Clinical trial results:
Double-Blind, Randomized, 8-Week Placebo-Controlled, and 16-Week Open Label Extension Study Investigating the Safety, Pharmacokinetics and Pharmacodynamics of SAR100842 Given Orally to Patients with Diffuse Cutaneous Systemic Sclerosis

Summary

EudraCT number	2012-001369-34
Trial protocol	GB DE IT
Global end of trial date	02 April 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	28 June 2015

Trial information

Trial identification

Sponsor protocol code	ACT12339

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01651143
WHO universal trial number (UTN)	U1111-1127-2854

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre, Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi-aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi-aventis recherche & développement, Contact-US@sanofi.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	28 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety and tolerability of 8-week oral administration of SAR100842 in subjects with diffuse cutaneous systemic sclerosis/scleroderma (dcSSc).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	04 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	32
EEA total number of subjects	12

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	29
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 12 sites in 5 countries. A total of 48 subjects were screened between 4 January 2013 and 12 September 2013.

Pre-assignment

Screening details:

Of 48 screened subjects, 16 were screen failure and 32 subjects were randomized and treated.

Period 1

Period 1 title	Core Part
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo-Core Part

Arm description:

Placebo matched to SAR100842 for 8 weeks.

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

Dosage and administration details:

Placebo matched to SAR100842 300 mg (100 mg +200 mg tablets), given twice daily (2 tablets in the morning and 2 tablets in the evening) for a total daily dose of 600 mg for 8 weeks.

Arm title	SAR100842-Core Part

Arm description:

SAR100842 300 mg BID for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	SAR100842
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

SAR100842 300 mg (100 mg + 200 mg tablets), given twice daily (2 tablets in the morning and 2 tablets in the evening) for a total daily dose of 600 mg for 8 weeks.

Number of subjects in period 1	Placebo-Core Part	SAR100842-Core Part
Started	17	15
Completed	17	14
Not completed	0	1
Personal request	-	1

Period 2

Period 2 title	Extension Part
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/SAR100842-Extension Part

Arm description:

Subjects who received placebo in core part were treated with SAR100842 for further 16 weeks.

Arm type	Experimental
Investigational medicinal product name	SAR100842
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

SAR100842 300 mg (100 mg + 200 mg tablets), given twice daily (2 tablets in the morning and 2 tablets in the evening) for a total daily dose of 600 mg for 16 weeks.

Arm title	SAR100842-Extension Part

Arm description:

Subjects who received SAR100842 in core part were treated with SAR100842 for further 16 weeks.

Arm type	Experimental
Investigational medicinal product name	SAR100842
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

SAR100842 300 mg (100 mg + 200 mg tablets), given twice daily (2 tablets in the morning and 2 tablets in the evening) for a total daily dose of 600 mg for 16 weeks.

Number of subjects in period 2[1]	Placebo/SAR100842 -Extension Part	SAR100842- Extension Part
Started	16	14
Completed	15	13
Not completed	1	1
Adverse event	1	1

Notes:

[1] - 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: One subject from placebo core part group did not continue in Extension part.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo-Core Part
Reporting group description:	
Placebo matched to SAR100842 for 8 weeks.	
Reporting group title	SAR100842-Core Part
Reporting group description:	
SAR100842 300 mg BID for 8 weeks.	

Reporting group values	Placebo-Core Part	SAR100842-Core Part	Total
Number of subjects	17	15	32
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	50.6	48.8	
standard deviation	± 11.3	± 10.3	-
Gender categorical Units: Subjects			
Female	12	9	21
Male	5	6	11

End points

End points reporting groups

Reporting group title	Placebo-Core Part
Reporting group description: Placebo matched to SAR100842 for 8 weeks.	
Reporting group title	SAR100842-Core Part
Reporting group description: SAR100842 300 mg BID for 8 weeks.	
Reporting group title	Placebo/SAR100842-Extension Part
Reporting group description: Subjects who received placebo in core part were treated with SAR100842 for further 16 weeks.	
Reporting group title	SAR100842-Extension Part
Reporting group description: Subjects who received SAR100842 in core part were treated with SAR100842 for further 16 weeks.	

Primary: Treatment Emergent Adverse Event - Safety Population

End point title	Treatment Emergent Adverse Event - Safety Population[1]
End point description: Adverse Event (AE) was defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. Analysis was performed on safety population defined as randomized and treated subjects in the core part (respectively extension part, for extension part analysis), analyzed according to the treatment actually received.	
End point type	Primary
End point timeframe: Baseline Up to Week 8 - Core part, Week 8 to Week 24 - Extension part	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The data reported are qualitative, hence, no statistical analysis is provided.

End point values	Placebo-Core Part	SAR100842-Core Part	Placebo/SAR100842-Extension Part	SAR100842-Extension Part
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	16	14
Units: subjects				
TEAE	12	12	13	10
Treatment emergent SAE	0	1	1	1
TEAE leading permanent treatment discontinuation	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Modified Rodnan Skin Score (mRSS)

score Up to Week 24: mITT Population

End point title	Change From Baseline in Total Modified Rodnan Skin Score (mRSS) score Up to Week 24: mITT Population

End point description:

mRSS (measurement of skin thickening) was assessed by palpation of the skin in 17 areas of the body using 0 - 3 scale (0 = normal, 1 = mild thickness, 2 = moderate thickness and 3 = severe thickness). Total skin score can range from 0 (no thickening) to 51 (severe thickening in all 17 areas).
Modified intent-to-treat (mITT)
population was defined as randomized and treated subjects with at least 1 post- Investigational medicinal product (IMP)-administration measurement during the core part (respectively extension part, for extension part analysis).

End point type	Secondary

End point timeframe:

Baseline, Week 8 - Core part, Week 8 to Week 24 - Extension part

End point values	Placebo-Core Part	SAR100842-Core Part	Placebo/SAR100842-Extension Part	SAR100842-Extension Part
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	13	14
Units: units on a scale				
arithmetic mean (standard deviation)	-2.76 (± 4.85)	-3.4 (± 4.08)	-7.31 (± 4.59)	-7.36 (± 4.24)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Scleroderma Health Assessment Questionnaire (SHAQ) Total Score Up to Week 24: mITT Population

End point title	Change From Baseline in Scleroderma Health Assessment Questionnaire (SHAQ) Total Score Up to Week 24: mITT Population

End point description:

The SHAQ included a standard Health Assessment Questionnaire Disability Index (HAQ-DI) subscore and 5 visual analog scales (VAS) for severity assessments of Raynaud’s phenomenon, breathing, digital ulcers, gastrointestinal disease and overall disease. The HAQ-DI was scored 0 to 3 from no disability to the most severe one. Analysis was performed on mITT population (core part and extension part).

End point type	Secondary

End point timeframe:

Baseline, Week 8 - Core part, Week 8 to Week 24 - Extension part

End point values	Placebo-Core Part	SAR100842-Core Part	Placebo/SAR100842-Extension Part	SAR100842-Extension Part
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	13	14
Units: units on a scale				
arithmetic mean (standard deviation)	0 (± 0.33)	-0.14 (± 0.3)	-0.23 (± 0.3)	-0.15 (± 0.33)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responder Based on 4 Skin Biomarkers At Week 8: PD Population

End point title	Percentage of Responder Based on 4 Skin Biomarkers At Week 8: PD Population

End point description:

A subjects was considered as a responder if at least 20% reduction from baseline was demonstrated in 2 of these 4 biomarkers (cartilage oligomeric matrix protein [COMP], Collagen 1A1 [COL1A1] messenger ribonucleic acid [mRNA], thrombospondin 1 [TSP1] and alpha-smooth muscle actin [α-SMA] positive cells. Pharmacodynamics (PD) population, included randomized and treated subjects who received at least 4 weeks of IMP with at least a baseline and a post-baseline assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Placebo-Core Part	SAR100842-Core Part		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	14		
Units: percentage of subjects				
number (not applicable)	47.1	64.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (core & extension part: Week 8, 24) regardless of seriousness or relationship to investigational product. Analysis was performed on safety population.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' [from the first administration of the study drug to the last administration of the study drug during the core/extension part + 5 days (5 half-lives)].

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo-Core Part

Reporting group description:

Placebo matched to SAR100842 for 8 weeks.

Reporting group title	SAR100842-Core Part

Reporting group description:

SAR100842 300 mg BID for 8 weeks.

Reporting group title	Placebo/SAR100842-Extension Part

Reporting group description:

Subjects who received placebo in core part were treated with SAR100842 for further 16 weeks.

Reporting group title	SAR100842-Extension Part

Reporting group description:

Subjects who received SAR100842 in core part were treated with SAR100842 for further 16 weeks.

Serious adverse events	Placebo-Core Part	SAR100842-Core Part	Placebo/SAR100842 -Extension Part
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	1 / 16 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infected Skin Ulcer			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SAR100842-Extension Part		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infected Skin Ulcer			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo-Core Part	SAR100842-Core Part	Placebo/SAR100842 -Extension Part
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)	11 / 15 (73.33%)	13 / 16 (81.25%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 17 (5.88%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Hot Flush			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Orthostatic Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Sinus Operation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Device Leakage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	2 / 16 (12.50%)
occurrences (all)	1	0	2
Feeling Abnormal			

subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oedema Peripheral			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Ulcer			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Menstruation Irregular			
subjects affected / exposed	2 / 17 (11.76%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Vaginal Discharge			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vaginal Haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	2 / 16 (12.50%)
occurrences (all)	1	0	2
Nasal Dryness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal Pain			

subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pleural Effusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pulmonary Mass			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Investigations			
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Prothrombin Time Prolonged			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Post Procedural Discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Procedural Pain			

subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Thermal Burn			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	1 / 17 (5.88%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 17 (0.00%)	3 / 15 (20.00%)	3 / 16 (18.75%)
occurrences (all)	0	3	3
Hyperaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Muscle Contractions Involuntary			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Lacrimation Increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pterygium			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vitreous Detachment			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Abdominal Pain Upper			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	2 / 17 (11.76%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	2 / 15 (13.33%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Dyspepsia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 17 (5.88%)	1 / 15 (6.67%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Mouth Ulceration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nausea			

subjects affected / exposed	1 / 17 (5.88%)	2 / 15 (13.33%)	2 / 16 (12.50%)
occurrences (all)	1	2	2
Oral Pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Tongue Ulceration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 17 (5.88%)	1 / 15 (6.67%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Keloid Scar			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Night Sweats			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Palmar Erythema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Photosensitivity Reaction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pruritus Generalised			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Skin Depigmentation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin Discolouration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin Discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Skin Induration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin Lesion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Skin Ulcer			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	2 / 16 (12.50%)
occurrences (all)	1	0	2
Swelling Face			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	0	3
Arthritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Back Pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Limb Discomfort			

subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Muscle Spasms			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal Discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal Stiffness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Pain In Extremity			
subjects affected / exposed	1 / 17 (5.88%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Temporomandibular Joint Syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Application Site Cellulitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis Viral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Herpes Zoster			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Urinary Tract Infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Non-serious adverse events	SAR100842-Extension Part		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hot Flush			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Orthostatic Hypotension			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Sinus Operation			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Device Leakage subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Fatigue subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Feeling Abnormal subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Non-Cardiac Chest Pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Oedema Peripheral subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Ulcer subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Reproductive system and breast disorders			
Menstruation Irregular subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Vaginal Discharge subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Vaginal Haemorrhage subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nasal Dryness			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Oropharyngeal Pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Pleural Effusion			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Pulmonary Mass			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Rales			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Investigations			
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Prothrombin Time Prolonged			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Accidental Overdose			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Post Procedural Discomfort			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Procedural Pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Thermal Burn			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hyperaesthesia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Migraine			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Muscle Contractions Involuntary			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Eye disorders			
Lacrimation Increased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Pterygium			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Vitreous Detachment			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Abdominal Pain Upper			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Dyspepsia			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Mouth Ulceration			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Oral Pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Tongue Ulceration			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Keloid Scar			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Night Sweats			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Palmar Erythema			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Photosensitivity Reaction subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Pruritus Generalised subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Skin Depigmentation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Skin Discolouration subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Skin Discomfort subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Skin Induration subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Skin Lesion subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Skin Ulcer subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Swelling Face subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Arthritis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Back Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Limb Discomfort			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Muscle Spasms			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Musculoskeletal Discomfort			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Pain In Extremity			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Temporomandibular Joint Syndrome			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infections and infestations			
Application Site Cellulitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Gastroenteritis Viral			

subjects affected / exposed occurrences (all) Herpes Zoster subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1 0 / 14 (0.00%) 0 1 / 14 (7.14%) 1		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2013	A 16 week extension was proposed to all subjects willing to continue on SAR100842, after they had completed the 8 week treatment and procedures. This longer exposure would provide additional long term safety data, and additional guidance for the selection and monitoring of subjects in longer further studies. Since SAR100842 was to be given in open label, subjects initially treated with placebo had the opportunity to receive the drug. The following sections was updated: A summary of the 6-month toxicology data supporting this extension was added, and the rationale of this extension was provided. A secondary objective and endpoint on safety and tolerability during the extension part was added. The inclusion/exclusion criteria for the extension were described. Only subjects who had completed the treatment and all procedures of the core part were included. All events described as reason for discontinuation in the core part were listed as exclusion criteria of the extension part, details of the volume of blood samples for the extension were provided (50ml to 65 ml depending on the number of blood samples taken). Clinical and laboratory safety were to be assessed through vital signs, physical examination, blood and urine samples. Depending on the duration of the window, additional physical examination, body weight and blood samples were to be performed at inclusion in the extension part. An optional skin biopsy was to be proposed at the end of the open label extension. Two informed consents were added, one for the extension part and another for the skin biopsy at the end of open label treatment, subjects who stopped the study treatment prematurely had the procedures listed in the end of treatment visit except that the last IMP was not to be given. Any procedure related to this intake such as PK sampling, and blood pressure measurement 4 hours after the intake, was not applicable. Mycophenolate mofetil greater than 2gm a day was added in exclusion criteria.
03 December 2013	One of the secondary objective of this study was to explore the effect of SAR100842 in subjects with diffuse cutaneous systemic sclerosis/scleroderma (dcSSc) as measured by disease related biomarkers.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported