Clinical trial results:
A Multicenter, Randomized, Open-Label, Parallel-Group Usability Study of the Sarilumab Auto-Injector Device and a Prefilled Syringe in Patients with Moderate to Severe Active Rheumatoid Arthritis who are Candidates for Anti-IL6R Therapy

Summary

EudraCT number	2012-004339-21
Trial protocol	PL
Global end of trial date	11 March 2016

Results information

Result version number	v1 (current)
This version publication date	22 March 2017
First version publication date	22 March 2017

Trial information

Trial identification

Sponsor protocol code	MSC12665

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02057250
WHO universal trial number (UTN)	U1111-1130-9931

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Sanofi aventis recherche & développement, Trial Transparency Team, contact-US@sanofi.com
Scientific contact	Sanofi aventis recherche & développement, Trial Transparency Team, 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	12 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To collect real-use data of the sarilumab auto-injector device (AID) used by rheumatoid arthritis (RA) subjects.

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:

Subjects received one or a combination of non-biologic disease modifying anti-rheumatic drug (DMARD) (hydroxychloroquine, methotrexate, sulfasalazine and/or Leflunomide, except for simultaneous combination use of leflunomide and methotrexate) as background therapy throughout the study.

Evidence for comparator: -

Actual start date of recruitment	18 March 2014
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	Chile: 30
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	South Africa: 23
Country: Number of subjects enrolled	United States: 97
Worldwide total number of subjects	217
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	166
From 65 to 84 years	50
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 53 centers in 6 countries. A total of 419 subjects were screened between 18 March 2014 and 14 October 2014, out of which 217 subjects were enrolled and treated.

Pre-assignment

Screening details:

Subjects were randomized in 1:1:1:1 ratio to Sarilumab 150 mg administered by AID or prefilled syringe (PFS) or Sarilumab 200 mg administered by AID or PFS. Subjects who completed 12-week AID assessment phase, were treated in open-label extension phase for 52 weeks.

Period 1

Period 1 title	AID Assessment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sarilumab 150 mg by AID (AID Assessment Phase)

Arm description:

Sarilumab 150 mg every 2 weeks (q2w) administered by AID with one or a combination of non-biologic DMARD for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Sarilumab
Investigational medicinal product code	SAR153191, REGN88
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sarilumab self-administered as a subcutaneous (SC) injection by AID in the abdomen or thigh.

Arm title	Sarilumab 150 mg by PFS (AID Assessment Phase)

Arm description:

Sarilumab 150 mg q2w administered by PFS with one or a combination of non-biologic DMARD for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Sarilumab
Investigational medicinal product code	SAR153191, REGN88
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sarilumab self-administered as SC injection by PFS in the abdomen or thigh.

Arm title	Sarilumab 200 mg by AID (AID Assessment Phase)

Arm description:

Sarilumab 200 mg q2w administered by AID with one or a combination of non-biologic DMARD for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	Sarilumab
Investigational medicinal product code	SAR153191, REGN88
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sarilumab self-administered as a SC injection by AID in the abdomen or thigh.

Arm title	Sarilumab 200 mg by PFS (AID Assessment Phase)

Arm description:

Sarilumab 200 mg q2w administered by PFS with one or a combination of non-biologic DMARD for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Sarilumab
Investigational medicinal product code	SAR153191, REGN88
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sarilumab self-administered as a SC injection by PFS in the abdomen or thigh.

Number of subjects in period 1	Sarilumab 150 mg by AID (AID Assessment Phase)	Sarilumab 150 mg by PFS (AID Assessment Phase)	Sarilumab 200 mg by AID (AID Assessment Phase)
Started	56	53	52
Completed	52	50	45
Not completed	4	3	7
Other than specified above	1	1	1
Adverse Event	3	2	6

Number of subjects in period 1	Sarilumab 200 mg by PFS (AID Assessment Phase)
Started	56
Completed	54
Not completed	2
Other than specified above	1
Adverse Event	1

Period 2

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

Arms

Arm title	Sarilumab 150 mg by PFS (Extension Phase)

Arm description:

Subjects who completed 12 week AID assessment phase received Sarilumab 150 mg q2w administered by PFS with one or a combination of non-biologic DMARD for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Sarilumab
Investigational medicinal product code	SAR153191, REGN88
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sarilumab self-administered as a SC injection by PFS in the abdomen or thigh.

Number of subjects in period 2[1]	Sarilumab 150 mg by PFS (Extension Phase)
Started	192
Treated	188
Completed	156
Not completed	36
Other than specified above	7
Adverse Event	15
Entered in this period but not treated	4
Lack of efficacy	10

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: 9 subjects who completed AID Assessment phase did not enter extension phase.

Baseline characteristics

Reporting groups	
Reporting group title	Sarilumab 150 mg by AID (AID Assessment Phase)
Reporting group description:	
Sarilumab 150 mg every 2 weeks (q2w) administered by AID with one or a combination of non-biologic DMARD for 12 weeks.	
Reporting group title	Sarilumab 150 mg by PFS (AID Assessment Phase)
Reporting group description:	
Sarilumab 150 mg q2w administered by PFS with one or a combination of non-biologic DMARD for 12 weeks.	
Reporting group title	Sarilumab 200 mg by AID (AID Assessment Phase)
Reporting group description:	
Sarilumab 200 mg q2w administered by AID with one or a combination of non-biologic DMARD for 12 weeks.	
Reporting group title	Sarilumab 200 mg by PFS (AID Assessment Phase)
Reporting group description:	
Sarilumab 200 mg q2w administered by PFS with one or a combination of non-biologic DMARD for 12 weeks.	

Reporting group values	Sarilumab 150 mg by AID (AID Assessment Phase)	Sarilumab 150 mg by PFS (AID Assessment Phase)	Sarilumab 200 mg by AID (AID Assessment Phase)
Number of subjects	56	53	52
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	53.7	54.2	55.9
standard deviation	± 13.8	± 14.2	± 12.3
Gender categorical			
Units: Subjects			
Female	45	43	44
Male	11	10	8

Reporting group values	Sarilumab 200 mg by PFS (AID Assessment Phase)	Total	
Number of subjects	56	217	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	50.3		
standard deviation	± 12.8	-	
Gender categorical			
Units: Subjects			
Female	49	181	
Male	7	36	

End points

End points reporting groups

Reporting group title	Sarilumab 150 mg by AID (AID Assessment Phase)
Reporting group description:	
Sarilumab 150 mg every 2 weeks (q2w) administered by AID with one or a combination of non-biologic DMARD for 12 weeks.	
Reporting group title	Sarilumab 150 mg by PFS (AID Assessment Phase)
Reporting group description:	
Sarilumab 150 mg q2w administered by PFS with one or a combination of non-biologic DMARD for 12 weeks.	
Reporting group title	Sarilumab 200 mg by AID (AID Assessment Phase)
Reporting group description:	
Sarilumab 200 mg q2w administered by AID with one or a combination of non-biologic DMARD for 12 weeks.	
Reporting group title	Sarilumab 200 mg by PFS (AID Assessment Phase)
Reporting group description:	
Sarilumab 200 mg q2w administered by PFS with one or a combination of non-biologic DMARD for 12 weeks.	
Reporting group title	Sarilumab 150 mg by PFS (Extension Phase)
Reporting group description:	
Subjects who completed 12 week AID assessment phase received Sarilumab 150 mg q2w administered by PFS with one or a combination of non-biologic DMARD for 52 weeks.	

Primary: Number of Validated AID Associated Product Technical Failures (PTFs)

End point title	Number of Validated AID Associated Product Technical Failures (PTFs)[1][2]
End point description:	
A PTF was defined as any product technical complaint (PTC) related to the use of the AID that had a validated technical cause. Each subject was given a diary having questions related to subject's ability to remove the cap, to start the injection, to complete the injection and regarding confirmation of completing the injection. Subjects were asked to answer the questions each time they self-inject the sarilumab. If the response was "no" to any of the first 3 questions, this was considered as a PTC. The used AID, for which PTC was reported, was sent to sponsor, examined and evaluated for the occurrence of a PTF. Modified intent-to-treat (mITT) population included all randomized subjects who received at least 1 dose of investigational medicinal product (IMP) with AID and attended at least 1 post-baseline visit during AID assessment phase of the study.	
End point type	Primary
End point timeframe:	
Baseline up to Week 12	

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: Only descriptive statistics were reported, inferential statistics were not planned for primary endpoint.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Sarilumab 150 mg by AID (AID Assessment Phase)	Sarilumab 200 mg by AID (AID Assessment Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56[3]	52[4]		
Units: PTFs				
number (not applicable)	0	0		

Notes:

[3] - Number of Injections Analyzed: 312

[4] - Number of Injections Analyzed: 288

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration Versus Time Curve Calculated Using the Trapezoidal Method During a Dose Interval (AUC[0-tau]) for Sarilumab

End point title	Area Under the Serum Concentration Versus Time Curve Calculated Using the Trapezoidal Method During a Dose Interval (AUC[0-tau]) for Sarilumab

End point description:

AUC(0-tau) is defined as area under the serum concentration versus time curve calculated using the trapezoidal method during a dose interval, where dose interval was 2 weeks. Serum concentrations of sarilumab were analyzed using validated enzyme linked immunosorbent assay (ELISA). Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of IMP and have least 1 PK parameter calculated using non compartmental methods following the first (Day 1) or sixth administration (Day 71). Here, 'n' signifies number of subjects with available data at specified category for each arm, respectively.

End point type	Secondary

End point timeframe:

Week 0-2: pre-dose on Day 1, anytime post-dose on Day 3, Day 5, Day 8, Day 12, Day 15; Week 10-12: pre-dose on Day 71, anytime post-dose on Day 73, Day 75, Day 78, Day 82, Day 85

End point values	Sarilumab 150 mg by AID (AID Assessment Phase)	Sarilumab 150 mg by PFS (AID Assessment Phase)	Sarilumab 200 mg by AID (AID Assessment Phase)	Sarilumab 200 mg by PFS (AID Assessment Phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	53	52	56
Units: mg*day/L				
arithmetic mean (standard deviation)				
Week 0-2 (n=39, 34, 34, 41)	131 (± 54.5)	152 (± 76.7)	235 (± 117)	227 (± 94.9)
Week 10-12 (n=44, 40, 36, 38)	205 (± 126)	220 (± 130)	455 (± 294)	405 (± 244)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to the final visit (74 Weeks) regardless of seriousness or relationship to study drug.

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs developed/worsened during'on treatment period' (first dose of IMP in AID phase up to last dose of IMP in extension phase+6 weeks). Safety population(SP) of AID phase: subjects who received at least 1 dose of IMP & SP of extension phase: subjects who continued extension phase & received at least 1 dose of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Sarilumab 150 mg by AID (AID Assessment Phase)

Reporting group description:

Sarilumab 150 mg SC injection q2w administered by AID with one or a combination of non-biologic DMARD for 12 weeks.

Reporting group title	Sarilumab 150 mg by PFS (AID Assessment Phase)

Reporting group description:

Sarilumab 150 mg SC injection q2w administered by PFS with one or a combination of non-biologic DMARD for 12 weeks.

Reporting group title	Sarilumab 200 mg by AID (AID Assessment Phase)

Reporting group description:

Sarilumab 200 mg SC injection q2w administered by AID with one or a combination of non-biologic DMARD for 12 weeks.

Reporting group title	Sarilumab 200 mg by PFS (AID Assessment Phase)

Reporting group description:

Sarilumab 200 mg SC injection q2w administered by PFS with one or a combination of non-biologic DMARD for 12 weeks.

Reporting group title	Sarilumab 150 mg by PFS (Extension Phase)

Reporting group description:

Subjects who completed 12 week AID assessment phase received Sarilumab 150 mg SC injection q2w administered by PFS with one or a combination of non-biologic DMARD for 52 weeks.

Serious adverse events	Sarilumab 150 mg by AID (AID Assessment Phase)	Sarilumab 150 mg by PFS (AID Assessment Phase)	Sarilumab 200 mg by AID (AID Assessment Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	3 / 52 (5.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic Carcinoma Metastatic			

subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis Superficial			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Reproductive system and breast disorders			
Endometrial Hyperplasia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Rheumatoid Lung			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Injury, poisoning and procedural complications			
Femoral Neck Fracture			

subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Traumatic Arthritis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Cardiac disorders			
Coronary Artery Occlusion			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Wolff-Parkinson-White Syndrome			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Nervous system disorders			
Transient Ischaemic Attack			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Vertebrobasilar Insufficiency			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Eye disorders			
Cataract			

subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Gastrointestinal disorders			
Small Intestinal Obstruction			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Vomiting			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Lumbar Spinal Stenosis			

subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Osteoarthritis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Arthritis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bursitis Infective Staphylococcal			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Erysipelas			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Pneumonia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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
Urinary Tract Infection			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	0 / 52 (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	Sarilumab 200 mg	Sarilumab 150 mg	

	by PFS (AID Assessment Phase)	by PFS (Extension Phase)	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 56 (7.14%)	19 / 188 (10.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 56 (1.79%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis Superficial			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial Hyperplasia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid Lung			

subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral Neck Fracture			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Arthritis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary Artery Occlusion			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wolff-Parkinson-White Syndrome			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient Ischaemic Attack			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar Insufficiency			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small Intestinal Obstruction			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	0 / 56 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 188 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
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			
Arthralgia			

subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid Arthritis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bursitis Infective Staphylococcal			
subjects affected / exposed	0 / 56 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 56 (1.79%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
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	Sarilumab 150 mg by AID (AID Assessment Phase)	Sarilumab 150 mg by PFS (AID Assessment Phase)	Sarilumab 200 mg by AID (AID Assessment Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 56 (51.79%)	21 / 53 (39.62%)	24 / 52 (46.15%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 56 (1.79%)	1 / 53 (1.89%)	5 / 52 (9.62%)
occurrences (all)	1	1	5
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 56 (0.00%)	0 / 53 (0.00%)	2 / 52 (3.85%)
occurrences (all)	0	0	2
Contusion			
subjects affected / exposed	3 / 56 (5.36%)	0 / 53 (0.00%)	0 / 52 (0.00%)
occurrences (all)	4	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 56 (3.57%)	1 / 53 (1.89%)	3 / 52 (5.77%)
occurrences (all)	2	2	3
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	3 / 56 (5.36%)	2 / 53 (3.77%)	0 / 52 (0.00%)
occurrences (all)	5	2	0
Neutropenia			
subjects affected / exposed	10 / 56 (17.86%)	9 / 53 (16.98%)	6 / 52 (11.54%)
occurrences (all)	15	16	8
Thrombocytopenia			
subjects affected / exposed	4 / 56 (7.14%)	1 / 53 (1.89%)	2 / 52 (3.85%)
occurrences (all)	4	1	2
General disorders and administration site conditions			

Injection Site Erythema			
subjects affected / exposed	2 / 56 (3.57%)	2 / 53 (3.77%)	4 / 52 (7.69%)
occurrences (all)	4	3	8
Injection Site Pruritus			
subjects affected / exposed	1 / 56 (1.79%)	2 / 53 (3.77%)	0 / 52 (0.00%)
occurrences (all)	2	3	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 56 (7.14%)	1 / 53 (1.89%)	1 / 52 (1.92%)
occurrences (all)	4	1	1
Nasopharyngitis			
subjects affected / exposed	4 / 56 (7.14%)	1 / 53 (1.89%)	1 / 52 (1.92%)
occurrences (all)	4	1	1
Pharyngitis			
subjects affected / exposed	5 / 56 (8.93%)	0 / 53 (0.00%)	1 / 52 (1.92%)
occurrences (all)	5	0	1
Sinusitis			
subjects affected / exposed	1 / 56 (1.79%)	3 / 53 (5.66%)	0 / 52 (0.00%)
occurrences (all)	1	3	0
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 56 (5.36%)	2 / 53 (3.77%)	1 / 52 (1.92%)
occurrences (all)	3	3	1
Urinary Tract Infection			
subjects affected / exposed	2 / 56 (3.57%)	2 / 53 (3.77%)	2 / 52 (3.85%)
occurrences (all)	2	2	2

Non-serious adverse events	Sarilumab 200 mg by PFS (AID Assessment Phase)	Sarilumab 150 mg by PFS (Extension Phase)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 56 (41.07%)	83 / 188 (44.15%)	
Investigations			
Alanine Aminotransferase Increased			

subjects affected / exposed	1 / 56 (1.79%)	9 / 188 (4.79%)	
occurrences (all)	1	9	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	3 / 56 (5.36%)	8 / 188 (4.26%)	
occurrences (all)	3	12	
Contusion			
subjects affected / exposed	0 / 56 (0.00%)	3 / 188 (1.60%)	
occurrences (all)	0	7	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 56 (3.57%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	4 / 56 (7.14%)	12 / 188 (6.38%)	
occurrences (all)	5	21	
Thrombocytopenia			
subjects affected / exposed	1 / 56 (1.79%)	3 / 188 (1.60%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	4 / 56 (7.14%)	7 / 188 (3.72%)	
occurrences (all)	14	33	
Injection Site Pruritus			
subjects affected / exposed	4 / 56 (7.14%)	5 / 188 (2.66%)	
occurrences (all)	5	25	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 56 (5.36%)	0 / 188 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 56 (1.79%)	8 / 188 (4.26%)	
occurrences (all)	1	9	
Nasopharyngitis			
subjects affected / exposed	2 / 56 (3.57%)	4 / 188 (2.13%)	
occurrences (all)	2	4	
Pharyngitis			
subjects affected / exposed	1 / 56 (1.79%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Sinusitis			
subjects affected / exposed	1 / 56 (1.79%)	12 / 188 (6.38%)	
occurrences (all)	1	13	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 56 (5.36%)	25 / 188 (13.30%)	
occurrences (all)	4	31	
Urinary Tract Infection			
subjects affected / exposed	2 / 56 (3.57%)	10 / 188 (5.32%)	
occurrences (all)	2	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2014	Following amendments were made: - Secondary endpoints ("use-related errors" were removed, "Failed drug deliveries" were added), as well as subject diary questions related to the AID user assessment were modified. - Caregivers were allowed to administer the investigational product under exceptional circumstances. - Analgesics with no anti-inflammatory properties were added to the permitted concomitant medication. - The reference to the Committee for Medicinal Products for Human Use (CHMP) guideline for supine blood pressure measurement was removed. - The objectives and the endpoints of the study were reordered.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported