



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 | - |
| Consent withdrawn by subject | 6 | 3 | 1 |

| | | | |
|--------------------------|----|----|----|
| Physician decision | 1 | 1 | - |
| Patient decision | 11 | 6 | 12 |
| 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 |
|-----------------|---|

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 (\pm 1.15) | 3 (\pm 1.09) | 3 (\pm 1.09) | |
| Week 16 (LOCF) | 2.7 (\pm 1.14) | 2.6 (\pm 0.99) | 2.7 (\pm 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 occurrences (all) | 4 / 94 (4.26%) 4 | 2 / 97 (2.06%) 2 | 5 / 97 (5.15%) 5 |
| General disorders and administration site conditions OEDEMA PERIPHERAL subjects affected / exposed occurrences (all) | 7 / 94 (7.45%) 7 | 6 / 97 (6.19%) 7 | 12 / 97 (12.37%) 12 |
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) | 4 / 94 (4.26%) 6 | 7 / 97 (7.22%) 9 | 8 / 97 (8.25%) 11 |
| Gastrointestinal disorders GASTROOESOPHAGEAL REFLUX DISEASE subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) | 0 / 94 (0.00%) 0 6 / 94 (6.38%) 8 5 / 94 (5.32%) 5 | 5 / 97 (5.15%) 5 7 / 97 (7.22%) 9 6 / 97 (6.19%) 7 | 6 / 97 (6.19%) 7 5 / 97 (5.15%) 6 4 / 97 (4.12%) 4 |
| Skin and subcutaneous tissue disorders SKIN ULCER subjects affected / exposed occurrences (all) | 6 / 94 (6.38%) 8 | 9 / 97 (9.28%) 12 | 8 / 97 (8.25%) 9 |
| Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed occurrences (all) ARTHRALGIA subjects affected / exposed occurrences (all) PAIN IN EXTREMITY subjects affected / exposed occurrences (all) | 3 / 94 (3.19%) 4 6 / 94 (6.38%) 8 4 / 94 (4.26%) 4 | 3 / 97 (3.09%) 3 7 / 97 (7.22%) 7 6 / 97 (6.19%) 6 | 5 / 97 (5.15%) 5 4 / 97 (4.12%) 4 4 / 97 (4.12%) 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: