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-1)

Summary

EudraCT number	2010-022710-77
Trial protocol	DE HU CZ DK BG FI IT PL
Global end of trial date	29 November 2013

Results information

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

Trial information

Trial identification

Sponsor protocol code	AC-055C301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01474109
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	20 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2013
Global end of trial reached?	Yes
Global end of trial date	29 November 2013
Was the trial ended prematurely?	No

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 in patients with systemic sclerosis and ongoing digital ulcer disease.

Protection of trial subjects:

This study was conducted in full conformance with the principles of the 'Declaration of Helsinki', with the ICH Guidelines on Good Clinical Practice (GCP), and with the laws and regulations of the country in which the research was conducted.
Written informed consent was obtained from each individual participating in the study prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study. It was made clear to each subject that he or she was completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

A 3-member Independent Data Monitoring Committee (IDMC) reviewed unblinded efficacy and safety data on a regular basis to ensure patient safety. The IDMC was empowered to recommend modifications to the protocol to enhance patient safety or early termination of the study if major concerns arose regarding patient safety at any time during the course of this or any other study with macitentan.

An independent International Liver Safety Board (ILSB), an external expert committee of 3 hepatologists organized by Actelion Global Drug Safety (GDS), provided assessment and advice regarding hepatic events at the request of the Sponsor.

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 i.v.). 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	11 January 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	United States: 37
Country: Number of subjects enrolled	Ukraine: 22
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Croatia: 10
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Bulgaria: 46
Country: Number of subjects enrolled	Belarus: 11
Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	Germany: 27
Worldwide total number of subjects	289
EEA total number of subjects	131

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)	245
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Conducted at 70 centers in 17 countries. First patient randomized was 11 January 2012 and last patient, last visit was 29 November 2013.

Pre-assignment

Screening details:

A screening visit was performed between Day −14 and Day −1 of the study. Of the 327 patients screened for the study, 38 were screen failures.

Period 1

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

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 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:

3 mg tablet 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 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:

10 mg tablet once daily

Number of subjects in period 1	Macitentan 3 mg	Placebo	Macitentan 10 mg
Started	95	97	97
Completed	88	95	91
Not completed	7	2	6
See "Overall Study" for details	7	2	6

Period 2

Period 2 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, Carer

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?	No
Arm title	Macitentan 3 mg

Arm description:

macitentan 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:

3 mg tablet once daily

Arm title	Macitentan 10 mg

Arm description:

macitentan 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:

10 mg tablet once daily

Arm title	Placebo

Arm description:

matching 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 2	Macitentan 3 mg	Macitentan 10 mg	Placebo
Started	88	91	95
Completed	70	73	83
Not completed	18	18	12
See "Overall Study" for details	18	18	12

Period 3

Period 3 title	Baseline period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

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 3 mg

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: 3 mg tablet once daily	
Arm title	Macitentan 10 mg
Arm description: Macitentan 10 mg	
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: 10 mg tablet once daily	
Arm title	Placebo
Arm description: 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	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 3 is the baseline. The Section "Subject disposition" does not allow sufficient flexibility to accurately reflect the study design, sequence of periods, and flow of subject numbers.

Number of subjects in period 3	Macitentan 3 mg	Macitentan 10 mg	Placebo
Started	95	97	97
Completed	95	97	97

Period 4

Period 4 title	Patients who completed study treatment
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

Arms

Are arms mutually exclusive?	Yes
Arm title	Macitentan 3 mg

Arm description:

Macitentan 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:

3 mg tablet once daily

Arm title	Macitentan 10 mg

Arm description:

Macitentan 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:

10 mg tablet 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 4[2]	Macitentan 3 mg	Macitentan 10 mg	Placebo
Started	94	97	97
Completed	62	69	74
Not completed	32	28	23
Adverse event, serious fatal	-	1	-
Patient decision	11	6	12

Physician decision	1	1	-
Consent withdrawn by subject	6	3	1
Administrative	-	1	-
Adverse event, non-fatal	12	14	10
Non-compliance	1	-	-
Lost to follow-up	1	2	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The Section "Subject disposition" does not allow sufficient flexibility to accurately reflect the study design, sequence of periods, and flow of subject numbers. The periods defined in this section, however, also serve as reference points for the subsequent presentation of results (Section Endpoints).

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 3 mg
Reporting group description: Macitentan 3 mg	
Reporting group title	Macitentan 10 mg
Reporting group description: Macitentan 10 mg	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Macitentan 3 mg	Macitentan 10 mg	Placebo
Number of subjects	95	97	97
Age categorical			
Age categorical description			
Units: participants			
Between 18 and 65 years	77	84	84
>=65 years	18	13	13
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	51.4	51.6	50.6
standard deviation	± 14.44	± 11.1	± 12.12
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	84	81	83
Male	11	16	14
Race/Ethnicity, Customized Units: Subjects			
White	86	82	88
Black or African American	0	3	1
Asian	5	6	4
Hispanic	3	4	3
Other	1	2	1
Region of Enrollment Units: Subjects			
Australia	10	9	9
Belarus	3	3	5
Bulgaria	13	16	17
Canada	1	3	2
Chile	6	7	4
Colombia	0	2	1
Croatia	3	1	6
Czech Republic	6	3	5

France	0	0	1
Germany	9	7	11
Hungary	4	7	3
India	4	5	4
Italy	3	3	2
Poland	5	3	3
Russian Federation	6	7	8
Ukraine	10	5	7
United States	12	16	9

Reporting group values	Total		
Number of subjects	289		
Age categorical			
Age categorical description			
Units: participants			
Between 18 and 65 years	245		
>=65 years	44		
Age continuous			
Age continuous description			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	248		
Male	41		
Race/Ethnicity, Customized			
Units: Subjects			
White	256		
Black or African American	4		
Asian	15		
Hispanic	10		
Other	4		
Region of Enrollment			
Units: Subjects			
Australia	28		
Belarus	11		
Bulgaria	46		
Canada	6		
Chile	17		
Colombia	3		
Croatia	10		
Czech Republic	14		
France	1		
Germany	27		
Hungary	14		
India	13		
Italy	8		
Poland	11		

Russian Federation	21		
Ukraine	22		
United States	37		

Subject analysis sets

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 main analysis of the primary endpoint, in line with the intention-to-treat principle as per ICH E9.

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 affected 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.

In addition, patients who received a study treatment different from that randomized were excluded from the PP set.
Measurements after the occurrence of any of the following deviations in study

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 (definition modified with Amendment 2. 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.

Reporting group values	Full analysis set	Per-protocol (PP) set	Modified intent-to-treat (mITT) set
Number of subjects	289	278	278
Age categorical			
Age categorical description			
Units: participants			
Between 18 and 65 years	245		
>=65 years	44		

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	51.2		
standard deviation	± 12.58	±	±
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	248		
Male	41		
Race/Ethnicity, Customized Units: Subjects			
White	256		
Black or African American	4		
Asian	15		
Hispanic	10		
Other	4		
Region of Enrollment Units: Subjects			
Australia	28		
Belarus	11		
Bulgaria	46		
Canada	6		
Chile	17		
Colombia	3		
Croatia	10		
Czech Republic	14		
France	1		
Germany	27		
Hungary	14		
India	13		
Italy	8		
Poland	11		
Russian Federation	21		
Ukraine	22		
United States	37		

Reporting group values	Safety set		
Number of subjects	288		
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			
Australia			
Belarus			
Bulgaria			
Canada			
Chile			
Colombia			
Croatia			
Czech Republic			
France			
Germany			
Hungary			
India			
Italy			
Poland			
Russian Federation			
Ukraine			
United States			

End points

End points reporting groups

Reporting group title	Macitentan 3 mg
Reporting group description: macitentan 3 mg once daily	
Reporting group title	Placebo
Reporting group description: placebo once daily	
Reporting group title	Macitentan 10 mg
Reporting group description: macitentan 10 mg once daily	
Reporting group title	Macitentan 3 mg
Reporting group description: macitentan 3 mg once daily	
Reporting group title	Macitentan 10 mg
Reporting group description: macitentan 10 mg once daily	
Reporting group title	Placebo
Reporting group description: matching placebo once daily	
Reporting group title	Macitentan 3 mg
Reporting group description: Macitentan 3 mg	
Reporting group title	Macitentan 10 mg
Reporting group description: Macitentan 10 mg	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Macitentan 3 mg
Reporting group description: Macitentan 3 mg once daily	
Reporting group title	Macitentan 10 mg
Reporting group description: Macitentan 10 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	
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 main analysis of the primary endpoint, in line with the intention-to-treat principle as per ICH E9.

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 affected 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.

In addition, patients who received a study treatment different from that randomized were excluded from the PP set.
Measurements after the occurrence of any of the following deviations in study

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 (definition modified with Amendment 2. 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.

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 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. 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. Measures are adjusted by the stratification factor (number of DUs at BL <=3 vs >3) by the model.

End point type	Primary

End point timeframe:

Baseline to week 16

End point values	Macitentan 3 mg	Macitentan 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	97	97	
Units: Number of new DUs/observation days				
number (not applicable)	0.94	1.081	0.852	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Macitentan 3 mg
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.706
Method	negative binomial-2 regression (NB-2)
Parameter estimate	NB-2 estimate of new DUs per patient
Point estimate	1.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.663
upper limit	1.834

Notes:

[1] - Negative binomial-2 regression (NB-2) on Full Analysis set

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Macitentan 10 mg
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.36
Method	negative binomial-2 regression (NB-2)
Parameter estimate	NB-2 estimate of new DUs per patient
Point estimate	1.268
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.763
upper limit	2.106

Notes:

[2] - Negative binomial-2 regression (NB-2) on Full Analysis set

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

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

End point values	Macitentan 3 mg	Macitentan 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	92	94	
Units: Percentage of participants				
number (not applicable)	64.1	63	67	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Macitentan 3 mg
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.667
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.875
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	1.606

Notes:

[3] - Chi-squared analysis on mITT analysis set

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Macitentan 10 mg
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.5518
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.832
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.454
upper limit	1.524

Notes:

[4] - Chi-squared analysis on mITT analysis set

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 approximately 90 weeks

End point values	Macitentan 3 mg	Macitentan 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	92	94	
Units: percentage of participants				
number (not applicable)	14.1	19.6	19.1	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Macitentan 3 mg v Placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.3625
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.696
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.319
upper limit	1.518

Notes:

[5] - Chi-squared analysis on mITT analysis set

Statistical analysis title	Statistical analysis 2
Comparison groups	Macitentan 10 mg v Placebo

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.9362
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.498
upper limit	2.133

Notes:

[6] - Chi-squared analysis on mITT analysis set

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 observation carried forward (LOCF) approach was applied for 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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	92	94	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	1.3 (± 0.73)	1.4 (± 0.7)	1.3 (± 0.68)	
Week 16 (LOCF)	1.2 (± 0.79)	1.2 (± 0.66)	1.2 (± 0.73)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Macitentan 3 mg

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.863
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Notes:

[7] - ANCOVA on mITT analysis set

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Macitentan 10 mg
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.649
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[8] - ANCOVA on mITT analysis set

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 observation carried forward (LOCF) approach was applied for 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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	92	94	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	1.1 (± 0.71)	1.2 (± 0.66)	1.1 (± 0.62)	
Week 16 (LOCF)	1.1 (± 0.73)	1.1 (± 0.64)	1.1 (± 0.67)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Macitentan 3 mg
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.456
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

Notes:

[9] - ANCOVA on mITT analysis set

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Macitentan 10 mg
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.44
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

Notes:

[10] - ANCOVA on mITT analysis set

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 observation carried forward (LOCF) approach was applied for 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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	92	94	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	3 (± 1.15)	3 (± 1.09)	3 (± 1.09)	
Week 16 (LOCF)	2.7 (± 1.14)	2.6 (± 0.99)	2.7 (± 1.1)	

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.342
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

Notes:

[11] - ANCOVA on mITT analysis set

Statistical analysis title	Statistical analysis 1
Comparison groups	Macitentan 3 mg v Placebo

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.464
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

Notes:

[12] - ANCOVA on mITT analysis set

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment up to 30 days after treatment discontinuation, up to approximately 90 weeks.	
Adverse event reporting additional description:	
Safety analysis set. One patient was excluded in the safety analysis set as the patient did not receive study drug after randomisation.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

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

Serious adverse events	Macitentan 3 mg	Placebo	Macitentan 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 94 (18.09%)	13 / 97 (13.40%)	14 / 97 (14.43%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
METASTATIC BRONCHIAL CARCINOMA			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
B-CELL LYMPHOMA			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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
Vascular disorders			
GRANULOMATOSIS WITH POLYANGIITIS			

subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
HYPERTENSION			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
HYPOTENSION			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
NECROSIS ISCHAEMIC			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
RAYNAUD'S PHENOMENON			
subjects affected / exposed	1 / 94 (1.06%)	1 / 97 (1.03%)	0 / 97 (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
EXTREMITY NECROSIS			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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
Surgical and medical procedures			
PROSTATIC OPERATION			

subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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			
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
FATIGUE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
PYREXIA			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
Reproductive system and breast disorders			
UTERINE PROLAPSE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDROTHORAX			

subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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 CONGESTION			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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 EMBOLISM			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CARDIAC ARREST			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PLEUROPERICARDITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	2 / 94 (2.13%)	0 / 97 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA PECTORIS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
ANGINA UNSTABLE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
ATRIAL FLUTTER			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL FIBROSIS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
MYOCARDIAL ISCHAEMIA			

subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
PERICARDITIS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
Nervous system disorders			
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
NEURALGIA			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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

Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLELITHIASIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	3 / 94 (3.19%)	3 / 97 (3.09%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKOCYTOCLASTIC VASCULITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRY GANGRENE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
HYPERKERATOSIS			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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			
RENAL FAILURE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
URINARY INCONTINENCE			

subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
NEPHROTIC SYNDROME			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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 DISORDER			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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
SCLERODERMA RENAL CRISIS			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYSTEMIC SCLEROSIS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
OSTEOARTHRITIS			

subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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
OSTEONECROSIS			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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
RHEUMATOID ARTHRITIS			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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
SCLERODERMA			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
INFECTED SKIN ULCER			
subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	3 / 97 (3.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACTERIAL SEPSIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	2 / 94 (2.13%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			

subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	0 / 94 (0.00%)	0 / 97 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GANGRENE			
subjects affected / exposed	3 / 94 (3.19%)	0 / 97 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
CELLULITIS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
ERYSIPELAS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
PNEUMOCOCCAL SEPSIS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
SINUSITIS			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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 CANDIDIASIS			

subjects affected / exposed	0 / 94 (0.00%)	1 / 97 (1.03%)	0 / 97 (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			
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
FAILURE TO THRIVE			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 94 (1.06%)	0 / 97 (0.00%)	0 / 97 (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

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	61 / 94 (64.89%)	69 / 97 (71.13%)	73 / 97 (75.26%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 94 (2.13%)	1 / 97 (1.03%)	6 / 97 (6.19%)
occurrences (all)	2	1	6
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 94 (3.19%)	1 / 97 (1.03%)	5 / 97 (5.15%)
occurrences (all)	5	1	5
Nervous system disorders			
HEADACHE			
subjects affected / exposed	14 / 94 (14.89%)	12 / 97 (12.37%)	19 / 97 (19.59%)
occurrences (all)	19	19	22
DIZZINESS			

subjects affected / exposed	4 / 94 (4.26%)	2 / 97 (2.06%)	5 / 97 (5.15%)
occurrences (all)	4	2	5
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	7 / 94 (7.45%)	6 / 97 (6.19%)	12 / 97 (12.37%)
occurrences (all)	7	7	12
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 94 (4.26%)	7 / 97 (7.22%)	8 / 97 (8.25%)
occurrences (all)	6	9	11
Gastrointestinal disorders			
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 94 (0.00%)	5 / 97 (5.15%)	6 / 97 (6.19%)
occurrences (all)	0	5	7
DIARRHOEA			
subjects affected / exposed	6 / 94 (6.38%)	7 / 97 (7.22%)	5 / 97 (5.15%)
occurrences (all)	8	9	6
NAUSEA			
subjects affected / exposed	5 / 94 (5.32%)	6 / 97 (6.19%)	4 / 97 (4.12%)
occurrences (all)	5	7	4
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	6 / 94 (6.38%)	9 / 97 (9.28%)	8 / 97 (8.25%)
occurrences (all)	8	12	9
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	3 / 94 (3.19%)	3 / 97 (3.09%)	5 / 97 (5.15%)
occurrences (all)	4	3	5
ARTHRALGIA			
subjects affected / exposed	6 / 94 (6.38%)	7 / 97 (7.22%)	4 / 97 (4.12%)
occurrences (all)	8	7	4
PAIN IN EXTREMITY			
subjects affected / exposed	4 / 94 (4.26%)	6 / 97 (6.19%)	4 / 97 (4.12%)
occurrences (all)	4	6	6
Infections and infestations			

INFECTED SKIN ULCER			
subjects affected / exposed	7 / 94 (7.45%)	11 / 97 (11.34%)	12 / 97 (12.37%)
occurrences (all)	11	15	22
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 94 (3.19%)	4 / 97 (4.12%)	7 / 97 (7.22%)
occurrences (all)	4	4	8
BRONCHITIS			
subjects affected / exposed	7 / 94 (7.45%)	5 / 97 (5.15%)	1 / 97 (1.03%)
occurrences (all)	10	8	1

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: