



Clinical trial results:

A randomized, double-blind, placebo-controlled, multicentre proof-of-concept trial of IVA337 in the treatment of diffuse cutaneous systemic sclerosis.

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2015-001617-27 |
| Trial protocol | IT ES GB DE NL SI BG |
| Global end of trial date | 12 October 2018 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 24 April 2021 |
| First version publication date | 24 April 2021 |
| Summary attachment (see zip file) | FASST synopsis CSR (INV_FASST_CSR_Final_20190925 SYNOPSIS.pdf) |

Trial information

Trial identification

| | |
|-----------------------|------------------------|
| Sponsor protocol code | IVA_01_337_HSSC_15_001 |
|-----------------------|------------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02503644 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Inventiva S.A. |
| Sponsor organisation address | 50 rue de Dijon, Daix, France, 21121 |
| Public contact | Regulatory Affairs Manager, Inventiva, +33 380447500, fasst.public@inventivapharma.com |
| Scientific contact | Chief Medical Officer, Inventiva, +33 380447500, fasst.scientists@inventivapharma.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 | 12 June 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 October 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate in patients suffering from diffuse cutaneous SSc (DcSSc) the effect of 800mg and 1200mg IVA337 daily on the skin compared to placebo. The modified Rodnan Skin Score (MRSS) was used to determine the changes in skin.

Protection of trial subjects:

The protocol, the patient information sheet, and the consent form were reviewed and approved by an appropriately constituted Ethics Committee (EC) at each study site and by the Competent Authorities (CA) before the start of the clinical study. All applicable European and local regulations were followed. All changes in the research activity and all unanticipated problems involving risks to humans were reported to the EC/CA as applicable. No substantial changes were made to the protocol without prior Sponsor and EC/CA approval, except where necessary to eliminate apparent immediate hazards to study patients.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 29 October 2015 |
| 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 | Poland: 57 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Slovenia: 4 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Bulgaria: 12 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Germany: 19 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | Switzerland: 4 |
| Worldwide total number of subjects | 145 |
| EEA total number of subjects | 141 |

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) | 136 |
| From 65 to 84 years | 9 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 29-Oct-2015, date of first patient first visit to 12-Oct-2018, and was conducted in 10 countries in Europe.

Pre-assignment

Screening details:

A total of 161 patients were screened, and 145 patients were randomized in the study.

Period 1

| | |
|------------------------------|---------------------------------------|
| Period 1 title | Core Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | LAN1200 |
|------------------|---------|

Arm description:

Patients who receive 1200mg of lanifibranor: 3 capsules of lanifibranor 200mg twice daily

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lanifibranor |
| Investigational medicinal product code | IVA337 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Capsules of 200mg to be taken orally

| | |
|------------------|--------|
| Arm title | LAN800 |
|------------------|--------|

Arm description:

Patients who receive 800 mg of lanifibranor: 2 capsules of lanifibranor 200mg and one capsule of placebo, twice daily

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lanifibranor |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Capsules of 200mg to be taken orally

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Patients who receive placebo: 3 capsules of placebo, twice daily

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|-------------------------------|
| Investigational medicinal product name | Placebo to match lanifibranor |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

3 capsules of placebo to be taken orally, twice a day

| Number of subjects in period 1 | LAN1200 | LAN800 | Placebo |
|---------------------------------------|---------|--------|---------|
| Started | 48 | 49 | 48 |
| Completed | 32 | 34 | 40 |
| Not completed | 16 | 15 | 8 |
| Adverse event, serious fatal | - | 1 | - |
| Consent withdrawn by subject | 1 | 2 | 3 |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | 13 | 11 | 4 |
| other | 1 | 1 | - |
| Protocol deviation | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | LAN1200 |
| Reporting group description: | |
| Patients who receive 1200mg of lanifibranor: 3 capsules of lanifibranor 200mg twice daily | |
| Reporting group title | LAN800 |
| Reporting group description: | |
| Patients who receive 800 mg of lanifibranor: 2 capsules of lanifibranor 200mg and one capsule of placebo, twice daily | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients who receive placebo: 3 capsules of placebo, twice daily | |

| Reporting group values | LAN1200 | LAN800 | Placebo |
|--|---------|--------|---------|
| Number of subjects | 48 | 49 | 48 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 45 | 46 | 45 |
| From 65-84 years | 3 | 3 | 3 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 40 | 45 | 35 |
| Male | 8 | 4 | 13 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 145 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 136 | | |
| From 65-84 years | 9 | | |
| 85 years and over | 0 | | |

| | | | |
|--------------------|-----|--|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 120 | | |
| Male | 25 | | |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | LAN1200 |
| Reporting group description: | |
| Patients who receive 1200mg of lanifibranor: 3 capsules of lanifibranor 200mg twice daily | |
| Reporting group title | LAN800 |
| Reporting group description: | |
| Patients who receive 800 mg of lanifibranor: 2 capsules of lanifibranor 200mg and one capsule of placebo, twice daily | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients who receive placebo: 3 capsules of placebo, twice daily | |

Primary: Absolute change of the MRSS from baseline to 48 weeks

| | |
|--|---|
| End point title | Absolute change of the MRSS from baseline to 48 weeks |
| End point description: | |
| MRSS is a validated measure of the skin thickness, which is a commonly used outcome measure of dcSSc. Measurement of skin thickness is a surrogate measure of disease severity and mortality in patients with dcSSc; increase in skin thickness is associated with involvement of internal organs and increased mortality. MRSS is calculated by adding skin thickness scores rated by clinical physician using a 0-3 scale (from 0 = severe thickness with inability to pinch the skin into a fold) for the following 17 anatomic surface areas of the body: face, anterior chest, abdomen, and right and left separately: fingers, forearms, upper arms, thighs, lower legs, dorsum of hands and feet. | |
| End point type | Primary |
| End point timeframe: | |
| From baseline to Week 48. | |

| End point values | LAN1200 | LAN800 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 48 | |
| Units: number | | | | |
| arithmetic mean (standard error) | -4.39 (± 0.65) | -3.75 (± 0.64) | -5.03 (± 0.65) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment effect : dose response relationship |
| Comparison groups | LAN1200 v LAN800 v Placebo |
| Number of subjects included in analysis | 145 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.3614 |
| Method | Mixed models analysis |

Notes:

[1] - For the primary analysis, the dose-response relationship at Week 48 was assessed in the mITT population using the MMRM (mixed model for repeated measures) and the primary missing data imputation method ('linear interpretation+placebo slope').

Secondary: Overall progression of the disease

| | |
|-----------------|------------------------------------|
| End point title | Overall progression of the disease |
|-----------------|------------------------------------|

End point description:

Overall progression of the disease is defined as presence of escape therapy and/or presence of severe organ involvement (SOI) or presence of an "unable to adjudicate" SOI.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 48

| End point values | LAN1200 | LAN800 | Placebo | |
|----------------------------------|--------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 48 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Yes | 10.4 (3.5 to 22.7) | 6.1 (1.3 to 16.9) | 8.3 (2.3 to 20) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in pulmonary function test: %FVC

| | |
|-----------------|--|
| End point title | Absolute change from baseline in pulmonary function test: %FVC |
|-----------------|--|

End point description:

% predictive Forced Vital Capacity

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 48. Missing data at Week 48 were imputed by taking the primary missing date imputation method (1 linear interpretation + placebo slope).

| End point values | LAN1200 | LAN800 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 48 | |
| Units: number | | | | |
| arithmetic mean (standard error) | -0.68 (± 1.07) | -0.34 (± 1.06) | 0.58 (± 1.07) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Digital Ulcer Count

End point title Digital Ulcer Count

End point description:

Evolution of digital ulcer over the study period for the mITT population.

End point type Secondary

End point timeframe:

From baseline to Week 48

| End point values | LAN1200 | LAN800 | Placebo | |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 31 | 34 | 39 | |
| Units: Decimal number | | | | |
| Missing | 1 | 0 | 1 | |
| Patients with at least one DU | 2 | 1 | 2 | |
| Decrease or no change from baseline | 29 | 33 | 38 | |
| Increase | 2 | 1 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in pulmonary function test: %pcDLCO

End point title Absolute change from baseline in pulmonary function test: %pcDLCO

End point description:

End point type Secondary

End point timeframe:

From baseline to Week 48. Missing data at Week 48 were imputed by taking the primary missing data imputation method (1 linear interpretation + placebo slope).

| End point values | LAN1200 | LAN800 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 48 | |
| Units: unit | | | | |
| arithmetic mean (standard error) | -3.6 (± 1.06) | 0.2 (± 1.06) | -0.47 (± 1.06) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Digital Ulcer burden over time

| | |
|-----------------|--|
| End point title | Change in the Digital Ulcer burden over time |
|-----------------|--|

End point description:

Total number of ulcers at a certain time point minus number of ulcers at baseline and proportion of patients with:

- decrease or no change OR
- increase

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Between baseline and Week 48.

| End point values | LAN1200 | LAN800 | Placebo | |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 31 | 34 | 39 | |
| Units: Decimal number | | | | |
| Decrease or no change from baseline | 29 | 33 | 38 | |
| Increase | 2 | 1 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in the HAQ-DI from SHAQ questionnaire

| | |
|-----------------|---|
| End point title | Absolute change from baseline in the HAQ-DI from SHAQ questionnaire |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 48 (observed cases under treatment).

| End point values | LAN1200 | LAN800 | Placebo | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 34 | 40 | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | -0.08 (± 0.37) | -0.10 (± 0.34) | -0.05 (± 0.34) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in VAS physician Global Assessment of Disease Activity

| | |
|-----------------|--|
| End point title | Absolute change from baseline in VAS physician Global Assessment of Disease Activity |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 48.

| End point values | LAN1200 | LAN800 | Placebo | |
|--------------------------------------|---------------------|---------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 46 | 48 | 47 | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | -12.9 (\pm 16.8) | -15.4 (\pm 16.6) | -7.1 (\pm 20.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in VAS patient Global Assessment of Disease activity

| | |
|-----------------|--|
| End point title | Absolute change from baseline in VAS patient Global Assessment of Disease activity |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 48.

| End point values | LAN1200 | LAN800 | Placebo | |
|--------------------------------------|---------------------|---------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 44 | 47 | 47 | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | -11.8 (\pm 16.9) | -10.2 (\pm 21.1) | -2.7 (\pm 19.3) | |

Statistical analyses

No statistical analyses for this end point

Secondary: MRSS responder rate at 48 weeks - initial definition

End point title MRSS responder rate at 48 weeks - initial definition

End point description:

Initial definition of responder is a reduction ≥ 5 points and $\geq 25\%$ of MRSS compared to baseline.

End point type Secondary

End point timeframe:

baseline to w48

| End point values | LAN1200 | LAN800 | Placebo | |
|---|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 48 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of responders (initial definition) | 35.4 (22.2 to 50.5) | 28.6 (16.6 to 43.3) | 54.2 (39.2 to 68.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: MRSS responder at Week 48- additional definition

End point title MRSS responder at Week 48- additional definition

End point description:

Additional definition of responder is a reduction ≥ 4 points and $\geq 20\%$ MRSS compared to baseline.

End point type Secondary

End point timeframe:

From baseline to Week 48.

| End point values | LAN1200 | LAN800 | Placebo | |
|---|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 48 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of responder (additional definition) | 45.8 (31.4 to 60.8) | 42.9 (28.8 to 57.8) | 60.4 (45.3 to 74.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: MRSS progressor rate at Week 48: initial definition

| | |
|--|---|
| End point title | MRSS progressor rate at Week 48: initial definition |
| End point description: | |
| Initial definition of progressor rate is a reduction ≥ 5 points and $\geq 25\%$ of MRSS compared to baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Week 48. | |

| End point values | LAN1200 | LAN800 | Placebo | |
|----------------------------------|-------------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 48 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Progressors (initial definition) | 4.2 (0.5 to 14.3) | 0 (0.0 to 7.3) | 0 (0.0 to 7.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: MRSS progressor rate at Week 48: additional definition

| | |
|--|--|
| End point title | MRSS progressor rate at Week 48: additional definition |
| End point description: | |
| Additional definition of progressor rate is a reduction ≥ 4 points and $\geq 20\%$ MRSS compared to baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Week 48. | |

| End point values | LAN1200 | LAN800 | Placebo | |
|------------------------------------|-------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 48 | |
| Units: number | | | | |
| number (confidence interval 95%) | | | | |
| Progressor (additional definition) | 4.2 (0.5 to 14.3) | 2.0 (0.1 to 10.9) | 2.1 (0.1 to 11.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in Cochin Hand Function Scale

| | |
|-----------------|---|
| End point title | Absolute change from baseline in Cochin Hand Function Scale |
|-----------------|---|

End point description:

To evaluate the changes in regard to hand function.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 48 (observed cases under treatment).

| End point values | LAN1200 | LAN800 | Placebo | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 31 | 33 | 40 | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -3.97 (± 5.31) | -3.27 (± 9.47) | -2.18 (± 10.48) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On or after the first dose of treatment up to 30 days post-last dose.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | LAN1200 |
|-----------------------|---------|

Reporting group description:

Patients who receive 1200mg of lanifibranor: 3 capsules of lanifibranor twice daily

| | |
|-----------------------|--------|
| Reporting group title | LAN800 |
|-----------------------|--------|

Reporting group description:

Patients who receive lanifibranor: 2 capsules of lanifibranor 200mg and one capsule of placebo, twice daily

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients who receive placebo: 3 capsules of placebo, twice daily.

| Serious adverse events | LAN1200 | LAN800 | Placebo |
|---|-----------------|------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 48 (14.58%) | 10 / 49 (20.41%) | 1 / 48 (2.08%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 0 / 48 (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 | | | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 0 / 48 (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 | | | |
| Myocardial ischaemia | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 0 / 48 (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 |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 0 / 48 (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 |
| Gastrointestinal disorders | | | |
| Oroantral fistula | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 0 / 48 (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 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 0 / 48 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Scleroderma associated digital ulcer | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Systemic scleroderma | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 2 / 49 (4.08%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 0 / 48 (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 |
| Fibromyalgia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 0 / 48 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 0 / 48 (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 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 0 / 48 (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 | LAN1200 | LAN800 | Placebo |
|--|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 41 / 48 (85.42%) | 44 / 49 (89.80%) | 43 / 48 (89.58%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 19 / 48 (39.58%) | 10 / 49 (20.41%) | 1 / 48 (2.08%) |
| occurrences (all) | 21 | 10 | 1 |
| Blood creatine phosphokinase | | | |

| | | | |
|--|------------------------|------------------------|----------------------|
| increased subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 1 / 49 (2.04%) 1 | 1 / 48 (2.08%) 1 |
| N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 2 / 49 (4.08%) 2 | 0 / 48 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 1 / 49 (2.04%) 1 | 3 / 48 (6.25%) 3 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 6 / 48 (12.50%) 6 | 2 / 49 (4.08%) 3 | 6 / 48 (12.50%) 6 |
| Headache subjects affected / exposed occurrences (all) | 4 / 48 (8.33%) 7 | 7 / 49 (14.29%) 9 | 2 / 48 (4.17%) 3 |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 4 / 49 (8.16%) 6 | 2 / 48 (4.17%) 2 |
| General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) | 13 / 48 (27.08%) 18 | 16 / 49 (32.65%) 23 | 0 / 48 (0.00%) 0 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 6 | 6 / 49 (12.24%) 10 | 1 / 48 (2.08%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 4 | 1 / 49 (2.04%) 1 | 0 / 48 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 6 / 48 (12.50%) 6 | 2 / 49 (4.08%) 2 | 3 / 48 (6.25%) 3 |
| Gastrointestinal disorders Diarrhoea | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 8 / 48 (16.67%) | 3 / 49 (6.12%) | 5 / 48 (10.42%) |
| occurrences (all) | 12 | 3 | 8 |
| Nausea | | | |
| subjects affected / exposed | 7 / 48 (14.58%) | 4 / 49 (8.16%) | 4 / 48 (8.33%) |
| occurrences (all) | 8 | 4 | 4 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 5 / 49 (10.20%) | 1 / 48 (2.08%) |
| occurrences (all) | 1 | 6 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | 2 / 49 (4.08%) | 2 / 48 (4.17%) |
| occurrences (all) | 4 | 2 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 3 / 49 (6.12%) | 1 / 48 (2.08%) |
| occurrences (all) | 3 | 4 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 3 / 49 (6.12%) | 3 / 48 (6.25%) |
| occurrences (all) | 1 | 3 | 4 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 4 / 49 (8.16%) | 1 / 48 (2.08%) |
| occurrences (all) | 1 | 4 | 1 |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 0 / 49 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 3 | 0 | 3 |
| Toothache | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 3 / 49 (6.12%) | 1 / 48 (2.08%) |
| occurrences (all) | 0 | 4 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 48 (10.42%) | 4 / 49 (8.16%) | 1 / 48 (2.08%) |
| occurrences (all) | 6 | 5 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 48 (10.42%) | 1 / 49 (2.04%) | 2 / 48 (4.17%) |
| occurrences (all) | 6 | 1 | 2 |
| Oropharyngeal pain | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 5 / 49 (10.20%) 6 | 1 / 48 (2.08%) 1 |
| Rales subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 1 / 49 (2.04%) 1 | 3 / 48 (6.25%) 3 |
| Skin and subcutaneous tissue disorders Scleroderma associated digital ulcer subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 5 / 49 (10.20%) 6 | 3 / 48 (6.25%) 6 |
| Swelling face subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 3 / 49 (6.12%) 4 | 0 / 48 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 1 / 49 (2.04%) 1 | 1 / 48 (2.08%) 1 |
| Dry skin subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 0 / 49 (0.00%) 0 | 0 / 48 (0.00%) 0 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 0 / 49 (0.00%) 0 | 3 / 48 (6.25%) 3 |
| Musculoskeletal and connective tissue disorders Systemic scleroderma subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 7 / 49 (14.29%) 9 | 3 / 48 (6.25%) 3 |
| Arthralgia subjects affected / exposed occurrences (all) | 6 / 48 (12.50%) 7 | 4 / 49 (8.16%) 5 | 4 / 48 (8.33%) 6 |
| Joint swelling subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 2 | 2 / 49 (4.08%) 3 | 3 / 48 (6.25%) 3 |
| Myalgia subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 4 | 3 / 49 (6.12%) 3 | 1 / 48 (2.08%) 3 |
| Infections and infestations | | | |

Additional description: All NSAEs coded as systemic scleroderma were associated with an exacerbation/worsening of SSc condition or increase in MRSS.

| | | | |
|---|----------------------|------------------------|-----------------------|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 48 (16.67%) 9 | 13 / 49 (26.53%) 18 | 4 / 48 (8.33%) 5 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 6 | 5 / 49 (10.20%) 8 | 8 / 48 (16.67%) 12 |
| Influenza subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 2 / 49 (4.08%) 2 | 3 / 48 (6.25%) 3 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 3 / 49 (6.12%) 3 | 3 / 48 (6.25%) 4 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 1 / 49 (2.04%) 1 | 3 / 48 (6.25%) 3 |
| Metabolism and nutrition disorders Hyperhomocysteinaemia subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 1 / 49 (2.04%) 1 | 5 / 48 (10.42%) 6 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 07 July 2015 | <ul style="list-style-type: none">- addition of visits V7 at Week 20, V11 at Week 36 and V13 at Week 44- modification of authorisation of emergency unblinding- addition of detailed description of birth control methods pertaining to exclusion criterion "pregnancy"- addition of development of SOI, deterioration in cardiac status, ALT levels >3xULN, jaundice, marked elevated CK levels (to be confirmed by a second test), myopathy, photo or hypersensitivity, to reasons for withdrawal from the study- addition of information on mycophenolic acid properties in the permitted concomitant treatments (low therapeutic index, large inter-individual pharmacokinetic variability and uncertain dose-concentration relationship)- patients who develop SOI were to be withdrawn from the study, to be treated adequately, and considered as non-responders in the subsequent analysis- changes in Raynaud's condition score assessment- detailed instructions for handling and preparing the blood samples provided with the kit supplied by the Sponsor- PK time points detailed and details on bioanalytical study removed- addition of hypoglycemia and additional urinary test for pregnancy at V0 |
| 10 December 2015 | <ul style="list-style-type: none">- addition of Dr Denton in the list of principal investigators- modification of patients to be included from 105 to 132- update of unblinding procedures- addition of 2 exclusion criteria: diabetic ketoacidosis and co-therapy with biologics- modification of adequate contraceptive measures: sexual abstinence was deleted and a warning regarding resumption of ovulation was added- update of the text on assignment to study groups- addition of iloprost for stable patients with mild vascular manifestations to the list of permitted concomitant treatments- addition of biologics and PPAR agonists to the list of prohibited concomitant treatments- modification of definition of SOI- update of assessment of other outcomes of interest- modification of the list of lab tests to be performed- rewriting of statistical part of the protocol |
| 27 February 2017 | <ul style="list-style-type: none">• A short name to the study was added: For A Systemic Sclerosis Treatment (FASST).• The follow-up after the completion of the study was changed from 12 weeks to 4 weeks and total protocol completion per patient and V15 modified from 60 to 52 weeks.• The planned inclusion period was increased from 12 to 24 months and the end of study was modified to December 2018. Additional countries and centres were added.• The following examinations scheduled for V15 were removed: MRSS, digital ulcer count, joint/tendon assessment, Cochin hand function test, patient reported outcomes (SHAQ, PROMIS-29, GIT, SF36) and patient/physician overall visual analogue scale test. Study drug accountability was added in the flowchart as procedure to perform.• Clinmark was added among the CRO monitoring.• A DSMB was set up and details of procedures were described.• Tocilizumab was added to the list of co-therapy with biologics exclusion criteria. Any other significant heart disease or any clinically significant ECG abnormality reported by central ECG reading was also added to the exclusion criteria.• Pregnancy was added to reasons for withdrawal from the study.• A general clarification was added regarding withdrawal management: patient withdrawn need to come for a follow-up study 4 weeks after the premature discontinuation. |

Notes:

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.

| |
|-----------------|
| Not applicable. |
|-----------------|

Notes: