Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Parallel-group, Proof-of-Concept (PoC) Study to Assess the Efficacy, Safety and Tolerability of SAR440340/REGN3500, in Patients With Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2017-003290-34
Trial protocol	DE PL
Global end of trial date	21 February 2020

Results information

Result version number	v1
This version publication date	07 March 2021
First version publication date	07 March 2021

Trial information

Trial identification

Sponsor protocol code	ACT15104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03546907
WHO universal trial number (UTN)	U1111-1194-2134

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	20 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate effects of SAR440340 (anti-interleukin-33 [IL33] monoclonal antibody [mAb]) compared with placebo, on the annualised rate of moderate-to-severe acute exacerbations of COPD (AECOPD) over up to 52 weeks of treatment.

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:

At screening, subjects were on standard of care background therapy, for 3 months prior to Visit 2/Randomisation and at a stable dose for at least 1 month prior to the Screening Visit 1, including either: Double therapy: long-acting beta2 [β2] adrenergic agonist (LABA) + Long-acting muscarinic antagonist (LAMA) or inhaled corticosteroid (ICS) + LABA or ICS + LAMA; or Triple therapy: ICS + LABA + LAMA.

Evidence for comparator: -

Actual start date of recruitment	16 July 2018
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	Argentina: 41
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Chile: 38
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	Turkey: 23
Country: Number of subjects enrolled	Ukraine: 40
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	343
EEA total number of subjects	67

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)	176
From 65 to 84 years	167
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 83 centers in 10 countries, out of which 78 centers randomised at least 1 subject. A total of 653 subjects were screened from 16-July-2018 to 01-April-2019, of which 310 subjects were screen failures mainly due to selection criteria not met.

Pre-assignment

Screening details:

A total of 343 subjects were randomised and treated in this study. Subjects were randomised in 1:1 ratio to receive treatment SAR440340 and matching placebo for SAR440340.

Period 1

Period 1 title	Overall (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:

Subjects received placebo matched to SAR440340 administered as 2 subcutaneous (SC) injections every 2 weeks (Q2W). Subjects were treated for a minimum of 24 weeks and up to a maximum of 52 weeks. End of Treatment (EOT) visit occurred 2 weeks after last administration of investigational medicinal product (IMP).

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

Dosage and administration details:

Placebo matched to SAR440340 Q2W was administered as 2 SC injection (1.5 millilitres [mL]).

Arm title	SAR440340

Arm description:

Subjects received SAR440340 300 milligrams (mg) administered as 2 SC injections Q2W. Subjects were treated for a minimum of 24 weeks and up to a maximum of 52 weeks. EOT visit occurred 2 weeks after last administration of IMP.

Arm type	Experimental
Investigational medicinal product name	Itepekimab
Investigational medicinal product code	SAR440340/REGN3500
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SAR440340 300 mg Q2W was administered as 2 SC injections (1.5 mL).

Number of subjects in period 1	Placebo	SAR440340
Started	171	172
Completed	154	151
Not completed	17	21
Adverse events (AEs)	7	10
Other-unspecified	1	1
Lack of efficacy	1	1
Withdrawal by subject	8	9

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to SAR440340 administered as 2 subcutaneous (SC) injections every 2 weeks (Q2W). Subjects were treated for a minimum of 24 weeks and up to a maximum of 52 weeks. End of Treatment (EOT) visit occurred 2 weeks after last administration of investigational medicinal product (IMP).	
Reporting group title	SAR440340
Reporting group description:	
Subjects received SAR440340 300 milligrams (mg) administered as 2 SC injections Q2W. Subjects were treated for a minimum of 24 weeks and up to a maximum of 52 weeks. EOT visit occurred 2 weeks after last administration of IMP.	

Reporting group values	Placebo	SAR440340	Total
Number of subjects	171	172	343
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.0	63.7	
standard deviation	± 6.5	± 6.8	-
Gender categorical Units: Subjects			
Female	76	73	149
Male	95	99	194
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	169	170	339
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Number of subjects with smoking history Units: Subjects			
Current	82	74	156
Former	89	98	187
Standard of care background therapy			
At screening, subjects were on standard of care background therapy, for 3 months prior to Visit 2/Randomisation and at a stable dose for at least 1 month prior to the Screening Visit 1, including either: Double therapy: LABA + LAMA or ICS + LABA or ICS + LAMA; or Triple therapy: ICS + LABA + LAMA.			
Units: Subjects			
LABA+LAMA	24	23	47
ICS+LABA	36	33	69
ICS+LAMA	0	1	1

ICS+LABA+LAMA	111	115	226

Age at diagnosis of chronic obstructive pulmonary disease (COPD) Units: years arithmetic mean standard deviation	 55.5 ± 8.0	 55.4 ± 7.8	 -
Mean number of moderate COPD exacerbations experienced within 1 year before screening visit			
Moderate exacerbations events were defined as acute exacerbation of chronic obstructive pulmonary disease (AECOPD) that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics.			
Units: exacerbations per subject-year arithmetic mean standard deviation	 1.8 ± 1.2	 1.8 ± 1.1	 -
Mean number of severe COPD exacerbations experienced within 1 year before screening visit			
Severe exacerbations events were defined as AECOPD requiring hospitalisation, emergency medical care visit or resulting in death.			
Units: exacerbations per subject-year arithmetic mean standard deviation	 0.4 ± 0.6	 0.3 ± 0.6	 -
Predicted baseline post-bronchodilator forced expiratory volume in 1 second (FEV1)			
FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer.			
Units: percent predicted arithmetic mean standard deviation	 49.02 ± 12.18	 49.62 ± 12.34	 -
Baseline COPD assessment test (CAT) score			
The CAT is a 8-item self-administered questionnaire that is designed for subjects with COPD to measure the effects of the disease on their quality of lives. Each question is scored in a range between 0-5 according to subject feelings about the disease, where 0 = "I am very happy"; 5 = "I am very sad" and total CAT score (sum of the 8 individual question scores) ranged from 0 to 40, where worse score indicated higher impact on health status.			
Units: scores on a scale arithmetic mean standard deviation	 21.66 ± 5.23	 21.89 ± 5.84	 -
Baseline blood eosinophil count Units: Giga cells per litre arithmetic mean standard deviation	 0.25 ± 0.19	 0.27 ± 0.24	 -

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to SAR440340 administered as 2 subcutaneous (SC) injections every 2 weeks (Q2W). Subjects were treated for a minimum of 24 weeks and up to a maximum of 52 weeks. End of Treatment (EOT) visit occurred 2 weeks after last administration of investigational medicinal product (IMP).

Reporting group title	SAR440340

Reporting group description:

Subjects received SAR440340 300 milligrams (mg) administered as 2 SC injections Q2W. Subjects were treated for a minimum of 24 weeks and up to a maximum of 52 weeks. EOT visit occurred 2 weeks after last administration of IMP.

Primary: Annualised Rate of Moderate to Severe Acute Exacerbation Events in Chronic Obstructive Pulmonary Disease (AECOPD) Subjects

End point title	Annualised Rate of Moderate to Severe Acute Exacerbation Events in Chronic Obstructive Pulmonary Disease (AECOPD) Subjects

End point description:

Moderate exacerbations events were recorded by the investigator and defined as AECOPD that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations events were defined as AECOPD requiring hospitalisation, emergency medical care visit or resulting in death. Annualised event rate was calculated as the total number of exacerbations that occurred during the treatment period divided by the total number of subject-years treated. Analysis was performed on modified intent-to-treat (mITT) population that included all randomised subjects who had received at least 1 dose of IMP, analysed according to the treatment group allocated by randomisation.

End point type	Primary

End point timeframe:

From Baseline up to Week 52

End point values	Placebo	SAR440340		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	172		
Units: exacerbation per subject-years				
number (confidence interval 95%)	1.610 (1.318 to 1.968)	1.301 (1.052 to 1.61)		

Statistical analyses

Statistical analysis title	SAR440340 versus (vs.) Placebo

Statistical analysis description:

Analysis was performed using negative binomial regression model with total number of events occurring during observation duration as response variable, treatment, baseline eosinophil strata, region, number of severe COPD exacerbations experienced in previous year(0 vs. 1+) at baseline, smoking history (current vs. former smoker), post-BD FEV1 percent(%) predicted (less than[<]50% vs greater than equal[>=]50%) at baseline as covariates, and log-transformed observation duration as offset variable.

Comparison groups	SAR440340 v Placebo
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1296 [1]
Method	Negative binomial regression model
Parameter estimate	Rate ratio
Point estimate	0.808
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.613
upper limit	1.065

Notes:

[1] - Threshold for significance for p-value was 0.05.

Secondary: Average Change in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) From Baseline to Week 16 Through Week 24

End point title	Average Change in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) From Baseline to Week 16 Through Week 24

End point description:

FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Spirometry was performed after a wash out period of bronchodilators according to their action duration. A mixed-effect model with repeated measures (MMRM) was first used to model the change from baseline at each post randomisation timepoint up to Week 24, then the predicted values of Week 16 to Week 24 were averaged to provide an overall assessment of change from baseline in FEV1. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 16 through Week 24

End point values	Placebo	SAR440340		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	172		
Units: litres				
least squares mean (standard error)	0.0 (± 0.02)	0.06 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 24

End point title	Change From Baseline in Post-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 24

End point description:

FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as

measured by spirometer. Post-bronchodilator FEV1 referred to the spirometry performed within 30 minutes after administration of bronchodilator (4 puffs of albutamol/albuterol [100 micrograms {mcg}] or ipratropium bromide [20 mcg]). Analysis was performed on mITT population. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	SAR440340		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	165		
Units: litres				
arithmetic mean (standard deviation)	0.01 (± 0.22)	0.04 (± 0.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Moderate or Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

End point title	Time to First Moderate or Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

End point description:

Time to first moderate or severe exacerbation was calculated as onset date of first moderate or severe AECOPD - randomisation date + 1. Subject without experiencing the event was considered as censored at end of planned treatment duration or last contact date, whichever occurred earlier. Median time to first severe exacerbation was derived from Kaplan-Meier estimates. Moderate exacerbations events were recorded by investigator and defined as AECOPD that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations events were defined as AECOPD requiring hospitalisation, emergency medical care visit or resulting in death. Analysis was performed on mITT population. Here, 'Number of subjects analysed' signifies subjects evaluable for this endpoint and '99999' signifies that upper limit of 95% confidence interval was not computable because the curve that represents upper confidence limits for survivor function lies above 0.5.

End point type	Secondary

End point timeframe:

From Baseline up to 52 weeks

End point values	Placebo	SAR440340		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	81		
Units: days				
median (confidence interval 95%)	199.0 (139.00 to 266.00)	277.0 (204.00 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from the signature of the informed consent form until the end of the study (i.e., minimum up to 46 weeks and a maximum of up to 72 weeks) regardless of seriousness or relationship to IMP.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent AEs that developed, worsened, or became serious during treatment-emergent period (from first administration of IMP up to 22 weeks after the last administration of IMP). Analysis was performed on safety population that included all randomised subjects who received at least 1 injection of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to SAR440340 administered as 2 SC injections Q2W. Subjects were treated for a minimum of 24 weeks and up to a maximum of 52 weeks. EOT visit occurred 2 weeks after last administration of IMP.

Reporting group title	SAR440340

Reporting group description:

Subjects received SAR440340 300 mg administered as 2 SC injections Q2W. Subjects were treated for a minimum of 24 weeks and up to a maximum of 52 weeks. EOT visit occurred 2 weeks after last administration of IMP.

Serious adverse events	Placebo	SAR440340	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 171 (21.05%)	29 / 172 (16.86%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial Adenocarcinoma			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Lobular Breast Carcinoma			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Squamous Cell Carcinoma			

subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Adenocarcinoma Stage Iii			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm Malignant			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Cell Lung Cancer			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep Vein Thrombosis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Ischaemia			

subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 171 (0.58%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	14 / 171 (8.19%)	11 / 172 (6.40%)	
occurrences causally related to treatment / all	0 / 19	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pickwickian Syndrome			

subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax Spontaneous			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 171 (1.17%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	4 / 171 (2.34%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol Abuse			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Burns Second Degree			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis Coronary Artery			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 171 (0.58%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary Failure			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary Artery Stenosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Cardiomyopathy			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress Cardiomyopathy			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial Paresis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage Intracranial			

subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic Cerebral Infarction			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	2 / 171 (1.17%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Chronic Gastritis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal Haemorrhage			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive Pancreatitis			
subjects affected / exposed	1 / 171 (0.58%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Chronic			

subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-Induced Liver Injury			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Babesiosis			

subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 171 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis Of Male External Genital Organ			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Infective			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation Of Chronic Obstructive Airways Disease			
subjects affected / exposed	5 / 171 (2.92%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 171 (1.75%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			

subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Sepsis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subperiosteal Abscess			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection Bacterial			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	SAR440340	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 171 (45.61%)	60 / 172 (34.88%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 171 (6.43%)	3 / 172 (1.74%)	
occurrences (all)	12	3	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 171 (13.45%)	14 / 172 (8.14%)	
occurrences (all)	35	24	
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 171 (8.19%)	16 / 172 (9.30%)	
occurrences (all)	17	20	
Nasopharyngitis			
subjects affected / exposed	29 / 171 (16.96%)	28 / 172 (16.28%)	
occurrences (all)	43	40	
Upper Respiratory Tract Infection			
subjects affected / exposed	14 / 171 (8.19%)	13 / 172 (7.56%)	
occurrences (all)	17	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2018	Following amendments were made: 1) Clarification for the biomarker blood eosinophils and neutrophils collection visits per Health Authorities' request. 2) Details added to the justification for dose. 3) Exclusion criteria was modified: -subjects with COPD diagnosed within the 6 months prior to randomisation was deleted. -Known allergy to doxycycline or related compounds was modified per the Healthy Authorities' request, to also exclude subjects with a history of systemic hypersensitivity to any excipients of the IMP. -Subjects with cardiovascular diseases/conditions was modified per the Health Authorities' request, to exclude subjects with grade 3 hypertension (high cardiovascular risk). 4) Removed intra-articular steroids from permitted concomitant therapy. 5) COPD exacerbation: "Any course of systemic steroids/antibiotics started <7 days of finishing a previous course should be considered as treatment for a single exacerbation" was added, to provide clarification with regard to reporting of COPD exacerbations. 6) Subject reported outcomes questionnaires: inconsistency between set-up of e-diary and the protocol e-diary language was corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported