



## 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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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     |
| <b>Arm title</b>             | 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.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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 Alaska 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 <sup>[1]</sup>                  |
| 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 ( $\pm$ 0.04) | -0.01 ( $\pm$ 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 ( $\pm$ 0.10) | -0.12 ( $\pm$ 0.10) |  |  |

## Statistical analyses



## 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          |  |
| <b>Pneumonia Bacterial</b>                      |                |                |  |
| 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          |  |
| <b>Pyelonephritis Acute</b>                     |                |                |  |
| 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 %

| <b>Non-serious adverse events</b>                            | Placebo          | SAR156597        |  |
|--|------------------|------------------|--|
| <b>Total subjects affected by non-serious adverse events</b> |                  |                  |  |
| subjects affected / exposed                                  | 27 / 49 (55.10%) | 31 / 48 (64.58%) |  |
| <b>Nervous system disorders</b>                              |                  |                  |  |
| Headache   |                  |                  |  |
| subjects affected / exposed                                  | 1 / 49 (2.04%)   | 4 / 48 (8.33%)   |  |
| occurrences (all)  | 1                | 7                |  |
| <b>Gastrointestinal disorders</b>                            |                  |                  |  |
| 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                |  |
| <b>Respiratory, thoracic and mediastinal disorders</b>       |                  |                  |  |
| Cough  |                  |                  |  |
| subjects affected / exposed                                  | 0 / 49 (0.00%)   | 5 / 48 (10.42%)  |  |
| occurrences (all)  | 0                | 5                |  |
| <b>Skin and subcutaneous tissue disorders</b>                |                  |                  |  |
| Pruritus   |                  |                  |  |

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 09 August 2017 | <p>Pulmonary function tests &amp; echocardiogram were added at screening, &amp; electrocardiogram (ECG) assessment was modified. Percent (%) predicted forced vital capacity (FVC) &amp; observed &amp; % predicted Carbon Monoxide diffusing lung capacity (DLco) (corrected for hemoglobin) &amp; observed were added to Visit 1 (V1) to screen for newly added exclusion criteria (At screening, % predicted FVC is less than or equal to [<math>\leq</math>] 75% &amp; % predicted DLco after hemoglobin correction is <math>\leq</math> 40%). A 2-Dimensional transthoracic echocardiogram was added to Visit 1 to screen for newly added exclusion criterion.</p> <p>Exclusion criteria was added:</p> <ul style="list-style-type: none"><li>- History of heart failure (including acutely decompensated in the setting of preserved ejection fraction), Left Ventricular Ejection Fraction (LVEF) <math>\leq</math>45%, coronary artery disease, angina, myocardial infarction, ischemic cardiomyopathy &amp;/or hypertrophic cardiomyopathy.</li><li>- Ischemic ECG changes (except those not supported by the findings of a left heart catheterisation performed in the last year within screening) &amp;/or other clinically significant ECG findings at screening. (All abnormal ECG finding was reviewed &amp; confirmed by a local cardiologist.)</li></ul> <p>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.</p> <p>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 &amp; status &amp; function of the four cardiac chambers, myocardium and valves.</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported