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 involvment 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, tights, 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 involvment (SOI) or presence of an "unable to adjucate" 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 basseline	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 basline 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 (± 16.8)	-15.4 (± 16.6)	-7.1 (± 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 (± 16.9)	-10.2 (± 21.1)	-2.7 (± 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 ≥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 ≥20% MRSS compared to baseline.

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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 pregressor rate is a reduction ≥5 points and ≥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 progessor rate is a reduction ≥4 points and ≥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	3 / 48 (6.25%)	1 / 49 (2.04%)	1 / 48 (2.08%)
occurrences (all)	3	1	1
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	3 / 48 (6.25%)	2 / 49 (4.08%)	0 / 48 (0.00%)
occurrences (all)	3	2	0
Weight decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	3 / 48 (6.25%)
occurrences (all)	0	1	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 48 (12.50%)	2 / 49 (4.08%)	6 / 48 (12.50%)
occurrences (all)	6	3	6
Headache			
subjects affected / exposed	4 / 48 (8.33%)	7 / 49 (14.29%)	2 / 48 (4.17%)
occurrences (all)	7	9	3
Sciatica			
subjects affected / exposed	0 / 48 (0.00%)	4 / 49 (8.16%)	2 / 48 (4.17%)
occurrences (all)	0	6	2
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	13 / 48 (27.08%)	16 / 49 (32.65%)	0 / 48 (0.00%)
occurrences (all)	18	23	0
Peripheral swelling			
subjects affected / exposed	3 / 48 (6.25%)	6 / 49 (12.24%)	1 / 48 (2.08%)
occurrences (all)	6	10	1
Fatigue			
subjects affected / exposed	3 / 48 (6.25%)	1 / 49 (2.04%)	0 / 48 (0.00%)
occurrences (all)	4	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 48 (12.50%)	2 / 49 (4.08%)	3 / 48 (6.25%)
occurrences (all)	6	2	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	0 / 48 (0.00%)	5 / 49 (10.20%)	1 / 48 (2.08%)
occurrences (all)	0	6	1
Rales			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	3 / 48 (6.25%)
occurrences (all)	0	1	3
Skin and subcutaneous tissue disorders			
Scleroderma associated digital ulcer			
subjects affected / exposed	3 / 48 (6.25%)	5 / 49 (10.20%)	3 / 48 (6.25%)
occurrences (all)	3	6	6
Swelling face			
subjects affected / exposed	3 / 48 (6.25%)	3 / 49 (6.12%)	0 / 48 (0.00%)
occurrences (all)	3	4	0
Pruritus			
subjects affected / exposed	3 / 48 (6.25%)	1 / 49 (2.04%)	1 / 48 (2.08%)
occurrences (all)	3	1	1
Dry skin			
subjects affected / exposed	3 / 48 (6.25%)	0 / 49 (0.00%)	0 / 48 (0.00%)
occurrences (all)	3	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	3 / 48 (6.25%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Systemic scleroderma	Additional description: All NSAEs coded as systemic scleroderma were associated with an exacerbation/worsening of SSc condition or increase in MRSS.		
subjects affected / exposed	3 / 48 (6.25%)	7 / 49 (14.29%)	3 / 48 (6.25%)
occurrences (all)	3	9	3
Arthralgia			
subjects affected / exposed	6 / 48 (12.50%)	4 / 49 (8.16%)	4 / 48 (8.33%)
occurrences (all)	7	5	6
Joint swelling			
subjects affected / exposed	1 / 48 (2.08%)	2 / 49 (4.08%)	3 / 48 (6.25%)
occurrences (all)	2	3	3
Myalgia			
subjects affected / exposed	3 / 48 (6.25%)	3 / 49 (6.12%)	1 / 48 (2.08%)
occurrences (all)	4	3	3
Infections and infestations			

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2015	- 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 pharmakokinetic 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	- 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 - rewritening of statistical part of the protocol
27 February 2017	• 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: