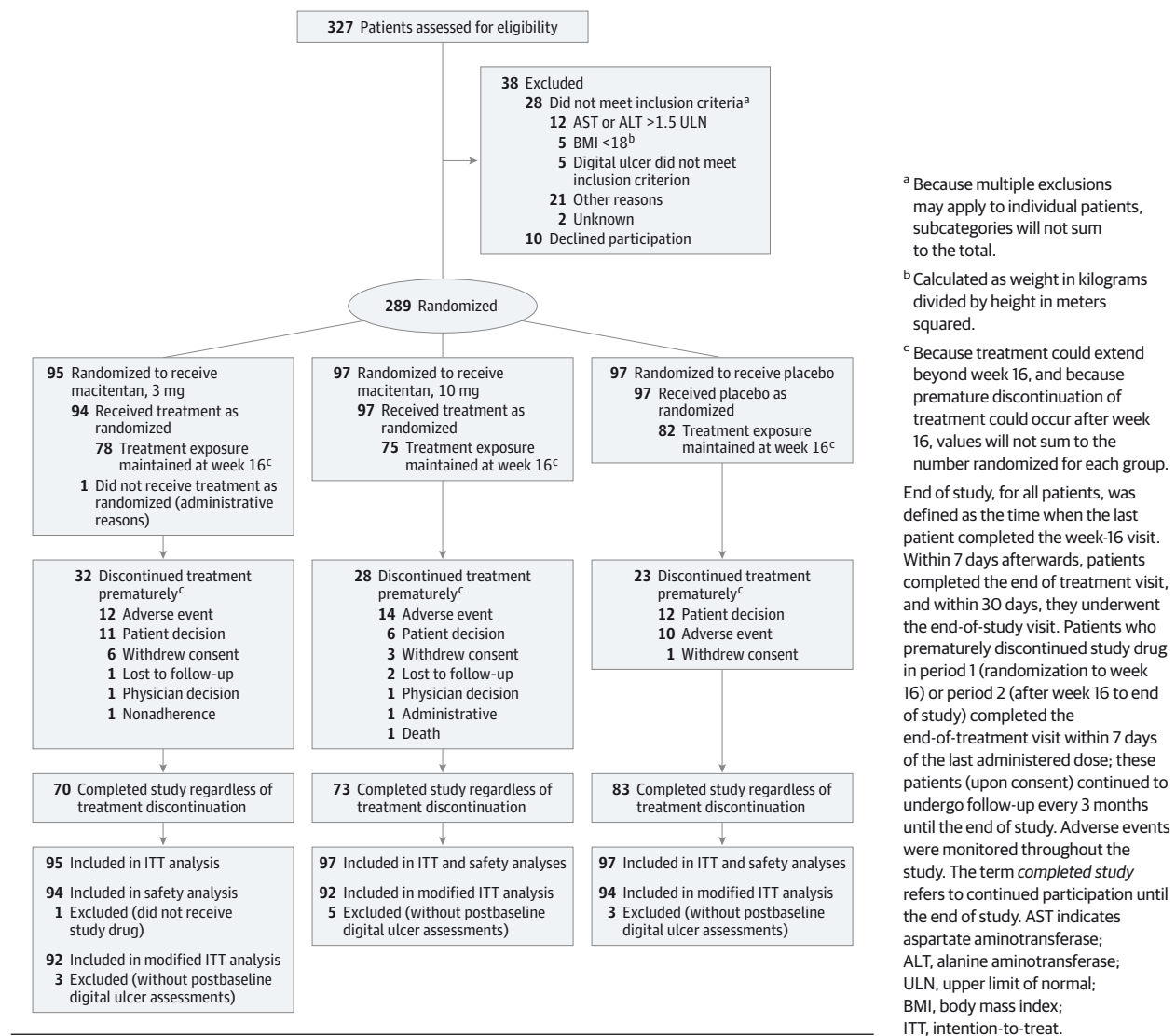
(adjusted mean number of new digital ulcers per patient over 16 weeks: 1.44 in the 3 mg of macitentan group, 1.46 in the 10 mg of macitentan group, and 1.21 in the placebo group). In DUAL-1, the absolute difference for the cumulative number of new digital ulcers from baseline to week 16 was 0.09 (95% CI, −0.37 to 0.54) and the rate ratio was 1.10 (95% CI, 0.66 to 1.83) (P = .71) for 3 mg of macitentan vs placebo; for 10 mg of macitentan vs placebo, the absolute difference was 0.23 (95% CI, −0.27 to 0.72) and the rate ratio was 1.27 (95% CI, 0.76 to 2.11) (P = .36).
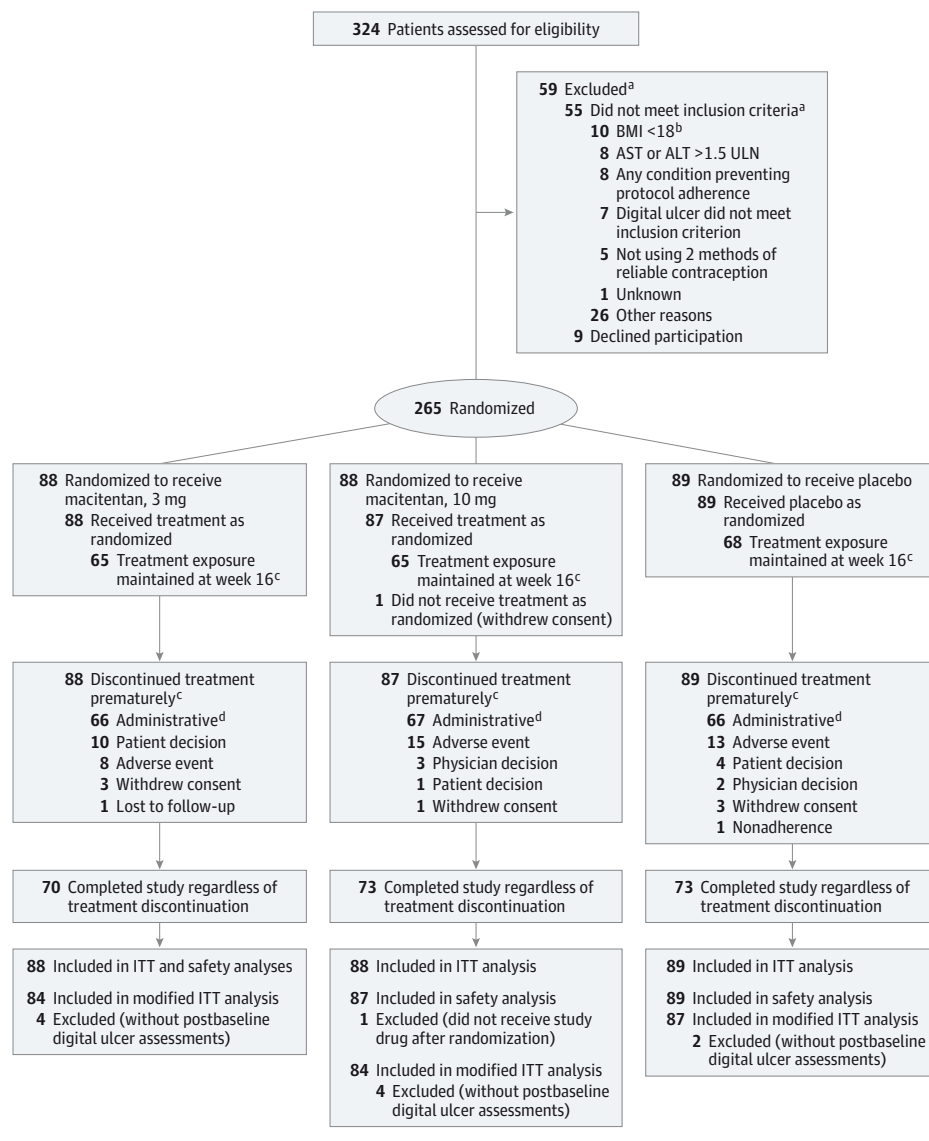
In DUAL-2, the absolute difference for the cumulative number of new digital ulcers from baseline to week 16 was 0.23 (95% CI, −0.35 to 0.82) and the rate ratio was 1.19 (95% CI, 0.77 to 1.86) (P = .43) for 3 mg of macitentan vs placebo; for 10 mg of macitentan vs placebo, the absolute difference was 0.25 (95% CI, −0.34 to 0.84) and the rate ratio was 1.21 (95% CI, 0.77 to 1.89) (P = .41). These results were confirmed using multiple imputation and other prespecified sensitivity analyses (eTable 4 in Supplement 1). The amount of missing data for the primary end point is shown in eTable 5 (Supplement 1; patients with

≥1 missing assessment: DUAL-1, 23.5% [n = 68]; DUAL-2, 24.9% [n = 66]). The absence of a treatment effect was also observed in the subgroups of patients with 3 or fewer digital ulcers at baseline vs greater than 3 (Table 2). In DUAL-1, 64.1% (59) of patients in the 3 mg of macitentan group, 63.0% (58) of patients in the 10 mg of macitentan group, and 67.0% (63) of patients in the placebo group had no new digital ulcers by week 16. In DUAL-2, 56.0% (47) of those in the 3 mg of macitentan group, 54.8% (46) of patients in the 10 mg of macitentan group, and 59.8% (52) of patients in the placebo group had no new digital ulcers by week 16 (Table 3).

Hand Function, Digital Ulcers Burden, and Time to Digital Ulcers Complications

There were no treatment effects with either dose of macitentan vs placebo in either trial with respect to other efficacy end points, including hand function, digital ulcer burden, patient- and physician-reported outcomes, complete healing of digital ulcers, and overall hand pain related to digital ulcers and

Figure 2. Flow of Study Participants for DUAL-2

324 Patients assessed for eligibility

59 Excluded[a]
- **55** Did not meet inclusion criteria[a]
  - **10** BMI <18[b]
  - **8** AST or ALT >1.5 ULN
  - **8** Any condition preventing protocol adherence
  - **7** Digital ulcer did not meet inclusion criterion
  - **5** Not using 2 methods of reliable contraception
  - **1** Unknown
- **26** Other reasons
- **9** Declined participation

265 Randomized

88 Randomized to receive macitentan, 3 mg
- **88** Received treatment as randomized
  - **65** Treatment exposure maintained at week 16[c]

88 Randomized to receive macitentan, 10 mg
- **87** Received treatment as randomized
  - **65** Treatment exposure maintained at week 16[c]
- **1** Did not receive treatment as randomized (withdrew consent)

89 Randomized to receive placebo
- **89** Received placebo as randomized
  - **68** Treatment exposure maintained at week 16[c]

88 Discontinued treatment prematurely[c]
- **66** Administrative[d]
- **10** Patient decision
- **8** Adverse event
- **3** Withdrew consent
- **1** Lost to follow-up

87 Discontinued treatment prematurely[c]
- **67** Administrative[d]
- **15** Adverse event
- **3** Physician decision
- **1** Patient decision
- **1** Withdrew consent

89 Discontinued treatment prematurely[c]
- **66** Administrative[d]
- **13** Adverse event
- **4** Patient decision
- **2** Physician decision
- **3** Withdrew consent
- **1** Nonadherence

70 Completed study regardless of treatment discontinuation

73 Completed study regardless of treatment discontinuation

73 Completed study regardless of treatment discontinuation

88 Included in ITT and safety analyses
84 Included in modified ITT analysis
- **4** Excluded (without postbaseline digital ulcer assessments)

88 Included in ITT analysis
87 Included in safety analysis
- **1** Excluded (did not receive study drug after randomization)
84 Included in modified ITT analysis
- **4** Excluded (without postbaseline digital ulcer assessments)

89 Included in ITT analysis
89 Included in safety analysis
87 Included in modified ITT analysis
- **2** Excluded (without postbaseline digital ulcer assessments)

[a] Because multiple exclusions may apply to individual patients, subcategories will not sum to the total.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Because treatment could extend beyond week 16, and because premature discontinuation of treatment could occur after week 16, values will not sum to the number randomized for each group.

[d] Indicates the independent data monitoring committee's early termination of the trial.

End of study, for all patients, was defined as the time when the last patient completed the week-16 visit. Within 7 days afterwards, patients completed the end of treatment visit, and within 30 days, they underwent the end-of-study visit. Patients who prematurely discontinued study drug in period 1 (randomization to week 16) or period 2 (after week 16 to end of study) completed the end-of-treatment visit within 7 days of the last administered dose; these patients (upon consent) continued to undergo follow-up every 3 months until the end of study. Adverse events were monitored throughout the study. The term *completed study* refers to continued participation until the end of study. BMI indicates body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; ITT, intention-to-treat.

SHAQ (Table 3). In all groups, patients showed reduction from baseline to week 16 in total number of digital ulcers, severity of disease (patient- and physician-rated), pain, and interference with daily activity. There was little change in hand function (Table 3). In both trials, no differences between groups were observed in time to first digital ulcer complications (**Figure 3**). Digital ulcer complications were observed in 17.6% of patients in DUAL-1 and in 21.2% of patients in DUAL-2 (eTable 6 in Supplement 1).

Safety and Tolerability
In both trials, patients were exposed to treatment on average for 40 weeks (eTable 7 in Supplement 1). In this period, the frequency of patients in DUAL-1 with at least 1 AE was 71.3% among those in the 3 mg of macitentan group, 76.3% for 10 mg of macitentan , and 73.2% for the placebo group, and in DUAL-2, the frequency of patients with at least 1 AE was 83.0% among

those in the 3 mg of macitentan group, 85.1% for 10 mg of macitentan, and 78.7% for the placebo group (eTable 7 in Supplement 1). The most frequently reported AEs (incidence rate, 10% and >3% difference between placebo and either macitentan group) in each trial were headache, peripheral edema, skin ulcer, anemia, upper respiratory tract infection, diarrhea, and nasopharyngitis. AEs leading to premature discontinuation occurred in 13.8% of patients in the 3 mg of macitentan group, 14.4% for 10 mg of macitentan, and 10.3% of patients in the placebo group in DUAL-1, and in DUAL-2, AEs leading to premature discontinuation occurred in 9.2% of patients in the 3 mg of macitentan group, 17.2% for 10 mg of macitentan, and 14.6% of patients in the placebo group. Skin ulcer, infected skin ulcer, and increased alanine aminotransferase/aspartate aminotransferase were the most frequently reported AEs leading to treatment discontinuation. Incidences of serious AEs in DUAL-1 were 18.1% in the 3 mg of macitentan group, 14.4% for 10 mg of macitentan,

Table 1. Patient and Disease Characteristics at Baseline

Characteristics	DUAL-1				DUAL-2			
	Placebo (n = 97)	3-mg Macitentan (n = 95)	10-mg Macitentan (n = 97)	All Patients (N = 289)	Placebo (n = 89)	3-mg Macitentan (n = 88)	10-mg Macitentan (n = 88)	All Patients (N = 265)
Female sex, No. (%)	83 (85.6)	84 (88.4)	81 (83.5)	248 (85.8)	71 (79.8)	75 (85.2)	71 (80.7)	217 (81.9)
Age, mean (SD), y	50.6 (12.1)	51.4 (14.4)	51.6 (11.1)	51.2 (12.6)	50.6 (12.9)	50.6 (13.2)	47.4 (13.0)	49.6 (13.1)
Race or ethnicity, No. (%)[a]								
White	88 (90.7)	86 (90.5)	82 (84.5)	256 (88.6)	68 (76.4)	62 (70.5)	63 (71.6)	193 (72.8)
Black	1 (1.0)	0	3 (3.1)	4 (1.4)	0	2 (2.3)	0	2 (0.8)
Asian	4 (4.1)	5 (5.3)	6 (6.2)	15 (5.2)	6 (6.7)	6 (6.8)	4 (4.5)	16 (6.0)
Hispanic	3 (3.1)	3 (3.2)	4 (4.1)	10 (3.5)	9 (10.1)	12 (13.6)	14 (15.9)	35 (13.2)
Other	1 (1.0)	1 (1.1)	2 (2.1)	4 (1.4)	6 (6.7)	6 (6.8)	7 (8.0)	19 (7.2)
Systemic sclerosis diffuse, No. (%)	62 (63.9)	55 (57.9)	57 (58.8)	174 (60.2)	39 (43.8)	45 (51.1)	51 (58.0)	135 (50.9)
Time since first non-Raynaud phenomenon symptom onset of systemic sclerosis, mean (SD), y[b]	9.2 (7.6)	9.5 (9.2)	10.2 (8.3)	9.7 (8.4)	11.4 (8.4)	12.5 (10.1)	9.4 (7.2)	11.1 (8.7)
Time since first Raynaud phenomenon diagnosis, mean (SD), y[c]	11.2 (9.1)	10.6 (9.3)	12.3 (10.2)	11.4 (9.5)	13.4 (9.1)	14.8 (11.0)	10.2 (7.8)	12.8 (9.6)
Time since first digital ulcer diagnosis, median (range), y[d]	4.1 (0.2-37.1)	3.8 (0.1-31.1)	5.3 (0.2-34.3)	4.5 (0.1-37.1)	7.0 (0.1-33.5)	4.9 (0.2-55.0)	5.3 (0.1-27.6)	5.3 (0.1-55.0)
Anticentromere positive ≥41 AU/mL, No. (%)[e]	22 (23.2)	27 (29.0)	22 (22.7)	71 (24.9)	30 (34.1)	17 (19.3)	21 (24.1)	68 (25.9)
Anti-Scl-70 positive ≥41 AU/mL, No. (%)[e]	42 (44.2)	40 (43.0)	37 (38.1)	119 (41.8)	42 (47.7)	43 (48.9)	42 (48.3)	127 (48.3)
Total No. of digital ulcers	3.4 (2.3)	3.4 (2.3)	3.5 (2.6)	3.4 (2.4)	3.7 (2.9)	3.4 (2.1)	3.3 (2.5)	3.5 (2.5)
Total No. of active digital ulcers	2.7 (1.8)	2.8 (2.0)	2.8 (2.0)	2.8 (1.9)	2.9 (2.7)	2.7 (1.9)	2.2 (1.7)	2.6 (2.1)
HAQ-DI[f,g]	1.3 (0.7)	1.3 (0.7)	1.4 (0.7)	1.3 (0.7)	1.4 (0.7)	1.4 (0.7)	1.3 (0.7)	1.3 (0.7)
HDISS-DU[g]	3.0 (1.1)	3.0 (1.2)	3.0 (1.1)	3.0 (1.1)	2.9 (1.2)	3.0 (1.1)	2.9 (1.0)	2.9 (1.1)
Patient-reported global assessment score of digital ulcer severity[h]	4.4 (1.3)	4.7 (1.1)	4.5 (1.2)	4.6 (1.2)	4.7 (1.1)	4.4 (1.3)	4.5 (1.1)	4.5 (1.2)
Physician-reported global assessment score of digital ulcer severity[h,i]	4.2 (1.0)	4.4 (0.9)	4.2 (0.9)	4.3 (0.9)	4.2 (1.0)	4.3 (0.9)	4.1 (0.9)	4.2 (1.0)
Overall hand pain related to digital ulcers[g]	5.9 (2.4)	6.2 (2.2)	6.3 (2.4)	6.1 (2.4)	6.8 (2.2)	6.2 (2.5)	6.1 (2.3)	6.4 (2.3)
SHAQ-VAS[g]								
Overall global assessment of disease, mean (SD)[j]	1.3 (0.5)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
Activity limitation due to digital ulcers, mean (SD)[k]	1.8 (0.9)	1.9 (0.8)	1.9 (0.8)	1.9 (0.8)	2.0 (0.8)	1.9 (0.9)	1.8 (0.8)	1.9 (0.8)
Activity limitation due to Raynaud phenomenon, mean (SD)[l]	1.7 (0.8)	1.6 (0.9)	1.7 (0.8)	1.7 (0.8)	1.8 (0.9)	1.7 (0.9)	1.7 (0.9)	1.7 (0.9)

(continued)

Table 1. Patient and Disease Characteristics at Baseline (continued)

Characteristics	DUAL-1				DUAL-2			
	Placebo (n = 97)	3-mg Macitentan (n = 95)	10-mg Macitentan (n = 97)	All Patients (N = 289)	Placebo (n = 89)	3-mg Macitentan (n = 88)	10-mg Macitentan (n = 88)	All Patients (N = 265)
Concomitant medication, No. (%)								
Dihydropyridine calcium channel blockers	34 (35.1)	37 (38.9)	32 (33.0)	103 (35.6)	51 (57.3)	39 (44.3)	40 (45.5)	130 (49.1)
Pentoxifylline	19 (19.6)	20 (21.1)	21 (21.6)	60 (20.8)	12 (13.5)	8 (9.1)	14 (15.9)	34 (12.8)
Platelet aggregation inhibitors[m]	39 (40.2)	35 (36.8)	33 (34.0)	107 (37.0)	47 (52.8)	34 (38.6)	29 (33.0)	110 (41.5)
Heparin	3 (3.1)	12 (12.6)	4 (4.1)	19 (6.6)	5 (5.6)	7 (8.0)	9 (10.2)	21 (7.9)
Angiotensin-converting enzyme inhibitors	21 (21.6)	21 (22.1)	12 (12.4)	54 (18.7)	20 (22.5)	9 (10.2)	17 (19.3)	46 (17.4)
Angiotensin II antagonists	4 (4.1)	10 (10.5)	5 (5.2)	19 (6.6)	7 (7.9)	13 (14.8)	13 (14.8)	33 (12.5)
Glucocorticoids (≤10 mg/d)	54 (55.7)	55 (57.9)	53 (54.6)	162 (56.1)	45 (50.6)	40 (45.5)	51 (58.0)	136 (51.3)
Immunosuppressants[n]	56 (57.7)	52 (54.7)	47 (48.5)	155 (53.6)	41 (46.1)	47 (53.4)	51 (58.0)	139 (52.4)
Concomitant disease, No. (%)								
Interstitial lung disease	16 (16.5)	27 (28.4)	24 (24.7)	67 (23.2)	32 (36.0)	27 (30.7)	25 (28.4)	84 (31.7)
Gastroesophageal reflux disease	29 (29.9)	27 (28.4)	27 (27.8)	83 (28.7)	36 (40.4)	27 (30.7)	31 (35.2)	94 (35.5)
Calcinosis	4 (4.1)	2 (2.1)	6 (6.2)	12 (4.2)	5 (5.6)	6 (6.8)	5 (5.7)	16 (6.0)

Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index; HDISS-DU, Hand Disability in Systemic Sclerosis-Digital Ulcers; SHAQ-VAS, Scleroderma Health Assessment Questionnaire visual analog scale.

a Defined by the investigator, another member of the medical staff, or the patient.

b In DUAL-1, data were missing for 1 patient in the placebo group; in DUAL-2, data were missing for 2 in the placebo group and 2 in the macitentan 3-mg group.

c In DUAL-2, data were missing for 1 patient in the macitentan 3-mg group.

d In DUAL-1, data were missing for 1 patient in the placebo group; in DUAL-2, data were missing for 3 in the macitentan 3-mg group and 1 in the macitentan 10-mg group.

e In DUAL-1, data were missing for 2 patients in both the placebo and macitentan 10-mg groups; in DUAL-2, data were missing for 1 in both the placebo and macitentan 10-mg groups.

f In DUAL-1, data were missing for 6 patients in the placebo group, 4 in the macitentan 3-mg group, and 8 in the macitentan 10-mg group; in DUAL-2, data were missing for 4 in the placebo group, 5 in the macitentan 3-mg group, and 2 in the macitentan 10-mg group.

g Higher score indicates a worse patient- or physician-reported score. Score ranges: HAQ-DI (0-3), HDISS-DU (0-7), overall hand pain related to digital ulcers (1-10), and SHAQ-VAS (0-3).

h Score is based on a 7-point Likert scale (range: 1, very much worse; 4, no change; 7, very much improved).

i In DUAL-1, data were missing for 1 patient in the macitentan 3-mg group.

j In DUAL-1, data were missing for 6 patients in the placebo group, 4 in the macitentan 3-mg group, and 8 in the macitentan 10-mg group; in DUAL-2, data were missing for 5 in the placebo group, 7 in the macitentan 3-mg group, and 4 in the macitentan 10-mg group.

k In DUAL-2, data were missing for 1 patient in the macitentan 3-mg group, 2 in the macitentan 3-mg group, and 2 in the macitentan 10-mg group.

l In DUAL-2, data were missing for 1 patient in the placebo group, 2 in the macitentan 3-mg group, and 3 in the macitentan 10-mg group.

m Platelet aggregation inhibitors used were beraprost, clopidogrel, acetylsalicylic acid, asasantin, cilostazol, and dipyridamole.

n Disease-modifying antirheumatic drugs used were aminoquinolines, azathioprine, cyclophosphamide, methotrexate, d-penicillamine, rituximab, and other selective immunosuppressants.

Table 2. Effect of Macitentan on the Incidence of Digital Ulcers to Week 16 in DUAL-1 and DUAL-2

Patients	Incidence to Week 16, Adjusted Mean (95% CI)[a]			Absolute Difference (95% CI), Macitentan vs Placebo		Treatment Effect			
						3-mg Macitentan vs Placebo		10-mg Macitentan vs Placebo	
	3-mg Macitentan	10-mg Macitentan	Placebo	3-mg Macitentan	10-mg Macitentan	RR (95% CI)	P Value	RR (95% CI)	P Value
DUAL-1									
Overall, No. of patients[b]	95	97	97						
New digital ulcers per patient, mean (95% CI)[c]	0.94 (0.65 to 1.35)	1.08 (0.75 to 1.56)	0.85 (0.59 to 1.23)	0.09 (−0.37 to 0.54)	0.23 (−0.27 to 0.72)	1.10 (0.66 to 1.83)	.71	1.27 (0.76 to 2.11)	.36
≤3 Digital ulcers at baseline, No. of patients[b]	67	67	67						
New digital ulcers per patient, mean (95% CI)[c]	0.69 (0.45 to 1.08)	0.89 (0.58 to 1.37)	0.64 (0.41 to 1.00)	0.06 (−0.37 to 0.48)	0.25 (−0.22 to 0.73)	1.09 (0.58 to 2.05)	.80	1.40 (0.75 to 2.60)	.29
>3 Digital ulcers at baseline, No. of patients[b]	28	30	30						
New digital ulcers per patient, mean (95% CI)[c]	1.32 (0.72 to 2.43)	1.20 (0.64 to 2.25)	1.16 (0.64 to 2.13)	0.16 (−0.91 to 1.22)	0.04 (−0.99 to 1.06)	1.14 (0.48 to 2.67)	.77	1.03 (0.43 to 2.46)	.95
DUAL-2									
Overall, No. of patients[b]	88	88	89						
New digital ulcers per patient, mean (95% CI)[c]	1.44 (1.06 to 1.96)	1.46 (1.07 to 1.99)	1.21 (0.87 to 1.67)	0.23 (−0.35 to 0.82)	0.25 (−0.34 to 0.84)	1.19 (0.77 to 1.86)	.43	1.21 (0.77 to 1.89)	.41
≤3 Digital ulcers at baseline, No. of patients[b]	60	60	60						
New digital ulcers per patient, mean (95% CI)[c]	0.80 (0.51 to 1.26)	0.89 (0.57 to 1.40)	0.78 (0.50 to 1.24)	0.02 (−0.49 to 0.53)	0.11 (−0.43 to 0.65)	1.02 (0.54 to 1.95)	.94	1.14 (0.60 to 2.17)	.69
>3 Digital ulcers at baseline, No. of patients[b]	28	28	29						
New digital ulcers per patient, mean (95% CI)[c]	2.66 (1.79 to 3.95)	2.36 (1.56 to 3.58)	1.79 (1.16 to 2.76)	0.87 (−0.44 to 2.17)	0.57 (−0.68 to 1.82)	1.48 (0.83 to 2.67)	.19	1.32 (0.73 to 2.40)	.37

Abbreviation: RR, rate ratio.

[a] Digital ulcer incidence was estimated from a negative binomial model.

[b] For the number of patients with imputed data for each visit over 16 weeks, see eTable 5 (Supplement 1).

[c] Analyses were adjusted for the number of digital ulcers at randomization (≤3 or >3).

Table 3. Effect of Macitentan at Week 16 on Selected Outcomes in DUAL-1 and DUAL-2

| Secondary Outcomes	3-mg Macitentan		10 mg Macitentan		Placebo		Treatment Effect[a]			
	No. (Imputed)[b]	Week-16 Value	No. (Imputed)[b]	Week-16 Value	No. (Imputed)[b]	Week-16 Value	3-mg Macitentan vs Placebo	P Value	10-mg Macitentan vs Placebo	P Value
DUAL-1										
HAQ-DI overall score, mean change (95% CI)[c]	85 (10)	-0.1 (-0.2 to 0)	79 (10)	-0.1 (-0.2 to 0)	86 (9)	0 (-0.1 to 0.1)	-0.1 (-0.2 to 0.1)	.46	-0.1 (-0.2 to 0.1)	.44
HDISS-DU overall score, mean change (95% CI)[c]	92 (14)	-0.3 (-0.5 to -0.1)	92 (16)	-0.3 (-0.5 to -0.2)	94 (10)	-0.2 (-0.4 to -0.1)	-0.1 (-0.3 to 0.1)	.46	-0.1 (-0.3 to 0.1)	.34
Patients with no new digital ulcers, No. (%)	92 (14)	59 (64)	92 (16)	58 (63)	94 (10)	63 (67)	0.88 (0.48 to 1.61)	.67	0.83 (0.45 to 1.52)	.55
Patients with >1 digital ulcer, No. (%)	92 (14)	22 (24)	92 (16)	16 (17)	94 (10)	17 (18)	1.45 (0.71 to 2.98)	.31	0.97 (0.46 to 2.08)	.94
Total No. of digital ulcers, mean change (95% CI)	92 (14)	-1.1 (-1.5 to -0.7)	92 (16)	-1.5 (-2.0 to -1.0)	94 (10)	-1.6 (-2.1 to -1.2)	0.46 (-0.04 to 0.97)	.07	0.16 (-0.34 to 0.66)	.53
Patient-reported global assessment of digital ulcer severity, mean change (95% CI)[d]	91 (15)	-1.1 (-1.4 to -0.8)	92 (18)	-1.0 (-1.3 to -0.7)	93 (11)	-1.2 (-1.4 to -0.9)	0.2 (-0.2 to 0.6)	.35	0.2 (-0.2 to 0.6)	.31
Global improvement, mean (95% CI)[d,e]	91 (15)	5.0 (4.7 to 5.2)	91 (17)	5.0 (4.8 to 5.3)	93 (11)	5.0 (4.7 to 5.2)	0 (-0.3 to 0.4)	.86	0.1 (-0.3 to 0.5)	.64
Physician-reported global assessment of digital ulcer severity, mean change (95% CI)[d]	92 (15)	-1.2 (-1.4 to -0.9)	92 (17)	-1.0 (-1.3 to -0.8)	94 (11)	-1.0 (-1.3 to -0.7)	0 (-0.4 to 0.3)	.79	0 (-0.3 to 0.3)	.95
Global improvement, mean (95% CI)[d,e]	92 (15)	5.0 (4.7 to 5.3)	91 (16)	5.2 (4.9 to 5.4)	94 (11)	5.1 (4.8 to 5.4)	-0.1 (-0.5 to 0.3)	.56	0.1 (-0.3 to 0.4)	.74
Patients with complete healing of all digital ulcers, No. (%)	92 (14)	26 (28.3)	92 (16)	29 (31.5)	94 (10)	35 (37.2)	0.66 (0.35 to 1.22)	.18	0.76 (0.41 to 1.41)	.39
Overall hand pain related to digital ulcers, mean change (95% CI)[c]	92 (15)	-2.1 (-2.6 to -1.6)	92 (17)	-2.1 (-2.7 to -1.5)	93 (11)	-1.9 (-2.4 to -1.3)	0 (-0.6 to 0.7)	.92	-0.1 (-0.7 to 0.6)	.87
SHAQ-VAS[c]										
Overall global assessment of disease, mean change (95% CI)	84 (10)	-0.2 (-0.3 to -0.1)	79 (10)	-0.3 (-0.4 to -0.2)	86 (10)	-0.2 (-0.3 to -0.1)	-0.1 (-0.1 to 0.1)	.96	0 (-0.2 to 0.1)	.52
Activity limitation due to digital ulcers, mean change (95% CI)	89 (11)	-0.6 (-0.8 to -0.4)	87 (11)	-0.7 (-0.9 to -0.5)	92 (9)	-0.7 (-0.9 to -0.5)	0.2 (-0.1 to 0.4)	.19	0.1 (-0.2 to 0.3)	.60
Activity limitation due to Raynaud phenomenon, mean change (95% CI)	88 (11)	-0.4 (-0.6 to -0.2)	87 (11)	-0.5 (-0.7 to -0.3)	92 (9)	-0.4 (-0.6 to -0.2)	0 (-0.2 to 0.2)	.91	-0.1 (-0.3 to 0.1)	.37
DUAL-2										
HAQ-DI overall score, mean change (95% CI)[c]	77 (12)	-0.1 (-0.2 to 0)	81 (17)	-0.1 (-0.2 to 0)	82 (16)	0 (-0.1 to 0)	-0.1 (-0.2 to 0.1)	.34	-0.1 (-0.2 to 0.1)	.31
HDISS-DU overall score, mean change (95% CI)[c]	84 (14)	-0.2 (-0.4 to 0)	83 (17)	-0.2 (-0.4 to 0)	87 (17)	-0.1 (-0.2 to 0.1)	-0.1 (-0.4 to 0.1)	.32	-0.2 (-0.4 to 0.1)	.22
Patients with no new digital ulcers, No. (%)	84 (14)	47 (56)	84 (18)	46 (55)	87 (16)	52 (60)	0.83 (0.44 to 1.56)	.57	0.79 (0.42 to 1.48)	.46
Patients with >1 digital ulcer, No. (%)	84 (14)	22 (26)	84 (18)	26 (31)	87 (16)	23 (26)	1.01 (0.49 to 2.07)	.98	1.31 (0.65 to 2.66)	.45
Total No. of digital ulcers, mean change (95% CI)	84 (14)	-1.3 (-1.7 to -0.8)	84 (18)	-1.5 (-2.0 to -1.0)	87 (16)	-1.6 (-2.1 to -1.1)	0.21 (-0.38 to 0.80)	.49	-0.09 (-0.68 to 0.51)	.77

(continued)

Table 3. Effect of Macitentan at Week 16 on Selected Outcomes in DUAL-1 and DUAL-2 (continued)

Secondary Outcomes	3-mg Macitentan		10 mg Macitentan		Placebo		Treatment Effect[a]			
	No. (Imputed)[b]	Week-16 Value	No. (Imputed)[b]	Week-16 Value	No. (Imputed)[b]	Week-16 Value	3-mg Macitentan vs Placebo	P Value	10-mg Macitentan vs Placebo	P Value
Patient-reported global assessment of digital ulcer severity, mean change (95% CI)[d]	82 (13)	−0.9 (−1.3 to −0.6)	82 (17)	−0.9 (−1.2 to −0.6)	86 (15)	−0.9 (−1.1 to −0.6)	−0.2 (−0.6 to 0.2)	.24	−0.2 (−0.6 to 0.2)	.40
Global improvement, mean (95% CI)[d,e]	82 (13)	5.1 (4.8 to 5.4)	82 (17)	4.8 (4.5 to 5.1)	86 (15)	4.9 (4.6 to 5.2)	0.2 (−0.2 to 0.6)	.31	−0.1 (−0.5 to 0.3)	.58
Physician-reported global assessment of digital ulcer severity, mean change (95% CI)[d]	83 (13)	−1.2 (−1.5 to −0.9)	83 (18)	−1.0 (−1.2 to −0.7)	87 (17)	−1.0 (−1.3 to −0.7)	−0.2 (−0.5 to 0.2)	.42	−0.1 (−0.4 to 0.3)	.76
Global improvement, mean (95% CI)[d,e]	83 (13)	5.1 (4.9 to 5.4)	83 (18)	5.1 (4.8 to 5.4)	87 (17)	5.1 (4.8 to 5.4)	0 (−0.4 to 0.4)	.94	0 (−0.4 to 0.4)	.97
Patients with complete healing of all digital ulcers at week 16, No. (%)	84 (14)	30 (35.7)	84 (18)	32 (38.1)	87 (16)	35 (40.2)	0.81 (0.43 to 1.52)	.52	0.90 (0.49 to 1.69)	.75
Overall hand pain related to digital ulcers, mean change (95% CI)[c]	83 (15)	−1.9 (−2.5 to −1.3)	82 (17)	−1.7 (−2.2 to −1.2)	86 (15)	−1.8 (−2.3 to −1.2)	−0.5 (−1.2 to 0.2)	.16	−0.3 (−1.0 to 0.4)	.41
SHAQ-VAS[c]										
Overall global assessment of disease, mean change (95% CI)	75 (12)	−0.2 (−0.3 to −0.1)	79 (17)	−0.2 (−0.3 to −0.1)	80 (15)	−0.1 (−0.2 to −0.1)	−0.1 (−0.2 to 0)	.14	−0.1 (−0.2 to 0.1)	.25
Activity limitation due to digital ulcers, mean change (95% CI)	80 (12)	−0.5 (−0.7 to −0.3)	81 (17)	−0.6 (−0.8 to −0.4)	85 (16)	−0.5 (−0.7 to −0.4)	−0.1 (−0.3 to 0.2)	.61	−0.1 (−0.3 to 0.1)	.46
Activity limitation due to Raynaud phenomenon, mean change (95% CI)	80 (12)	−0.5 (−0.7 to −0.3)	81 (17)	−0.4 (−0.6 to −0.3)	85 (16)	−0.3 (−0.5 to −0.1)	−0.2 (−0.5 to 0)	.06	−0.2 (−0.4 to 0.1)	.17

Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index; HDISS-DU, Hand Disability in Systemic Sclerosis-Digital Ulcers; SHAQ-VAS, Scleroderma Health Assessment Questionnaire visual analog scale.

[a] Treatment differences are presented as adjusted mean differences for continuous outcomes and odds ratios for binary responses. All analyses are adjusted for the baseline score of the same variable (except the global improvement scale which has no baseline value) and the stratification factor (digital ulcers ≥3 vs digital ulcers <3).

[b] Heading indicates "total No. (No. imputed)."

[c] Higher score indicates a worse patient- or physician-reported score. Score ranges: HAQ-DI (0-3), HDISS-DU (0-7), overall hand pain related to digital ulcers (1-10), and SHAQ-VAS (0-3).

[d] Score is based on a 7-point Likert scale (range: 1, very much worse; 4, no change; 7, very much improved).

[e] The global improvement scale is only measured at follow-up visits and the analysis for this outcome is based on the between-group (adjusted for baseline digital ulcers ≥3 vs <3) mean difference at week 16.

Figure 3. Time to First Digital Ulcer Complication Up to End of Treatment in DUAL-1 and DUAL-2
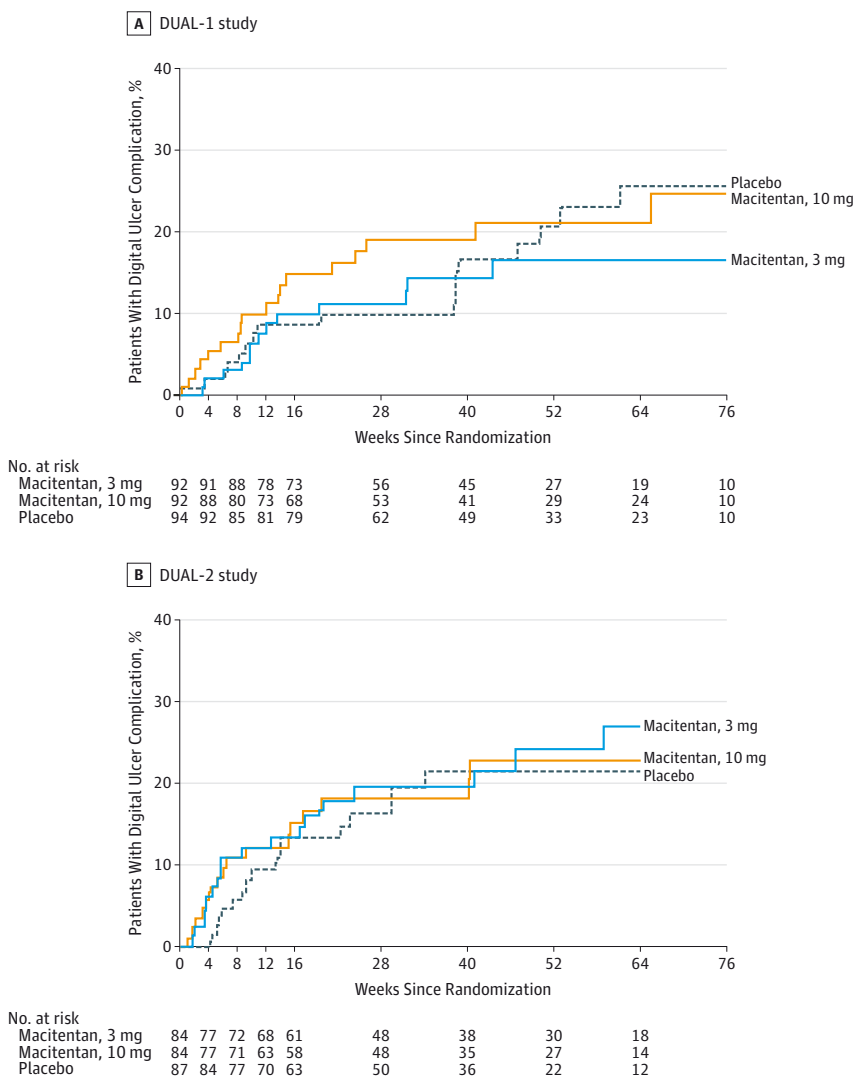
Digital ulcer complications were defined as any of the following (resulting from digital ulcer worsening): (1) critical ischemic crisis necessitating hospitalization; (2) gangrene, (auto) amputation; (3) failure of conservative management: surgical and chemical sympathectomy, vascular reconstructions, or any unplanned surgery in the management of hand systemic sclerosis manifestations; (4) use of parenteral prostanoids; (5) use of endothelin receptor antagonists; (6) required class 2, 3, or 4 narcotics or a >50%-increase in the existing dose compared with baseline; (7) initiation of systemic antibiotics for the treatment of infection attributed to digital ulcers.

A, Treatment effect for macitentan, 3 mg vs placebo: hazard ratio (HR), 0.77 (95% CI, 0.38-1.57); log-rank P = .47; for macitentan, 10 mg vs placebo: HR, 1.12 (95% CI, 0.58-2.15); log-rank P = .74. The median duration (Q1, Q3) of treatment exposure was 41.4 weeks (22.1, 59.9) in the macitentan, 3-mg group, 37.4 weeks (18.3, 63.5) in the macitentan, 10-mg group, and 43.1 weeks (22.9, 65.1) in the placebo group.

B, Treatment effect of macitentan, 3 mg vs placebo: HR, 1.19 (95% CI, 0.61-2.33); log-rank P = .62; for macitentan, 10 mg vs placebo: HR, 1.08 (95% CI, 0.4-2.15); log-rank P = .84. The median duration (Q1, Q3) of treatment exposure was 40.5 weeks (17.7, 61.7) in the macitentan, 3-mg group, 38.6 weeks (15.0, 62.1) in the macitentan, 10-mg group, and 37.4 weeks (17.0, 58.1) in the placebo group.

and 13.4% in the placebo group, and in DUAL-2, 11.4% in the 3 mg of macitentan group, 24.1% for 10 mg of macitentan, and 14.6% in the placebo group, with infections being the most common. There was 1 death due to cardiac arrest in DUAL-1 in a patient receiving 10 mg of macitentan. There were 2 deaths (1 due to unspecified natural causes and 1 due to cardiac failure) in DUAL-2. Both patients were in the 10 mg of macitentan group. All deaths were considered unrelated to study treatment. There were no differences in alanine aminotransferase, aspartate aminotransferase, bilirubin, or hemoglobin between study groups (eTable 7 in Supplement 1).

Discussion

In 2 randomized, placebo-controlled trials of patients with systemic sclerosis and active ischemic digital ulcers at baseline, macitentan did not reduce the cumulative number of new digital ulcers over 16 weeks compared with placebo. Re-

gardless of treatment, patients had few new digital ulcers, and their overall digital ulcer condition remained stable over 16 weeks. Macitentan was well tolerated, with a safety profile similar to that observed in patients with pulmonary arterial hypertension[22] and idiopathic pulmonary fibrosis.[23]

Few therapies are available for digital ulcers in patients with systemic sclerosis. The EUSTAR 2009 treatment recommendations in systemic sclerosis for managing digital ulcers endorse using intravenous iloprost and bosentan,[24] and evidence supporting the use of PDE-5 inhibitors is recently available.[25] Bosentan is the only treatment indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease, following 2 randomized clinical trials, RAPIDS-1 and RAPIDS-2.[11,12] Because bosentan is not approved in all of the countries where the DUAL studies were conducted, DUAL-1 and DUAL-2 did not compare macitentan to bosentan. Instead, the trials were placebo-controlled with safeguards in place in case of progression of digital ulcer severity. The choice of bosentan as an active

comparator would have limited the scope of the studies. Current European guidelines state that bosentan should be considered in diffuse systemic sclerosis with multiple digital ulcers after failure of calcium antagonists and prostanoids.[24] DUAL-1 and DUAL-2 were designed to fulfill the regulatory requirements for demonstrating the effectiveness of macitentan vs placebo.

Based on results of the RAPIDS trials, the inclusion criteria of DUAL-1 and DUAL-2 were designed to enroll patients with high likelihood of developing new digital ulcers. The number of active digital ulcers at baseline ranged from 1 to 18 in the 2 studies. Although most participants (69.6%) had 3 or fewer digital ulcers at baseline, the average number of digital ulcers was 3.5, thus the study population consisted of systemic sclerosis patients with active digital ulcers.

The average number of new digital ulcers over 16 weeks was low, ranging from 0.85 to 1.46 ulcers across the treatment groups in both studies. Approximately 60% of patients did not develop new digital ulcers. Even among patients with more than 3 active digital ulcers at baseline, the average number of new digital ulcers over 16 weeks ranged from 1.16 to 2.66 in the 3 treatment groups. In RAPIDS-1,[11] patients treated with placebo with 1 to 3 active digital ulcers at baseline developed, a mean (SD) of 2.2 (2.0) new digital ulcers over 16 weeks, and those with more than 3 active digital ulcers at baseline developed 5.1 (3.9) new ulcers. Overall, 42% of the patients in RAPIDS-1 had more than 3 new digital ulcers over 16 weeks.[11] Results were similar in RAPIDS-2.[12] DUAL-1 and DUAL-2 were designed with the expectation that patients receiving placebo would develop more digital ulcers.

Patients enrolled in DUAL-1 and DUAL-2 had similar demographics and disease characteristics as patients enrolled in prior systemic sclerosis digital ulcer trials. The low number of new digital ulcers observed suggests that the epidemiology of digital ulcers in systemic sclerosis may be changing and reflect earlier diagnosis, better care, and greater availability of treatments. A similarly low incidence of new digital ulcers in patients with systemic sclerosis was also observed in a recent study.[26] Standard management of digital ulcers has improved in recent years with the widespread use of bosentan, PDE-5 inhibitors, and prostacyclin and its analogs.[27,28] It is possible that patients with more severe active ulcers were treated with these medications and not recruited into the DUAL trials or that the studies enrolled a population with refractory digital ulcers that did not respond well to standard treatments. Enrolled patients may have exhausted other treatment options.

The overexpression of ET-1 and ET receptors in skin, the epidermis, and blood vessels in systemic sclerosis is well documented.[10,29-31] However, the specific role of ET-1 in the pathogenesis of digital vasculopathy and the development of digital ulcers in systemic sclerosis is incompletely understood. Although bosentan and macitentan both block the ET_A and ET_B receptors, a reduction in the formation of new digital ulcers has only been observed with bosentan.[11,12] Macitentan is a more potent ERA than bosentan on ET receptors in vitro and on biomarkers (eg, plasma ET-1) and other measures (eg, blood pressure and cardiac remodeling) in in vivo models of pulmonary hypertension.[32] It is unclear why this relative higher potency of macitentan did not result in an effect on digital ulcers. Further research is necessary to delineate mechanisms of vascular involvement in systemic sclerosis as it relates to digital ulcers. The etiology of digital ulceration in systemic sclerosis is multifactorial, involving ischemic, inflammatory, and mechanical mechanisms, all of which influence clinical outcomes of digital ulcers, including repetitive microtrauma, thinning, dry skin, and underlying calcinosis.

Limitations of the DUAL-1 and DUAL-2 studies include the lack of a clear classification system of digital ulcers that considers digital ulcer morphology and the different ulcer features, including presence of underlying calcinosis, size, bedding, perilesional skin, and borders, which potentially affect digital ulcer assessment and counts.[6,7] The DUAL studies involved 73 centers in 20 countries. Although efforts were made to standardize the definition and the reporting of new active digital ulcers, some variability across the study sites in measuring new digital ulcers was likely, and the absence of interrater reliability data to quantify this is a limitation. In addition, 23.5% of participants in DUAL-1 and 24.9% of those in DUAL-2 were missing primary outcome data at 16-week follow-up. However, the primary end point considers the cumulative number of new digital ulcers up to week 16, and the consistency of sensitivity analyses suggests that missing data did not significantly affect statistical inference. Differences in physician attitudes and standard practices,[17] and the lower than expected number of new digital ulcers after 16 weeks may have ultimately influenced the ability to demonstrate any treatment effect in the DUAL trials.

Conclusions

Among patients with systemic sclerosis and active ischemic digital ulcers, treatment with macitentan did not reduce the number of new digital ulcers over 16 weeks. These results do not support the use of macitentan for the treatment of digital ulcers in this patient population.

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