Clinical trial results:
Prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group study to assess the efficacy, safety, and tolerability of macitentan in patients with ischemic
digital ulcers associated with systemic sclerosis (DUAL-2)

Summary

EudraCT number	2010-022969-95
Trial protocol	GB DE IE ES BE NL PT PL GR
Global end of trial date	02 February 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	AC-055C302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01474122
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd.
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Trials Disclosure Desk, Actelion Pharmaceuticals Ltd., clinical-trials-disclosure@actelion.com
Scientific contact	Clinical Trials Disclosure Desk, Actelion Pharmaceuticals Ltd., clinical-trials-disclosure@actelion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2014
Global end of trial reached?	Yes
Global end of trial date	02 February 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the effect of macitentan on the reduction of the number of new digital ulcers (DUs) in patients with systemic sclerosis (SSc) and ongoing DU disease

Protection of trial subjects:

Prior to the start of the trial, each study center consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation.
The investigator ensured that this study was conducted in full conformance with the principles of the 'Declaration of Helsinki' (and its amendments) and with the laws and regulations of the country in which the clinical research was conducted. The study was to be conducted according to International Committee on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and, if applicable, the US Code of Federal Regulations (CFR) and other GCP guidelines.
Documentary evidence of adequate GCP training of the investigator was collected prior to site initiation.
Both Actelion and the investigator had the right to terminate the study at any time and, in such a case, were responsible for protecting the patients' interests.

Background therapy:

Allowed concomitant therapy:
• Patients' usual treatments for DUs. Treatments with vasodilators (including calcium channel blockers, ACE inhibitors, nitroglycerin, alpha-adrenergic blockers, angiotensin II receptor antagonists), N-acetylcysteine, antiplatelet aggregation therapy, and low molecular weight heparin were to be administered at a stable dose for at least 2 weeks prior to screening and during Period 1. During Period 2, dose adjustments of these treatments were discouraged but may have been justified for the treatment of Raynauds phenomenon.
• Analgesics given for DU pain or for any other reason. Receipt of analgesics and any dose adjustments during the study was to be recorded in a patient diary.
• Topical treatments for DUs such as antiseptics, antibiotics, nitrate ointment, protective ointments, etc. (except for growth factors, hyperbaric oxygen). Topical treatments were to be recorded in the concomitant medication section of the eCRF.
• Statins (e.g., atorvastatin, simvastatin) that had been administered at a stable dose for at least 3 months prior to screening and were to remain unchanged during the study.
• Disease-modifying treatments (e.g., methotrexate, cyclophosphamide) that had been administered for at least 3 months and at a stable dose for at least 1 month prior to screening and was to remain unchanged during the study.
• Systemic antibiotics (oral or intravenous). Systemic antibiotics for the treatment of DUs within the 4 weeks prior to screening was an exclusion criterion to exclude patients who had recalcitrant, chronic, hard-to-heal ulcers that were not amenable to healing. However, during the study, systemic antibiotics were allowed. Initiation of systemic antibiotics for the treatment of infection attributed to DUs was reported as a DU complication.

Evidence for comparator: -

Actual start date of recruitment	09 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Colombia: 14
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Mexico: 21
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Ukraine: 20
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	265
EEA total number of subjects	75

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	234
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Conducted at 73 centers in 20 countries.The first patient randomized was 9 Feb 2012 and last patient, last visit was 6 Feb 2014

Pre-assignment

Screening details:

A screening visit was performed between Day −14 and Day −1 of the study. Of the 324 patients screened for the study, 59 were screen failures.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

To ensure double-blind conditions, each dose strength of the investigational drug and its matching placebo were indistinguishable with respect to appearance, taste, weight, and shape, and all medication bottles were identically packaged and labeled.

Arms

Are arms mutually exclusive?	Yes
Arm title	Macitentan 3 mg

Arm description:

Macitentan tablet 3 mg once daily

Arm type	Experimental
Investigational medicinal product name	Macitentan 3 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan tablet 3 mg once daily

Arm title	Placebo

Arm description:

Matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo once daily

Arm title	Macitentan 10 mg

Arm description:

Macitentan tablet 10 mg once daily

Arm type	Experimental

Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan tablet 10 mg once daily

Number of subjects in period 1	Macitentan 3 mg	Placebo	Macitentan 10 mg
Started	88	89	88
Completed	88	89	88

Period 2

Period 2 title	Period 1: Baseline to Week 16
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

To ensure double-blind conditions, each dose strength of the investigational drug and its matching placebo were indistinguishable with respect to appearance, taste, weight, and shape, and all medication bottles were identically packaged and labeled.
IMPORTANT NOTE for "Period Milestone Achievement": Overall Period 1&2: Administrative: 1-0-2; AE nonfatal: 8-15-13; Lost to follow-up:1-0-1; Non-conformity: 0-0-1; Pat. dec.: 10-1-4; Phys. dec.: 0-3-2; Consent withdr.: 3-1-3

Arms

Are arms mutually exclusive?	Yes
Arm title	Macitentan 3 mg

Arm description:

Macitentan tablet 3 mg once daily

Arm type	Experimental
Investigational medicinal product name	Macitentan 3 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan tablet 3 mg once daily

Arm title	Placebo

Arm description:

Placebo once daily

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo once daily

Arm title	Macitentan 10 mg

Arm description:

Macitentan tablet 10 mg once daily

Arm type	Experimental
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan tablet 10 mg once daily

Number of subjects in period 2	Macitentan 3 mg	Placebo	Macitentan 10 mg
Started	88	89	88
Completed	87	88	86
Not completed	1	1	2
see "Blinding details"	1	1	2

Period 3

Period 3 title	Period 2: Week 16 to End of Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

To ensure double-blind conditions, each dose strength of the investigational drug and its matching placebo were indistinguishable with respect to appearance, taste, weight, and shape, and all medication bottles were identically packaged and labeled.
IMPORTANT NOTE for "Period Milestone Achievement": Overall Period 1&2: Administrative: 1-0-2; AE nonfatal: 8-15-13; Lost to follow-up:1-0-1; Non-conformity: 0-0-1; Pat. dec.: 10-1-4; Phys. dec.: 0-3-2; Consent withdr.: 3-1-3

Arms

Are arms mutually exclusive?	Yes

Arm title	Macitentan 3 mg
Arm description: Macitentan 3 mg tablet once daily	
Arm type	Experimental
Investigational medicinal product name	Macitentan 3 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Macitentan tablet 3 mg once daily	
Arm title	Macitentan 10 mg
Arm description: Macitentan 10 mg tablet once daily	
Arm type	Experimental
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Macitentan tablet 10 mg once daily	
Arm title	Placebo
Arm description: Placebo once daily	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Matching placebo once daily	

Number of subjects in period 3	Macitentan 3 mg	Macitentan 10 mg	Placebo
Started	87	86	88
Completed	70	73	73
Not completed	17	13	15
see "Blinding details"	17	13	15

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 3 mg
Reporting group description: Macitentan tablet 3 mg once daily	
Reporting group title	Macitentan 10 mg
Reporting group description: Macitentan tablet 10 mg once daily	
Reporting group title	Placebo
Reporting group description: Matching placebo	

Reporting group values	Macitentan 3 mg	Macitentan 10 mg	Placebo
Number of subjects	88	88	89
Age categorical			
Age categorical description			
Units: participants			
Between 18 and 65 years	76	83	75
>=65 years	12	5	14
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	50.6	47.4	50.6
standard deviation	± 13.2	± 13.02	± 12.88
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	75	71	71
Male	13	17	18
Race/Ethnicity, Customized Units: Subjects			
White	62	63	68
Black or African American	2	0	0
Asian	6	4	6
Hispanic	12	14	9
Other	6	7	6
Region of Enrollment Units: Subjects			
Argentina	12	3	3
Belgium	0	1	0
China	3	3	5
Colombia	3	5	6
Germany	2	3	2
Greece	2	4	5
Ireland	1	2	1
Israel	5	7	12

Mexico	6	9	6
Netherlands	3	2	1
New Zealand	2	1	3
Poland	7	11	5
Portugal	1	2	4
Puerto Rico	1	1	0
Russian Federation	5	4	7
South Africa	3	4	2
Turkey	0	0	1
Ukraine	9	7	4
United Kingdom	7	3	6
United States	16	16	16

Reporting group values	Total		
Number of subjects	265		
Age categorical			
Age categorical description			
Units: participants			
Between 18 and 65 years	234		
>=65 years	31		
Age continuous			
Age continuous description			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	217		
Male	48		
Race/Ethnicity, Customized			
Units: Subjects			
White	193		
Black or African American	2		
Asian	16		
Hispanic	35		
Other	19		
Region of Enrollment			
Units: Subjects			
Argentina	18		
Belgium	1		
China	11		
Colombia	14		
Germany	7		
Greece	11		
Ireland	4		
Israel	24		
Mexico	21		
Netherlands	6		
New Zealand	6		

Poland	23		
Portugal	7		
Puerto Rico	2		
Russian Federation	16		
South Africa	9		
Turkey	1		
Ukraine	20		
United Kingdom	16		
United States	48		

Subject analysis sets

Subject analysis set title	Per-protocol (PP) set
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set comprised all patients in the mITT set until the occurrence of a major protocol deviation that might affect the evaluation of the effect of study treatment on the primary endpoint. The protocol deviations affecting this set were identified before database lock.
Patients were excluded from the PP set if they did not meet any of the following entry criteria:
• Diagnosis of limited or diffuse SSc according to the ACR classification or met the criteria for CREST syndrome
• Active DU according to protocol-defined qualifications
• History of at least 1 additional active ischemic DU up to 6 months, or at least 2 up to 12 months prior to screening
• No DUs due to conditions other than SSc
• No comorbidities, other than SSc, that could seriously affect the assessment of hand function
• Received study treatment different from that randomized
Measurements after the occurrence of certain pre-defined deviations in study conduct were excluded from the PP set.

Subject analysis set title	Modified intent-to-treat (mITT) set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This analysis set included all patients in the Full analysis set who received at least one dose of study treatment and had at least one post-baseline primary efficacy assessment (i.e., an on-treatment post-baseline DU assessment during Period 1). Assignment to treatment arms was as randomized, regardless of the actual treatment received.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

This analysis set included all patients who received at least one dose of study treatment. Assignment to treatment arms was as treated, regardless of the randomization allocation, according to the following algorithm:
• Patients who were dispensed macitentan 10 mg at least once were assigned to the macitentan 10 mg arm.
• Patients who were dispensed macitentan 3 mg at least once, but not macitentan 10 mg, were assigned to the macitentan 3 mg arm.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

This analysis set included all randomized patients as identified in the IVRS dataset. Assignment to treatment arms was as randomized, regardless of the treatment received. This analysis set was added in the SAP to use for the analysis of the primary endpoint, in line with the intention-to-treat principle as per ICH E9.

Reporting group values	Per-protocol (PP) set	Modified intent-to-treat (mITT) set	Safety set
Number of subjects	255	255	264

Age categorical			
Age categorical description			
Units: participants			
Between 18 and 65 years			
>=65 years			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Gender categorical description			
Units: Subjects			
Female			
Male			
Race/Ethnicity, Customized			
Units: Subjects			
White			
Black or African American			
Asian			
Hispanic			
Other			
Region of Enrollment			
Units: Subjects			
Argentina			
Belgium			
China			
Colombia			
Germany			
Greece			
Ireland			
Israel			
Mexico			
Netherlands			
New Zealand			
Poland			
Portugal			
Puerto Rico			
Russian Federation			
South Africa			
Turkey			
Ukraine			
United Kingdom			
United States			

Reporting group values	Full analysis set		
Number of subjects	265		
Age categorical			
Age categorical description			
Units: participants			

Between 18 and 65 years	234		
>=65 years	31		

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	49.6		
standard deviation	± 13.06		
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	217		
Male	48		
Race/Ethnicity, Customized			
Units: Subjects			
White	193		
Black or African American	2		
Asian	16		
Hispanic	35		
Other	19		
Region of Enrollment			
Units: Subjects			
Argentina	18		
Belgium	1		
China	11		
Colombia	14		
Germany	7		
Greece	11		
Ireland	4		
Israel	24		
Mexico	21		
Netherlands	6		
New Zealand	6		
Poland	23		
Portugal	7		
Puerto Rico	2		
Russian Federation	16		
South Africa	9		
Turkey	1		
Ukraine	20		
United Kingdom	16		
United States	48		

End points

End points reporting groups

Reporting group title	Macitentan 3 mg
Reporting group description: Macitentan tablet 3 mg once daily	
Reporting group title	Placebo
Reporting group description: Matching placebo	
Reporting group title	Macitentan 10 mg
Reporting group description: Macitentan tablet 10 mg once daily	
Reporting group title	Macitentan 3 mg
Reporting group description: Macitentan tablet 3 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	
Reporting group title	Macitentan 10 mg
Reporting group description: Macitentan tablet 10 mg once daily	
Reporting group title	Macitentan 3 mg
Reporting group description: Macitentan 3 mg tablet once daily	
Reporting group title	Macitentan 10 mg
Reporting group description: Macitentan 10 mg tablet once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	
Subject analysis set title	Per-protocol (PP) set
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set comprised all patients in the mITT set until the occurrence of a major protocol deviation that might affect the evaluation of the effect of study treatment on the primary endpoint. The protocol deviations affecting this set were identified before database lock.
Patients were excluded from the PP set if they did not meet any of the following entry criteria:
• Diagnosis of limited or diffuse SSc according to the ACR classification or met the criteria for CREST syndrome
• Active DU according to protocol-defined qualifications
• History of at least 1 additional active ischemic DU up to 6 months, or at least 2 up to 12 months prior to screening
• No DUs due to conditions other than SSc
• No comorbidities, other than SSc, that could seriously affect the assessment of hand function
• Received study treatment different from that randomized
Measurements after the occurrence of certain pre-defined deviations in study conduct were excluded from the PP set.

Subject analysis set title	Modified intent-to-treat (mITT) set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This analysis set included all patients in the Full analysis set who received at least one dose of study treatment and had at least one post-baseline primary efficacy assessment (i.e., an on-treatment post-baseline DU assessment during Period 1). Assignment to treatment arms was as randomized, regardless of the actual treatment received.

Subject analysis set title	Safety set

Subject analysis set type	Safety analysis

Subject analysis set description:

This analysis set included all patients who received at least one dose of study treatment. Assignment to treatment arms was as treated, regardless of the randomization allocation, according to the following algorithm:
• Patients who were dispensed macitentan 10 mg at least once were assigned to the macitentan 10 mg arm.
• Patients who were dispensed macitentan 3 mg at least once, but not macitentan 10 mg, were assigned to the macitentan 3 mg arm.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

This analysis set included all randomized patients as identified in the IVRS dataset. Assignment to treatment arms was as randomized, regardless of the treatment received. This analysis set was added in the SAP to use for the analysis of the primary endpoint, in line with the intention-to-treat principle as per ICH E9.

Primary: Cumulative number of New Digital Ulcers (DUs) up to Week 16 (NB-2 model adjusted)

End point title	Cumulative number of New Digital Ulcers (DUs) up to Week 16 (NB-2 model adjusted)

End point description:

DUs were assessed at each visit starting with the screening visit. Only DUs from the proximal interphalangeal joint (PIP) distally (both on the dorsal and volar surface of the hand, including the digital tip) were recorded. The location of each DU was noted. At each subsequent visit the location of each new DU was noted. DUs that occurred and healed between visits and were reported by patients were not recorded as new DUs. The evaluation was performed by an experienced physician or a trained rater with expertise in the assessment of DUs in systemic sclerosis (SSc). For a given patient, DUs were assessed by the same rater at each visit, whenever possible. Any DU that developed over a previously healed ulcer was recorded as a new DU. Incidence rate is adjusted for 16 weeks of observation, hence is calculated as the number of new DUs/total number of observation days. Note that NB-2 model estimates are presented.

End point type	Primary

End point timeframe:

Baseline to Week 16

End point values	Macitentan 3 mg	Macitentan 10 mg	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	88	88	89	0[1]
Units: number of newDUs/observation days				
number (not applicable)	1.44	1.457	1.206	

Notes:

[1] - Not applicable

Statistical analyses

Statistical analysis title	Statistical analysis 1 (Full analysis set)
Comparison groups	Macitentan 3 mg v Placebo

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.434
Method	negative binomial-2 regression (NB-2)
Parameter estimate	NB-2 estimate of new DUs per patient
Point estimate	1.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.766
upper limit	1.861

Statistical analysis title	Statistical analysis 2 (Full analysis set)
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.407
Method	NB-2
Parameter estimate	NB-2 estimate of new DUs per patient
Point estimate	1.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.773
upper limit	1.886

Secondary: Percentage of Participants Without a New DU Up To Week 16

End point title	Percentage of Participants Without a New DU Up To Week 16[2]

End point description:

DUs were assessed at each visit starting with the screening visit. Only DUs from the proximal interphalangeal joint (PIP) distally (both on the dorsal and volar surface of the hand, including the digital tip) were recorded. The location of each DU was noted. At each subsequent visit the location of each new DU was noted. DUs that occurred and healed between visits and were reported by patients were not recorded as new DUs. The evaluation was performed by an experienced physician or a trained rater with expertise in the assessment of DUs in systemic sclerosis (SSc). For a given patient, DUs were assessed by the same rater at each visit, whenever possible. Any DU that developed over a previously healed ulcer was recorded as a new DU. Numbers of patients with no new DU at Week 16 are imputed using the last observation carried forward method.

End point type	Secondary

End point timeframe:

Baseline to Week 16

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis to be reported for this endpoint.

End point values	Placebo	Macitentan 3 mg	Macitentan 10 mg	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	87	84	84	0[3]
Units: percentage of participants				
number (not applicable)	59.8	56	54.8	

Notes:

[3] - Not applicable

Statistical analyses

Statistical analysis title	Statistical analysis 2 (full analysis set)
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4624
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.789
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.484

Statistical analysis title	Statistical analysis 1 (full analysis set)
Comparison groups	Macitentan 3 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5668
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.831
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.442
upper limit	1.564

Secondary: Percentage of Participants With at Least One DU Complication

End point title	Percentage of Participants With at Least One DU Complication

End point description:

DU complications were defined as any one of the following, resulting from DU worsening: critical ischemic crisis necessitating hospitalization; gangrene, (auto)amputation; failure of conservative management; surgical and chemical sympathectomy, vascular reconstructions, or any unplanned

surgery in the management of hand SSc manifestations; use of parenteral prostanoids; use of endothelin-receptor antagonists; class II, III, or IV narcotics or a > 50% increase in the existing dose compared with baseline; initiation of systemic antibiotics for the treatment of infection attributed to DUs.

End point type	Secondary
End point timeframe:	
Up to 95 weeks	

End point values	Macitentan 3 mg	Macitentan 10 mg	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	84	87	0[4]
Units: percentage of participants				
number (not applicable)	21.4	19	18.4	

Notes:

[4] - Not applicable

Statistical analyses

Statistical analysis title	Statistical analysis 1 (full analysis set)
Comparison groups	Macitentan 3 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6117
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.216
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.572
upper limit	2.582

Statistical analysis title	Statistical analysis 2 (full analysis set)
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9047
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.048

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.485
upper limit	2.264

Secondary: Change in Hand Functionality Health Assessment Questionnaire – Disability Index (HAQ-DI) Hand Component From Baseline to Week 16

End point title	Change in Hand Functionality Health Assessment Questionnaire – Disability Index (HAQ-DI) Hand Component From Baseline to Week 16

End point description:

HAQ-DI assesses functional ability regarding fine movements of the upper extremities, locomotor activities in the lower extremities, and movements of the upper and lower limbs. Responses were extracted from the Scleroderma Health Assessment Questionnaire covering 8 domains of functional disability (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities). A mean score ranging from 0-3 was calculated for each domain, and a composite score by dividing the summed domain scores by the number of domains. The composite score was interpreted as 0 (no impairment in function) to 3 (maximal impairment of function). Hand functionality was assessed using a composite of 4 domains (dressing and grooming, grip, hygiene, and eating).
Note that the last observed carried forward (LOCF) approach was applied to Week 16 data.

End point type	Secondary

End point timeframe:

Baseline to Week 16 (LOCF)

End point values	Macitentan 3 mg	Macitentan 10 mg	Placebo	Modified intent-to-treat (mITT) set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	84	87	0[5]
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	1.4 (± 0.73)	1.3 (± 0.7)	1.4 (± 0.72)	()
Week 16 (LOCF)	1.2 (± 0.75)	1.1 (± 0.76)	1.3 (± 0.77)	()

Notes:

[5] - Not applicable

Statistical analyses

Statistical analysis title	Statistical analysis 1 (mITT-analysis)

Statistical analysis description:

ANCOVA on mITT analysis set

Comparison groups	Macitentan 3 mg v Placebo

Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.347
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Statistical analysis title	Statistical analysis 2 (mITT-analysis)
Statistical analysis description:	
ANCOVA on mITT analysis set	
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.165
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0

Secondary: Health Assessment Questionnaire – Disability Index (HAQ-DI) Overall Score From Baseline to Week 16

End point title	Health Assessment Questionnaire – Disability Index (HAQ-DI) Overall Score From Baseline to Week 16

End point description:

HAQ-DI assesses functional ability regarding fine movements of the upper extremities, locomotor activities in the lower extremities, and movements of the upper and lower limbs. Responses were extracted from the Scleroderma Health Assessment Questionnaire covering 8 domains of functional disability (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities). A mean score ranging from 0-3 was calculated for each domain, and a composite score by dividing the summed domain scores by the number of domains. The composite score was interpreted as 0 (no impairment in function) to 3 (maximal impairment of function).
Note that the last observed carried forward (LOCF) approach was applied to Week 16 data.

End point type	Secondary

End point timeframe:

Baseline to Week 16 (LOCF)

End point values	Macitentan 3 mg	Macitentan 10 mg	Placebo	Modified intent-to-treat (mITT) set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	84	87	0[6]
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	1.2 (± 0.67)	1.1 (± 0.65)	1.2 (± 0.66)	()
Week 16 (LOCF)	1.1 (± 0.7)	1 (± 0.71)	1.2 (± 0.68)	()

Notes:

[6] - Not applicable

Statistical analyses

Statistical analysis title	Statistical analysis 2 (mITT-analysis)
Statistical analysis description: ANCOVA on mITT analysis set	
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.312
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Statistical analysis title	Statistical analysis 1 (mITT-analysis)
Statistical analysis description: ANCOVA on mITT analysis set	
Comparison groups	Macitentan 3 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.339
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Secondary: Change in Hand Functionality - Hand Disability in Systemic Sclerosis – Digital Ulcers (HDISS-DU) Score From Baseline to Week 16

End point title	Change in Hand Functionality - Hand Disability in Systemic Sclerosis – Digital Ulcers (HDISS-DU) Score From Baseline to Week 16

End point description:

Patients were asked to answer 24 questions on the use of the hand(s) affected by DUs over the past 7 days on a 6-point scale from 0 (yes without difficulty) to 5 (impossible). The HDISS-DU score is the arithmetic mean of the valid non-missing items. The scores are interpreted as 1 (better ability in completing activities) to 6 (worst ability in completing activities).
Note that the last observed carried forward (LOCF) approach was applied to Week 16 data.

End point type	Secondary

End point timeframe:

Baseline to Week 16 (LOCF)

End point values	Macitentan 3 mg	Macitentan 10 mg	Placebo	Modified intent-to-treat (mITT) set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	84	87	0[7]
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	3 (± 1.08)	2.9 (± 1.05)	2.9 (± 1.14)	()
Week 16 (LOCF)	2.8 (± 1.17)	2.7 (± 1.11)	2.9 (± 1.12)	()

Notes:

[7] - Not applicable

Statistical analyses

Statistical analysis title	Statistical analysis 2 (mITT-analysis)

Statistical analysis description:

ANCOVA on mITT analysis set

Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.221
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1

Statistical analysis title	Statistical analysis 1
Statistical analysis description: ANCOVA on mITT analysis set	
Comparison groups	Macitentan 3 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.319
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events occurring during treatment period, up to 95 weeks and up to 30 days after treatment discontinuation	
Adverse event reporting additional description:	
Safety set - all treated patients	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Macitentan 3 mg
Reporting group description:	
Macitentan tablet 3 mg once daily	
Reporting group title	Placebo
Reporting group description:	
Matching placebo once daily	
Reporting group title	Macitentan 10 mg
Reporting group description:	
Macitentan tablet 10 mg once daily	

Serious adverse events	Macitentan 3 mg	Placebo	Macitentan 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 88 (11.36%)	13 / 89 (14.61%)	21 / 87 (24.14%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
GASTRIC CANCER			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RAYNAUD'S PHENOMENON			

subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
DEBRIDEMENT			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FINGER AMPUTATION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMMUNOSUPPRESSANT DRUG THERAPY			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERY ANGIOPLASTY			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYMPATHECTOMY			
subjects affected / exposed	1 / 88 (1.14%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG THERAPY			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC ULCER			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PULMONARY FIBROSIS			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY HYPERTENSION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 88 (1.14%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY ALVEOLAR HAEMORRHAGE			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
PELVIC FRACTURE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL CORD INJURY			

subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONCUSSION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
CARDIAC FAILURE			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDITIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARRHYTHMIA			

subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AORTIC VALVE STENOSIS			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA PECTORIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
VESTIBULAR DISORDER			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

SUBILEUS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTERITIS			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL ULCER			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	1 / 88 (1.14%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
ISCHAEMIC HEPATITIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

SKIN NECROSIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
SCLERODERMA RENAL CRISIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROPATHY TOXIC			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROLITHIASIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GLOMERULONEPHRITIS RAPIDLY PROGRESSIVE			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
SYSTEMIC SCLEROSIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOPATHY			

subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
INFECTED SKIN ULCER			
subjects affected / exposed	1 / 88 (1.14%)	2 / 89 (2.25%)	3 / 87 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GANGRENE			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	2 / 88 (2.27%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARONYCHIA			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 88 (0.00%)	1 / 89 (1.12%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Macitentan 3 mg	Placebo	Macitentan 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 88 (82.95%)	70 / 89 (78.65%)	73 / 87 (83.91%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	5 / 88 (5.68%)	2 / 89 (2.25%)	3 / 87 (3.45%)
occurrences (all)	5	2	3
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	5 / 88 (5.68%)	1 / 89 (1.12%)	2 / 87 (2.30%)
occurrences (all)	6	1	2
Nervous system disorders			
HEADACHE			
subjects affected / exposed	17 / 88 (19.32%)	19 / 89 (21.35%)	15 / 87 (17.24%)
occurrences (all)	31	66	30
DIZZINESS			
subjects affected / exposed	5 / 88 (5.68%)	3 / 89 (3.37%)	7 / 87 (8.05%)
occurrences (all)	6	3	8
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	10 / 88 (11.36%)	4 / 89 (4.49%)	14 / 87 (16.09%)
occurrences (all)	12	5	16
FATIGUE			
subjects affected / exposed	2 / 88 (2.27%)	4 / 89 (4.49%)	7 / 87 (8.05%)
occurrences (all)	3	5	7
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	6 / 88 (6.82%)	5 / 89 (5.62%)	10 / 87 (11.49%)
occurrences (all)	6	5	12
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	10 / 88 (11.36%)	6 / 89 (6.74%)	10 / 87 (11.49%)
occurrences (all)	14	9	13
NAUSEA			

subjects affected / exposed	4 / 88 (4.55%)	2 / 89 (2.25%)	5 / 87 (5.75%)
occurrences (all)	4	3	6
DYSPEPSIA			
subjects affected / exposed	1 / 88 (1.14%)	6 / 89 (6.74%)	3 / 87 (3.45%)
occurrences (all)	1	7	3
CONSTIPATION			
subjects affected / exposed	7 / 88 (7.95%)	3 / 89 (3.37%)	2 / 87 (2.30%)
occurrences (all)	9	3	2
Respiratory, thoracic and mediastinal disorders			
OROPHARYNGEAL PAIN			
subjects affected / exposed	3 / 88 (3.41%)	6 / 89 (6.74%)	1 / 87 (1.15%)
occurrences (all)	3	7	1
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	14 / 88 (15.91%)	9 / 89 (10.11%)	8 / 87 (9.20%)
occurrences (all)	21	10	17
DERMATITIS			
subjects affected / exposed	5 / 88 (5.68%)	1 / 89 (1.12%)	2 / 87 (2.30%)
occurrences (all)	5	1	2
Musculoskeletal and connective tissue disorders			
PAIN IN EXTREMITY			
subjects affected / exposed	8 / 88 (9.09%)	13 / 89 (14.61%)	9 / 87 (10.34%)
occurrences (all)	15	15	18
ARTHRALGIA			
subjects affected / exposed	7 / 88 (7.95%)	4 / 89 (4.49%)	3 / 87 (3.45%)
occurrences (all)	8	4	5
MYALGIA			
subjects affected / exposed	5 / 88 (5.68%)	3 / 89 (3.37%)	4 / 87 (4.60%)
occurrences (all)	7	3	4
BACK PAIN			
subjects affected / exposed	8 / 88 (9.09%)	6 / 89 (6.74%)	2 / 87 (2.30%)
occurrences (all)	8	6	2
BURSITIS			
subjects affected / exposed	2 / 88 (2.27%)	5 / 89 (5.62%)	2 / 87 (2.30%)
occurrences (all)	2	6	2
Infections and infestations			

NASOPHARYNGITIS			
subjects affected / exposed	7 / 88 (7.95%)	5 / 89 (5.62%)	10 / 87 (11.49%)
occurrences (all)	11	5	10
INFECTED SKIN ULCER			
subjects affected / exposed	15 / 88 (17.05%)	13 / 89 (14.61%)	9 / 87 (10.34%)
occurrences (all)	33	18	15
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	11 / 88 (12.50%)	6 / 89 (6.74%)	8 / 87 (9.20%)
occurrences (all)	14	10	9
INFLUENZA			
subjects affected / exposed	2 / 88 (2.27%)	3 / 89 (3.37%)	5 / 87 (5.75%)
occurrences (all)	2	3	5
PHARYNGITIS			
subjects affected / exposed	5 / 88 (5.68%)	0 / 89 (0.00%)	0 / 87 (0.00%)
occurrences (all)	5	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Mean number of new DUs over 16 wks was lower than historic observations. Up to 60% of pts did not develop any new DUs. Epidemiology of DUs in SSc may be changing, reflective of earlier diagnosis, better wound care, greater availability of treatments.

Notes: