Clinical trial results:
A Randomized, Double-Masked and Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sarilumab Administered Subcutaneously Every 2 Weeks in Patients with Non-Infectious, Intermediate, Posterior or Pan-Uveitis (NIU)

Summary

EudraCT number	2012-004845-34
Trial protocol	CZ DE IT ES
Global end of trial date	19 April 2016

Results information

Result version number	v1 (current)
This version publication date	04 May 2017
First version publication date	04 May 2017

Trial information

Trial identification

Sponsor protocol code	ACT13480

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01900431
WHO universal trial number (UTN)	U1111-1130-6500

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 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 200 mg sarilumab every 2 weeks (q2w) at Week 16 in subjects with NIU.

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:

Following background therapy was given to subjects during the study: Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.

Evidence for comparator: -

Actual start date of recruitment	30 October 2013
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	Spain: 7
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Turkey: 16
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	58
EEA total number of subjects	31

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)	54
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 18 centers in 6 countries. A total of 82 subjects were screened between 30 October 2013 and 17 March 2015 of whom 58 subjects were randomized and 24 were screen failures. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

Subjects were randomized in 2:1 ratio (Sarilumab : Placebo) and treated for 16 weeks during principal treatment period (Part A), 30 responders treated up to Week 50 with same dose during extension treatment period (Part B) while 10 non-responders and 11 subjects (not completed Part A) treated with open label treatment up to Week 50 (Part C).

Period 1

Period 1 title	Principal Treatment Period (Part A)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Part A)

Arm description:

Placebo (for Sarilumab) subcutaneous (SC) injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.

Arm type	Placebo
Investigational medicinal product name	Placebo (for Sarilumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo (for Sarilumab) as SC injection in the abdomen, thigh or upper arm.

Arm title	Sarilumab 200 mg q2w (Part A)

Arm description:

Sarilumab 200 mg SC injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.

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

Dosage and administration details:

Sarilumab as SC injection in the abdomen, thigh or upper arm.

Number of subjects in period 1	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)
Started	20	38
Completed	13	28
Not completed	7	10
Other than specified above	-	1
Adverse Event	1	3
Lack of efficacy	6	6

Period 2

Period 2 title	Extended Treatment Period (Part B)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Part B)

Arm description:

During extension treatment period (Part B), responders defined as subjects with decrease in vitreous haze (VH) ≥2; or corticosteroids dose <10 mg/day at Week 16 continued with placebo SC injection q2w as per principal treatment period (Part A) up to Week 50.

Arm type	Placebo
Investigational medicinal product name	Placebo (for Sarilumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo (for Sarilumab) as SC injection in the abdomen, thigh or upper arm.

Arm title	Sarilumab 200 mg q2w (Part B)

Arm description:

During extension treatment period (Part B), responders defined as subjects with decrease in vitreous haze (VH) ≥2; or corticosteroids dose <10 mg/day at Week 16 continued with Sarilumab 200 mg SC injection q2w as per principal treatment period (Part A) up to Week 50.

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

Dosage and administration details:

Sarilumab as SC injection in the abdomen, thigh or upper arm.

Number of subjects in period 2[1]	Placebo (Part B)	Sarilumab 200 mg q2w (Part B)
Started	8	22
Completed	7	12
Not completed	1	10
Other than specified above	-	1
Adverse Event	-	2
Lack of efficacy	1	7

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: Out of 41 subjects who completed Part A, 30 responders (8 Placebo, 22 Sarilumab) entered Part B.

Period 3

Period 3 title	Open-Label Treatment Period (Part C)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Sarilumab 200 mg q2w : Open-Label Treatment (Part C)

Arm description:

During Open-Label Treatment Period (Part C), Non-responders (defined as no decrease in VH ≥2 steps and corticosteroids dose missing at Week 16) and non-completers (not-completed) Part A were treated with Sarilumab 200 mg SC injection q2w for 34 weeks as open-label treatment in open-label treatment period (Part C) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.

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

Dosage and administration details:

Sarilumab as SC injection in the abdomen, thigh or upper arm.

Number of subjects in period 3[2]	Sarilumab 200 mg q2w : Open-Label Treatment (Part C)
Started	10
Completed	13
Not completed	8
Adverse Event	2
Withdrawal by Subject	3
Lack of efficacy	3

Joined	11
Non-completers from Part A	11

Notes:

[2] - 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: Total 21 subjects entered Part C. 10 non-responders as started (5 placebo, 5 Sarilumab) and 11 non-completers (Also non-responders) from Part A as joined (6 placebo, 5 Sarilumab).

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (Part A)
Reporting group description:	
Placebo (for Sarilumab) subcutaneous (SC) injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.	
Reporting group title	Sarilumab 200 mg q2w (Part A)
Reporting group description:	
Sarilumab 200 mg SC injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.	

Reporting group values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)	Total
Number of subjects	20	38	58
Age categorical			
Age categorical is not provided as it was presented in Population of trial subjects under Trial information section.			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	41.5	39.3	
standard deviation	± 13	± 15.3	-
Gender categorical			
Units: Subjects			
Female	13	23	36
Male	7	15	22

End points

End points reporting groups

Reporting group title	Placebo (Part A)

Reporting group description:

Placebo (for Sarilumab) subcutaneous (SC) injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.

Reporting group title	Sarilumab 200 mg q2w (Part A)

Reporting group description:

Sarilumab 200 mg SC injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.

Reporting group title	Placebo (Part B)

Reporting group description:

During extension treatment period (Part B), responders defined as subjects with decrease in vitreous haze (VH) ≥2; or corticosteroids dose <10 mg/day at Week 16 continued with placebo SC injection q2w as per principal treatment period (Part A) up to Week 50.

Reporting group title	Sarilumab 200 mg q2w (Part B)

Reporting group description:

During extension treatment period (Part B), responders defined as subjects with decrease in vitreous haze (VH) ≥2; or corticosteroids dose <10 mg/day at Week 16 continued with Sarilumab 200 mg SC injection q2w as per principal treatment period (Part A) up to Week 50.

Reporting group title	Sarilumab 200 mg q2w : Open-Label Treatment (Part C)

Reporting group description:

During Open-Label Treatment Period (Part C), Non-responders (defined as no decrease in VH ≥2 steps and corticosteroids dose missing at Week 16) and non-completers (not-completed) Part A were treated with Sarilumab 200 mg SC injection q2w for 34 weeks as open-label treatment in open-label treatment period (Part C) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.

Subject analysis set title	Sarilumab 200 mg q2w (Part A + Part B)
Subject analysis set type	Per protocol

Subject analysis set description:

Sarilumab 200 mg SC injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice. Responders continued with the same treatment regimen up to Week 50 during extension treatment period (Part B).

Primary: Percentage of Subjects With at Least 2-step Reduction in Vitreous Haze (VH) or Prednisone Dose <10 mg/Day at Week 16

End point title	Percentage of Subjects With at Least 2-step Reduction in Vitreous Haze (VH) or Prednisone Dose <10 mg/Day at Week 16

End point description:

At least 2-step reduction in VH per central review from baseline was evaluated on Miami 9-step scale. VH is the obscuration of fundus by vitreous cells and protein exudation. Each of the 9-step scale (from grade 0 [low opacity] to 8 [more opacity]) images (in increasing order of opacity) are equivalent to approximately 0.3 log units of degradation in visual acuity based on the Bangerter calibration. Subjects with prednisone dose <10 mg/day (or equivalent oral corticosteroid) were also evaluated. Modified intent-to-treat population (mITT) included all randomized subjects who received at least 1 injection analyzed according to the group to which the subject was allocated by the randomization schedule. Modified multiple imputation approach was used on VH missing adjudicated scores.

End point type	Primary

End point timeframe:

Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	38		
Units: Percentage of subjects				
number (not applicable)	30	46.1		

Statistical analyses

Statistical analysis title	Sarilumab 200 mg q2w (Part A) vs Placebo (Part A)

Statistical analysis description:

Analysis was performed using combined estimate for odds ratio obtained by combining the log-transformation of odds ratio from Cochran Mantel-Haenszel (CMH) analyses of the different imputed datasets, using Rubin's formulae, and then by back-transforming the combined estimate. The CMH analyses were adjusted for randomization stratification factor VH level (VH >= 4 versus VH<4).

Comparison groups	Placebo (Part A) v Sarilumab 200 mg q2w (Part A)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2354 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	5.6

Notes:

[1] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in VH Scale at Week 16

End point title	Change From Baseline in VH Scale at Week 16

End point description:

Change from baseline in VH scale was evaluated on Miami 9-step scale. VH is the obscuration of fundus by vitreous cells and protein exudation. Each of the 9-step scale (from grade 0 [low opacity] to 8 [more opacity]) images (in increasing order of opacity) were equivalent to approximately 0.3 log units of degradation in visual acuity based on the Bangerter calibration. Least squares (LS) mean was calculated using mixed model for repeated measurements (MMRM) model with treatment groups, visits and visit-by- treatment groups interaction as fixed categorical effects as well as fixed continuous covariate of baseline adjudicated VH. Analysis was performed on mITT population. Number of subjects analyzed = subjects with VH assessment at baseline and post-baseline visits.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	28		
Units: units on a scale				
least squares mean (standard error)	-0.1 (± 0.23)	-0.9 (± 0.16)		

Statistical analyses

Statistical analysis title	Sarilumab 200 mg q2w (Part A) vs Placebo (Part A)

Statistical analysis description:

Analysis was performed using mixed effect model with repeated measures (MMRM) with treatment groups, visits and visit-by-treatment groups interaction as fixed categorical effects, as well as, fixed continuous covariate of baseline adjudicated VH.

Comparison groups	Sarilumab 200 mg q2w (Part A) v Placebo (Part A)
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0127 [2]
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.223
upper limit	-0.262
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects With Anterior Chamber (AC) Cell Score = 0 or At Least 2-step Reduction in Score at Week 16

End point title	Percentage of Subjects With Anterior Chamber (AC) Cell Score = 0 or At Least 2-step Reduction in Score at Week 16

End point description:

Subjects with AC cell score = 0 or with ≥2 step reduction from baseline at Week 16 were evaluated. Slit lamp examinations were conducted at each visit to assess AC cell count. The number of AC cells observed within a 1 mm × 1 mm slit beam was used to determine the grade according to the Standardization of Uveitis Nomenclature (SUN) criteria: grade 0 = no cells; grade +0.5 = 1 - 5 cells; grade +1 = 6 - 25 cells; grade +2= 26 - 50 cells; grade +3 = too many to count. Analysis was performed on mITT population. Number of subjects analyzed = subjects with non-missing AC cell score at Week 16.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	29		
Units: Percentage of subjects				
number (not applicable)	86.7	86.2		

Statistical analyses

Statistical analysis title	Sarilumab 200 mg q2w (Part A) vs Placebo (Part A)

Statistical analysis description:

Analysis was performed using common odds ratio which came from CMH analysis adjusted for randomization stratification factor VH level (VH>=4 versus VH<4).

Comparison groups	Placebo (Part A) v Sarilumab 200 mg q2w (Part A)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.11
upper limit	6.093

Notes:

[3] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in Best Corrected Visual Acuity (BCVA) Score at Week 16

End point title	Change From Baseline in Best Corrected Visual Acuity (BCVA) Score at Week 16

End point description:

BCVA score is based on the number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart assessed at a starting distance of 4 meters, and then at 1 meter. The range of ETDRS is 0 to 100 letters. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). An increase in the number of letters read correctly means that vision has improved. LS mean was calculated using MMRM model with treatment groups, randomization strata of VH level (<4, >=4), visits and visit-by-treatment groups interaction as fixed categorical effects, as well as, fixed continuous covariate of baseline BCVA. Analysis was performed on mITT population. Number of subjects analyzed = subjects with BCVA score assessment at baseline and post-baseline visits.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	29		
Units: units on a scale				
least squares mean (standard error)	3.5 (± 1.84)	9.3 (± 1.36)		

Statistical analyses

Statistical analysis title	Sarilumab 200 mg q2w (Part A) vs Placebo (Part A)

Statistical analysis description:

Analysis was performed using MMRM model with treatment groups, randomization strata of VH level (<4, >=4), visits and visit-by-treatment groups interaction as fixed categorical effects, as well as, fixed continuous covariate of baseline BCVA.

Comparison groups	Placebo (Part A) v Sarilumab 200 mg q2w (Part A)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0153 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	5.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.99
upper limit	9.67
Variability estimate	Standard error of the mean
Dispersion value	2.26

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in Central Retinal Thickness (CRT) At Week 16

End point title	Change From Baseline in Central Retinal Thickness (CRT) At Week 16

End point description:

CRT was measured by spectral domain optical coherence tomography (SD-OCT), a non-invasive diagnostic system providing high-resolution imaging sections of the retina. All images were transmitted to the central reading center. SD-OCT was performed in the study eye after pupil dilation. LS mean was calculated using MMRM model with treatment groups, randomization strata of VH level (<4, >=4), visits and visit-by-treatment groups interaction as fixed categorical effects, as well as, fixed continuous covariate of baseline CRT. Analysis was performed on mITT population. Number of subjects analyzed = subjects with CRT assessment at baseline and post-baseline visits.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	29		
Units: µm (microns)				
least squares mean (standard error)	-8.9 (± 11.46)	-35.4 (± 8.36)		

Statistical analyses

Statistical analysis title	Sarilumab 200 mg q2w (Part A) vs Placebo (Part A)

Statistical analysis description:

Analysis was performed using MMRM model with treatment groups, randomization strata of VH level (<4, >=4), visits and visit-by-treatment groups interaction as fixed categorical effects, as well as, fixed continuous covariate of baseline CRT (Automatic measurement from SD-OCT).

Comparison groups	Placebo (Part A) v Sarilumab 200 mg q2w (Part A)
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0683 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-26.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-50.41
upper limit	-2.68
Variability estimate	Standard error of the mean
Dispersion value	14.2

Notes:

[5] - Threshold for significance at 0.05 level.

Secondary: Percent Change From Baseline in CRT at Week 16

End point title	Percent Change From Baseline in CRT at Week 16

End point description:

CRT was measured by SD-OCT, a non-invasive diagnostic system providing high-resolution imaging sections of the retina. All images were transmitted to the central reading center. SD-OCT was performed in the study eye after pupil dilation. LS mean was calculated using MMRM model with treatment groups, randomization strata of VH level (<4, >=4), visits and visit-by-treatment groups interaction as fixed categorical effects, as well as, fixed continuous covariate of baseline CRT. Analysis was performed on mITT population. Number of subjects analyzed = subjects with CRT assessment at baseline and post-baseline visits.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	29		
Units: percent change				
least squares mean (standard error)	0 (± 2.9)	-6.4 (± 2.15)		

Statistical analyses

Statistical analysis title	Sarilumab 200 mg q2w (Part A) vs Placebo (Part A)

Statistical analysis description:

Analysis was performed using MMRM model with treatment groups, randomization strata of VH level (<4, >=4), visits and visit-by-treatment groups interaction as fixed categorical effects, as well as, fixed continuous covariate of baseline CRT (Automatic measurement from SD-OCT).

Comparison groups	Placebo (Part A) v Sarilumab 200 mg q2w (Part A)
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0825 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-6.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.374
upper limit	-0.35
Variability estimate	Standard error of the mean
Dispersion value	3.55

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects With CRT Thickness <300 Microns at Week 16

End point title	Percentage of Subjects With CRT Thickness <300 Microns at Week 16

End point description:

This endpoint was replaced by the percent change from baseline in CRT at Week 16 as this is more clinically relevant. Zero subject was analyzed.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: percentage of subjects				
number (not applicable)				

Notes:

[7] - Zero subject analyzed as this endpoint was replaced with another more clinically relevant endpoint.

[8] - Zero subject analyzed as this endpoint was replaced with another more clinically relevant endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without Retinal Vessel Leakage on Fluorescein Angiography (FA) at Week 16

End point title	Percentage of Subjects Without Retinal Vessel Leakage on Fluorescein Angiography (FA) at Week 16

End point description:

Analysis of this endpoint was not performed as no retinal vessel leakage data was collected at Week 16. Zero subjects were analyzed.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: percentage of subjects				
number (not applicable)				

Notes:

[9] - No retinal vessel leakage data was collected at Week 16.

[10] - No retinal vessel leakage data was collected at Week 16.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Prednisone Dose of ≤ 5 mg/Day (or Equivalent Oral Corticosteroid) at Week 16

End point title	Percentage of Subjects With Prednisone Dose of ≤ 5 mg/Day (or Equivalent Oral Corticosteroid) at Week 16

End point description:

Subjects with prednisone dose ≤5mg/day (or equivalent oral corticosteroid) at Week 16 were evaluated. Analysis was performed on mITT population. Number of subjects analyzed = subjects with non-missing data for prednisone (or equivalent oral corticosteroid) dose at Week 16.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo (Part A)	Sarilumab 200 mg q2w (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	29		
Units: percentage of subjects				
number (not applicable)	40	41.4		

Statistical analyses

Statistical analysis title	Sarilumab 200 mg q2w (Part A) vs Placebo (Part A)

Statistical analysis description:

Analysis was performed using common odds ratio which came from CMH analysis adjusted for randomization stratification factor VH level (VH>=4 versus VH<4).

Comparison groups	Placebo (Part A) v Sarilumab 200 mg q2w (Part A)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.306
upper limit	3.845

Notes:

[11] - Threshold for significance at 0.05 level.

Secondary: Pharmacokinetics (PK) Assessment: Serum Functional Sarilumab Concentration

End point title	Pharmacokinetics (PK) Assessment: Serum Functional Sarilumab Concentration

End point description:

Serum functional (unbound) sarilumab concentrations were determined using enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantification (LLOQ) of 294 ng/mL. Concentrations below LLOQ were set to zero for samples at pre-dose. Post-treatment concentrations below LLOQ were replaced by LLOQ/2. The samples were considered non-eligible for analysis if previous dosing time was <11 days or >17 days before sampling time for every other week regimens. PK population: all subjects who received at least one dose or part of a dose of investigational medicinal product (IMP) with at least one post-dose, non-missing serum concentration value & were analyzed according to treatment actually received. Data of this endpoint was planned to be analyzed for Sarilumab 200 mg q2w arm in Part A & B only. Here, 'n' signifies number of subjects with available data for specified category. 99999 represents that only one subject was analyzed at EOS, standard deviation could not be calculated.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 (Baseline), Week 2, 4, 8, 12, 16, 24, 36, 52, and end of study (EOS) (Week 56)

End point values	Sarilumab 200 mg q2w (Part A + Part B)			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: ng/mL				
arithmetic mean (standard deviation)				
At Baseline (n=37)	0 (± 0)			
At Week 2 (n=29)	7383.3 (± 6547.1)			
At Week 4 (n=32)	9876.6 (± 8262.9)			
At Week 8 (n=31)	15958.9 (± 12813.1)			
At Week 12 (n=26)	19705.2 (± 15480.9)			
At Week 16 (n=26)	19598.4 (± 17280.8)			
At Week 24 (n=19)	22406.8 (± 14584.2)			
At Week 36 (n=14)	24375.4 (± 19121.7)			
At Week 52 (n=5)	25046 (± 17870.7)			
EOS (Week 56) (n=1)	1730 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (6 weeks after the last treatment administration [Week 56]) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (time from the first injection of IMP to the last injection of IMP + 6 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo (Part A + Part B)

Reporting group description:

Placebo (for Sarilumab) SC injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice. Responders continued with the same treatment regimen up to Week 50 during extension treatment period (Part B).

Reporting group title	Sarilumab 200mg q2w (Part A + Part B)

Reporting group description:

Sarilumab 200 mg SC injection q2w for 16 weeks during principal treatment period (Part A) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice. Responders continued with the same treatment regimen up to Week 50 during extension treatment period (Part B).

Reporting group title	Sarilumab 200 mg q2w : Open-Label Treatment (Part C)

Reporting group description:

Non-responders and non-completers observed in Part A were proposed to be treated with Sarilumab 200 mg SC injection q2w for 34 weeks as open-label treatment in open-label treatment period (Part C) with background therapy of Prednisone (or equivalent oral corticosteroid) ≥15 mg/day and <80 mg/day as single therapy or in combination with MTX 10 to 25 mg/week and folic acid per local prescribing practice.

Serious adverse events	Placebo (Part A + Part B)	Sarilumab 200mg q2w (Part A + Part B)	Sarilumab 200 mg q2w : Open-Label Treatment (Part C)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	5 / 38 (13.16%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Intraocular Pressure Increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 38 (0.00%)	0 / 21 (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
Liver Function Test Increased			

subjects affected / exposed	0 / 20 (0.00%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 38 (0.00%)	0 / 21 (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
Surgical and medical procedures			
Abortion Induced			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Staphylococcal Sepsis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo (Part A + Part B)	Sarilumab 200mg q2w (Part A + Part B)	Sarilumab 200 mg q2w : Open-Label Treatment (Part C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 20 (65.00%)	25 / 38 (65.79%)	15 / 21 (71.43%)
Vascular disorders			
Behcet's Syndrome			
subjects affected / exposed	1 / 20 (5.00%)	1 / 38 (2.63%)	3 / 21 (14.29%)
occurrences (all)	1	1	4
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	3 / 38 (7.89%)	0 / 21 (0.00%)
occurrences (all)	0	4	0
Injection Site Bruising			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Injection Site Swelling			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	10	0
Pyrexia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 38 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 20 (15.00%)	4 / 38 (10.53%)	0 / 21 (0.00%)
occurrences (all)	3	4	0
Psychiatric disorders			
Middle Insomnia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Investigations			
Alanine Aminotransferase Increased			

subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	7	0
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	4 / 20 (20.00%)	3 / 38 (7.89%)	1 / 21 (4.76%)
occurrences (all)	5	3	1
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	3 / 38 (7.89%)	0 / 21 (0.00%)
occurrences (all)	0	4	0
Headache			
subjects affected / exposed	2 / 20 (10.00%)	4 / 38 (10.53%)	2 / 21 (9.52%)
occurrences (all)	2	5	2
Hypoaesthesia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 20 (0.00%)	4 / 38 (10.53%)	1 / 21 (4.76%)
occurrences (all)	0	5	1
Eye disorders			
Cataract			
subjects affected / exposed	1 / 20 (5.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Retinal Infiltrates			
subjects affected / exposed	1 / 20 (5.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Uveitis			
subjects affected / exposed	2 / 20 (10.00%)	6 / 38 (15.79%)	1 / 21 (4.76%)
occurrences (all)	3	6	1
Visual Impairment			
subjects affected / exposed	1 / 20 (5.00%)	0 / 38 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2

Gastrointestinal disorders			
Aphthous Ulcer			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	2 / 21 (9.52%)
occurrences (all)	0	3	2
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 38 (2.63%)	3 / 21 (14.29%)
occurrences (all)	0	2	4
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	3 / 38 (7.89%)	1 / 21 (4.76%)
occurrences (all)	1	4	1
Hepatobiliary disorders			
Hepatic Steatosis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 20 (10.00%)	1 / 38 (2.63%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Ear Infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Influenza			
subjects affected / exposed	0 / 20 (0.00%)	4 / 38 (10.53%)	2 / 21 (9.52%)
occurrences (all)	0	4	2
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	2 / 38 (5.26%)	6 / 21 (28.57%)
occurrences (all)	1	2	8
Upper Respiratory Tract Infection			

subjects affected / exposed	1 / 20 (5.00%)	2 / 38 (5.26%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Urinary Tract Infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 38 (5.26%)	2 / 21 (9.52%)
occurrences (all)	0	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2013	Following were the changes: • Facilitate the enrollment of subjects, with fewer constraints, on the dose of corticosteroids as background therapy before randomization. • Added a clear definition of worsening and to consider sensitivity analysis. • Revised and added treatment failure and non-responder definitions. • Address the comments from some Ethic Committees regarding the continuation of non-responder subjects in the optional open-label treatment part of the study (part C, open-label administration of sarilumab) without breaking the randomization code. • Considered more appropriate rules for corticosteroid tapering depending on the activity status of the disease at study entry (active disease and recently active disease) in order to prevent inducing disease flare ups that may be a consequence of tapering the corticosteroid dose too fast. • Revised the safety follow-up of subjects receiving sarilumab in the optional open-label part C with the addition of safety visits at Week 6, Week 10, and Week 14 and to include additional blood samples to measure antinuclear antibodies and anti-ds-DNA antibody in order to assess the effect of sarilumab to induce autoimmune disorders, more specifically systemic lupus erythematosus. • Added specific ocular AEs on the list of AEs of Special Interest list.
09 September 2014	Following were the changes: • Added other conventional standard of care immunomodulatory therapies to methotrexate and corticosteroids as therapies allowed at study entry and during the study treatment period. • Facilitated and hastened the enrollment of subjects by removing the restriction of the number of subjects in the VH <4 and VH ≥4 categories. • Facilitated enrollment by allowing subjects presenting with more severe 'active disease' that was not adequately controlled by the existing standard of care. • Revisions were implemented in order to ensure consistency with the ongoing rheumatoid arthritis clinical trials with Sarilumab including infliximab and etanercept washout periods, management of alanine aminotransferase elevation, updates to laboratories values exclusion criterion, changes to blood pressure measurements, and chest X-ray only mandatory at screening or within the 90 days preceding screening. • The role of the Reading Center in the selection of the subjects was clarified. • The selection of the study eye was clarified. • Steroids tapering could begin as early as Visit 4 (ie, after 2 treatment injections). • Exclusion criterion, E11 (glaucoma treatment) and E35 (magnetic resonance imaging in intermediate uveitis subjects) were rewritten to be clearer. • The flow chart was updated in order to clarify some items.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported