Clinical trial results:
Efficacy and Safety of SAR156597 in the Treatment of Diffuse Cutaneous Systemic Sclerosis (dcSSc): A Randomized, Double-blind, Placebo-controlled, 24-week, Proof of Concept Study

Summary

EudraCT number	2016-001028-80
Trial protocol	DE AT BE EE IT
Global end of trial date	01 April 2019

Results information

Result version number	v1
This version publication date	10 April 2020
First version publication date	10 April 2020

Trial information

Trial identification

Sponsor protocol code	ACT14604

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02921971
WHO universal trial number (UTN)	U1111-1179-4690

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	29 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate, in comparison with placebo, the efficacy of SAR156597 administered subcutaneously for 24 weeks on skin fibrosis in subjects with diffuse cutaneous systemic sclerosis (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 was 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	21 December 2016
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: 14
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	97
EEA total number of subjects	52

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)	88
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 13 countries. A total of 97 subjects were involved in the study from 21 December 2016 to 01 April 2019.

Pre-assignment

Screening details:

Subjects were randomised in 1:1 ratio (placebo and SAR156597). Randomisation was stratified based upon the subject's medical history of systemic sclerosis (SSc) associated interstitial lung disease (SSc-ILD) (yes or no). Assignment was done by Interactive Voice Response System (IVRS).

Period 1

Period 1 title	Overall study (overall period)
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

Arm description:

Placebo (for SAR156597), single subcutaneous (SC) injection once in a week (QW) up to Week 24.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo (for SAR156597 200 milligram [mg]), single SC injection in abdomen.

Arm title	SAR156597

Arm description:

SAR156597 200 mg, single SC injection QW up to Week 24.

Arm type	Experimental
Investigational medicinal product name	Romilkimab
Investigational medicinal product code	SAR156597
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SAR156597 200 mg, single SC injection in abdomen.

Number of subjects in period 1	Placebo	SAR156597
Started	49	48
Completed	43	44
Not completed	6	4
Other than specified above	2	1
Adverse Event	1	2
Lack of efficacy	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo (for SAR156597), single subcutaneous (SC) injection once in a week (QW) up to Week 24.	

Reporting group title	SAR156597
Reporting group description:	
SAR156597 200 mg, single SC injection QW up to Week 24.	

Reporting group values	Placebo	SAR156597	Total
Number of subjects	49	48	97
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	47.2	52.3	
standard deviation	± 12.1	± 10.8	-
Gender categorical Units: Subjects			
Female	38	39	77
Male	11	9	20
Race Units: Subjects			
American Indian or Alska Native	0	1	1
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	2	2	4
White	45	45	90
Modified Rodnan Skin Score (mRSS)			
mRSS: an accepted clinical measure of the skin thickness (fibrosis). Investigator physicians or qualified medical personnel assessed the thickening of skin in 17 skin sites, including fingers, hands, forearms, arms, feet, legs and thighs, face, chest and abdomen. Each skin site was rated on a 0-3 scale; where 0 = normal skin, 1 = mild thickness, 2 = moderate thickness and 3 = severe thickness. Total mRSS (sum of individual scores) ranged from 0 (normal skin) to 51 (severe thickening in all 17 areas), where higher score indicated more severity of skin thickening/worst outcome.			
Units: units on a scale			
arithmetic mean	20.6	20.5	
standard deviation	± 7.0	± 6.1	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo (for SAR156597), single subcutaneous (SC) injection once in a week (QW) up to Week 24.

Reporting group title	SAR156597

Reporting group description:

SAR156597 200 mg, single SC injection QW up to Week 24.

Primary: Change From Baseline in Modified Rodnan Skin Score to Week 24

End point title	Change From Baseline in Modified Rodnan Skin Score to Week 24

End point description:

mRSS, an accepted clinical measure of the skin thickness (fibrosis). Investigator physicians or qualified medical personnel assessed the thickening of skin in 17 skin sites including fingers, hands, forearms, arms, feet, legs and thighs, face, chest and abdomen. Each skin site was rated on a 0-3 scale; where 0 = normal skin, 1 = mild thickness, 2 = moderate thickness and 3 = severe thickness. Total mRSS ranged from 0 (no thickening) to 51 (severe thickening in all 17 areas), where higher score indicated more severity of skin thickening/worst outcome. The analysis was performed on the intent to treat (ITT) population which included all randomised subjects and were analysed according to the treatment group allocated by randomisation. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Placebo	SAR156597		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: score on a scale				
least squares mean (standard error)	-2.45 (± 0.85)	-4.76 (± 0.86)		

Statistical analyses

Statistical analysis title	SAR156597 Versus Placebo

Statistical analysis description:

Analysis was performed using mixed model repeated measures (MMRM) model. The model included fixed categorical effects of treatment group, randomisation strata as per IVRS, timepoint, treatment-by-timepoint and strata-by-timepoint interactions, as well as the continuous fixed covariate of baseline and baseline-by-timepoint interactions.

Comparison groups	SAR156597 v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0291 [1]
Method	Mixed-effect model with repeated measure
Parameter estimate	Least square (LS) Mean difference
Point estimate	-2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.71
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	1.21

Notes:

[1] - Above p-value is one-sided p-value. Threshold for significance is at 0.05 level.

Secondary: Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) Score to Week 24

End point title	Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) Score to Week 24

End point description:

HAQ-DI assessed the degree of difficulty subjects experienced in 8 daily living activity domains during past week: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Each activity category consisted of 2-3 items. For each items, level of difficulty was scored from 0-3 (0=no difficulty, 1=some difficulty, 2=much difficulty, 3=unable to do). Overall HAQ-DI score was computed as the sum of domain scores divided by the number of domains answered, providing a score from 0 (no difficulty) to 3 (maximum difficulty), where higher score indicated greater disability. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	SAR156597		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: score on a scale				
least squares mean (standard error)	-0.12 (± 0.08)	-0.09 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Observed Forced Vital Capacity (FVC) Level to Week 24

End point title	Change From Baseline in Mean Observed Forced Vital Capacity (FVC) Level to Week 24

End point description:

FVC was the total amount of air (in litres) exhaled from the lungs during the lung function test measured by spirometer which assessed the change in lung function related to the disease status of an underlying ILD. Change from Baseline was calculated by subtracting Baseline value from Week 24 value. Analysis was performed on the ITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	SAR156597		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: litres				
least squares mean (standard error)	-0.08 (± 0.04)	-0.01 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Observed Diffusing Lung Capacity for Carbon Monoxide (DLco) to Week 24

End point title	Change From Baseline in Mean Observed Diffusing Lung Capacity for Carbon Monoxide (DLco) to Week 24

End point description:

DLco is a measurement of the ability of the lungs to transfer gases from the air to the blood. Subject breathe in (inhale) air containing a very small, harmless amount of a tracer gas, such as carbon monoxide. Subject hold the breath for 10 seconds, then rapidly blow it out (exhale). The exhaled gas was tested to determine amount of the tracer gas absorbed during the breath. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	SAR156597		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	47		
Units: millimoles per minute per kilopascal				
least squares mean (standard error)	-0.27 (± 0.10)	-0.12 (± 0.10)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were collected from the signature of the informed consent form until the end of the study, regardless of seriousness or relationship to investigational medicinal product (IMP).

Adverse event reporting additional description:

Reported treatment-emergent AEs (TEAEs) & deaths were AEs that developed/worsened/became serious during TEAE period (time from 1st IMP administration up to 12 weeks [84 days] from last IMP dose [i.e. up to 36 weeks]). Safety population: subjects who received at least 1 dose/part of a dose of IMP and were analysed as per treatment actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo (for SAR156597), single SC injection QW up to Week 24.

Reporting group title	SAR156597

Reporting group description:

SAR156597 200 mg single SC injection QW up to Week 24.

Serious adverse events	Placebo	SAR156597	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 49 (10.20%)	4 / 48 (8.33%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Echocardiogram Abnormal			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			

subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal Pseudo-Obstruction			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Scleroderma Renal Crisis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Bacterial			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	SAR156597	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 49 (55.10%)	31 / 48 (64.58%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 49 (2.04%)	4 / 48 (8.33%)	
occurrences (all)	1	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 49 (8.16%)	7 / 48 (14.58%)	
occurrences (all)	5	8	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 49 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 49 (0.00%)	5 / 48 (10.42%)	
occurrences (all)	0	5	
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	1 / 49 (2.04%)	3 / 48 (6.25%)	
occurrences (all)	1	4	
Skin Ulcer			
subjects affected / exposed	15 / 49 (30.61%)	8 / 48 (16.67%)	
occurrences (all)	23	20	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 49 (2.04%)	4 / 48 (8.33%)	
occurrences (all)	1	4	
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 49 (4.08%)	3 / 48 (6.25%)	
occurrences (all)	2	3	
Nasopharyngitis			
subjects affected / exposed	6 / 49 (12.24%)	6 / 48 (12.50%)	
occurrences (all)	6	6	
Oral Herpes			
subjects affected / exposed	1 / 49 (2.04%)	5 / 48 (10.42%)	
occurrences (all)	1	7	
Pharyngitis			
subjects affected / exposed	0 / 49 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 49 (4.08%)	5 / 48 (10.42%)	
occurrences (all)	2	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2017	Pulmonary function tests & echocardiogram were added at screening, & electrocardiogram (ECG) assessment was modified. Percent (%) predicted forced vital capacity (FVC) & observed & % predicted Carbon Monoxide diffusing lung capacity (DLco) (corrected for hemoglobin) & observed were added to Visit 1 (V1) to screen for newly added exclusion criteria (At screening, % predicted FVC is less than or equal to [<=] 75% & % predicted DLco after hemoglobin correction is <= 40%). A 2-Dimensional transthoracic echocardiogram was added to Visit 1 to screen for newly added exclusion criterion. Exclusion criteria was added: - History of heart failure (including acutely decompensated in the setting of preserved ejection fraction), Left Ventricular Ejection Fraction (LVEF) <=45%, coronary artery disease, angina, myocardial infarction, ischemic cardiomyopathy &/or hypertrophic cardiomyopathy. - Ischemic ECG changes (except those not supported by the findings of a left heart catheterisation performed in the last year within screening) &/or other clinically significant ECG findings at screening. (All abnormal ECG finding was reviewed & confirmed by a local cardiologist.) Electrocardiogram variables were updated: At Visit 1, all abnormal ECG interpretation was confirmed by a local cardiologist. All findings of ischemic ECG changes were to result in exclusion unless there was a left heart catheterisation performed in the last year within screening that is not supportive of the current ECG finding. Appendix for clinically significant ECG was added. Echocardiogram variable was updated: A standard 2-Dimensional transthoracic echocardiogram was to be obtained at Visit 1 (unless one had been previously obtained within 6 months of Visit 1) to help determine subject's eligibility. At a minimum, the echocardiogram was to be able to assess for the LVEF & status & function of the four cardiac chambers, myocardium and valves.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported