Clinical trial results:
A Randomized, Double-blind, Parallel, Placebo-controlled Study Assessing the Efficacy and Safety of Sarilumab Added to Non-biologic DMARD Therapy in Patients With Rheumatoid Arthritis Who Are Inadequate Responders to or Intolerant of TNF- Antagonists

Summary

EudraCT number	2011-003538-16
Trial protocol	LT CZ HU ES DE PT GR AT IT SK PL
Global end of trial date	23 March 2015

Results information

Result version number	v1
This version publication date	07 April 2016
First version publication date	07 April 2016

Trial information

Trial identification

Sponsor protocol code	EFC10832

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709578
WHO universal trial number (UTN)	U1111-1115-8466

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	22 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that sarilumab added to non-biologic disease modifying anti-rheumatic drugs (DMARDs) was effective in reducing the signs and symptoms at Week 24 and improving physical function at Week 12 in subjects with active rheumatoid arthritis (RA) who were inadequate responders to or intolerant of tumor necrosis factor alpha (TNF-α) antagonists.

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 continued to receive regular treatment with at least one of the permitted background therapies that included hydroxychloroquine, methotrexate, sulfasalazine, leflunomide which were dispensed according to the local practice.

Evidence for comparator: -

Actual start date of recruitment	29 October 2012
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	Canada: 2
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Colombia: 19
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Ecuador: 11
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Guatemala: 13
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Lithuania: 5

Country: Number of subjects enrolled	Mexico: 62
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Peru: 49
Country: Number of subjects enrolled	Poland: 59
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	United States: 147
Country: Number of subjects enrolled	Argentina: 52
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Brazil: 13
Worldwide total number of subjects	546
EEA total number of subjects	131

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)	456
From 65 to 84 years	88
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 240 centres in 27 countries. A total of 1224 subjects were screened between 29 October 2012 and 7 August 2014, of whom 546 subjects were randomized and 678 were screen failures. Screen failures were mainly due to failure to meet inclusion criteria.

Pre-assignment

Screening details:

Subjects were randomized 1:1:1 (placebo q2w: sarilumab 150 mg q2w: sarilumab 200 mg q2w) via a centralized randomization system using an interactive voice response system stratified by region and number of previous anti-tumor necrosis factor therapy (1 versus >1).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo q2w

Arm description:

Placebo matched to sarilumab once every 2 weeks (q2w) was added to one or a combination of the non-biologic DMARD for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
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 matched to sarilumab administered subcutaneously in abdomen, thigh or upper arm.

Arm title	Sarilumab 150 mg q2w

Arm description:

Sarilumab 150 mg q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.

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

Dosage and administration details:

Sarilumab 150 mg administered subcutaneously in abdomen, thigh or upper arm.

Arm title	Sarilumab 200 mg q2w

Arm description:

Sarilumab 200 mg q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.

Arm type	Experimental

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

Dosage and administration details:

Sarilumab 200 mg administered subcutaneously in abdomen, thigh or upper arm.

Number of subjects in period 1	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w
Started	181	181	184
Completed	101	125	133
Not completed	80	56	51
Adverse Event	9	18	17
Rescued and entered in long term safety	63	25	26
Poor compliance to protocol	1	2	1
Other, not related to safety or efficacy	2	7	5
Lack of efficacy	5	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo q2w
Reporting group description:	
Placebo matched to sarilumab once every 2 weeks (q2w) was added to one or a combination of the non-biologic DMARD for 24 weeks.	
Reporting group title	Sarilumab 150 mg q2w
Reporting group description:	
Sarilumab 150 mg q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.	
Reporting group title	Sarilumab 200 mg q2w
Reporting group description:	
Sarilumab 200 mg q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.	

Reporting group values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w
Number of subjects	181	181	184
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 51.9 ± 12.4	 54 ± 11.7	 52.9 ± 12.9
Gender categorical Units: Subjects			
Female	154	142	151
Male	27	39	33

Reporting group values	Total		
Number of subjects	546		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	447		
Male	99		

End points

End points reporting groups

Reporting group title	Placebo q2w
Reporting group description:	
Placebo matched to sarilumab once every 2 weeks (q2w) was added to one or a combination of the non-biologic DMARD for 24 weeks.	
Reporting group title	Sarilumab 150 mg q2w
Reporting group description:	
Sarilumab 150 mg q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.	
Reporting group title	Sarilumab 200 mg q2w
Reporting group description:	
Sarilumab 200 mg q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.	

Primary: Percentage of Subjects Who Achieved at Least 20% Improvement in the American College of Rheumatology (ACR20) Criteria at Week 24

End point title	Percentage of Subjects Who Achieved at Least 20% Improvement in the American College of Rheumatology (ACR20) Criteria at Week 24
End point description:	
ACR responses were assessed with a composite rating scale of the American College of Rheumatology that includes 7 variables: tender joint count (TJC); swollen joint count (SJC); levels of an acute phase reactant (C-reactive Protein levels [CRP]); subject's assessment of pain; subject's global assessment of disease activity; physician's global assessment of disease activity; subject's assessment of physical function (HAQ-DI). ACR20 is defined as achieving at least 20% improvement in both TJC and SJC, and at least 20% improvement in at least 3 of the 5 other assessments of the ACR. Analysis was performed on intent-to-treat (ITT) population included all randomized subjects.	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	181	184	
Units: percentage of subjects				
number (not applicable)	33.7	55.8	60.9	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w
Statistical analysis description:	
A hierarchical testing procedure was used to control type I error rate at 0.05 and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints were reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.025 level.	
Comparison groups	Placebo q2w v Sarilumab 150 mg q2w

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.711
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.73
upper limit	4.247

Notes:

[1] - Threshold for significance at 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.108
upper limit	5.115

Notes:

[2] - Threshold for significance at 0.025 level

Primary: Change From Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 12

End point title	Change From Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 12

End point description:

Physical function was assessed by HAQ-DI. It consisted of at least 2 questions per category, subject reported ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week rated on a 4-point scale where 0 = no difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do. Overall score was the sum of category scores and divided by the number of categories answered, ranging from 0 to 3, where 0 = no disability and 3 = unable to do, high-dependency disability. Least-squares (LS) means and standard errors (SE) at Week 12 were obtained from a mixed-effect model with repeated measures (MMRM) with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline HAQ-DI as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = number of subjects with HAQ-DI assessment at both baseline and Week 12.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	165	171	
Units: units on a scale				
least squares mean (standard error)	-0.26 (± 0.043)	-0.46 (± 0.044)	-0.47 (± 0.043)	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [3]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.318
upper limit	-0.086

Notes:

[3] - Threshold for significance at 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.325
upper limit	-0.095

Notes:

[4] - Threshold for significance at 0.025 level

Secondary: Change From Baseline in Disease Activity Score for 28 Joints -C-Reactive Protein (DAS28-CRP) Score at Week 24

End point title	Change From Baseline in Disease Activity Score for 28 Joints - C-Reactive Protein (DAS28-CRP) Score at Week 24

End point description:

DAS28 is a composite score of 4 variables:TJC (28 joints);SJC (28 joints);General health (GH) assessment by the subject assessed from the ACR (RA) core set questionnaire (subject global assessment) in 100 mm visual analog scale(VAS). Marker of inflammation assessed by the high sensitivity C-reactive protein (hs-CRP) in mg/L. The DAS28 score indicate the current disease activity of the RA. DAS28 total score ranges from 2-10. A DAS28 score above 5.1 means high disease activity, score below 3.2 indicates low disease activity and a score below 2.6 means disease remission. LS means and SE at Week 24 by MMRM with treatment, region, number of previous anti-TNFs,visit,and treatment-by-visit interaction as fixed effects and baseline DAS28-CRP score as a covariate. Analysis was performed on ITT population. Number of subjects analyzed=number of subjects with DAS28-CRP Score at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	126	136	
Units: units on a scale				
least squares mean (standard error)	-1.38 (± 0.119)	-2.35 (± 0.111)	-2.82 (± 0.108)	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.971

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.283
upper limit	-0.658

Notes:

[5] - Threshold for significance at 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.444
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.752
upper limit	-1.135

Notes:

[6] - Threshold for significance at 0.025 level

Secondary: Percentage of Subjects Achieving ACR50 Criteria at Week 24

End point title	Percentage of Subjects Achieving ACR50 Criteria at Week 24

End point description:

ACR responses were assessed with a composite rating scale of the American College of Rheumatology that includes 7 variables: TJC; SJC; levels of an acute phase reactant (CRP level); subject's assessment of pain; subject's global assessment of disease activity; physician's global assessment of disease activity; subject's assessment of physical function (HAQ-DI). ACR50 is defined as achieving at least 50% improvement in both TJC and SJC, and at least 50% improvement in at least 3 of the 5 other assessments of the ACR. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	181	184	
Units: percentage of subjects				
number (not applicable)	18.2	37	40.8	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.958
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.764
upper limit	4.959

Notes:

[7] - Threshold for significance at 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.374
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.045
upper limit	5.566

Notes:

[8] - Threshold for significance was 0.025 level

Secondary: Percentage of Subjects Achieving ACR70 Criteria at Week 24

End point title	Percentage of Subjects Achieving ACR70 Criteria at Week 24

End point description:

ACR responses were assessed with a composite rating scale of the American College of Rheumatology that includes 7 variables: TJC; SJC; levels of an acute phase reactant (CRP level); subject's assessment of pain; subject's global assessment of disease activity; physician's global assessment of disease activity; subject's assessment of physical function (HAQ-DI). ACR70 is defined as achieving at least 70% improvement in both TJC and SJC, and at least 70% improvement in at least 3 of the 5 other assessments of the ACR. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	181	184	
Units: Percentage of subjects				
number (not applicable)	7.2	19.9	16.3	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [9]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.607
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.774
upper limit	7.332

Notes:

[9] - Threshold for significance at 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w

Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056 [10]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.653
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.308
upper limit	5.383

Notes:

[10] - Threshold for significance at 0.025 level

Secondary: Percentage of Subjects Achieving Clinical Remission Score (DAS28-CRP) <2.6 at Week 24

End point title	Percentage of Subjects Achieving Clinical Remission Score (DAS28-CRP) <2.6 at Week 24

End point description:

DAS28 is a composite score that includes 4 variables: TJC (based on 28 joints); SJC (based on 28 joints); GH by the subject assessed from the ACR rheumatoid arthritis core set questionnaire (subject global assessment) in 100 mm VAS; marker of inflammation assessed by hs-CRP in mg/L. The DAS28 provides a number indicating the current activity of the RA. DAS28 total score ranges from 2-10. A DAS28 score above 5.1 means high disease activity, whereas a DAS28 score below 3.2 indicates low disease activity and a DAS28 score below 2.6 means disease remission. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	181	184	
Units: percentage of subjects				
number (not applicable)	7.2	24.9	28.8	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.622
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.339
upper limit	9.132

Notes:

[11] - Threshold for significance at 0.025 level

Statistical analysis title	Copy of Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.801
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.948
upper limit	11.413

Notes:

[12] - Threshold for significance at 0.025 level

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) at Week 24

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) at Week 24

End point description:

CDAI is a composite index constructed to measure clinical remission in RA that does not include a laboratory test, and is a numerical summation of 4 components: TJC (28 joints), SJC (28 joints), Subject's Global Assessment of Disease Activity VAS (in cm), and Physician's Global Assessment of Disease VAS (in cm). Total scores ranges from 0 to 76 with a negative change in CDAI score indicating an improvement in disease activity and a positive change in score indicating a worsening of disease activity. LS means and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline CDAI as a covariate. Analysis was performed on ITT population. Number of subjects analyzed=number of subjects with CDAI assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	127	136	
Units: units on a scale				
least squares mean (standard error)	-16.35 (± 1.195)	-23.65 (± 1.136)	-26.08 (± 1.109)	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-7.306
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.444
upper limit	-4.167

Notes:

[13] - Threshold for significance at 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-9.727

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.833
upper limit	-6.622

Notes:

[14] - Threshold for significance at 0.025 level

Secondary: Change From Baseline in HAQ-DI at Week 24

End point title	Change From Baseline in HAQ-DI at Week 24

End point description:

Physical function was assessed by HAQ-DI. It consisted of at least 2 questions per category, subject reported assessment of ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week rated on a 4-point scale where 0 = no difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do. Overall score was computed as the sum of category scores and divided by the number of categories answered, ranging from 0 to 3, where 0 = no disability and 3 = unable to do, high-dependency disability. LS means and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline HAQ-DI as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = number of subjects with HAQ-DI assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	127	136	
Units: units on a scale				
least squares mean (standard error)	-0.34 (± 0.051)	-0.52 (± 0.049)	-0.58 (± 0.048)	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078 [15]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.183

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.318
upper limit	-0.048

Notes:

[15] - Threshold for significance was 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [16]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.242
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.376
upper limit	-0.109

Notes:

[16] - Threshold for significance was 0.025 level

Secondary: Change From Baseline in 36-Item Short-Form Health Survey (SF-36) Physical Component Summary Scores (PCS) at Week 24

End point title	Change From Baseline in 36-Item Short-Form Health Survey (SF-36) Physical Component Summary Scores (PCS) at Week 24

End point description:

SF-36 a 36-item questionnaire measuring health-related quality of life (HRQL) covering 2 summary measures: PCS and mental component summary (MCS). The SF-36 consists of 8 subscales. The PCS had 4 subscales: physical function, role limitations due to physical problems, pain, and general health perception. The MCS had 4 subscales: vitality, social function, role limitations due to emotional problems, and mental health. Reporting on subscale that have between 2-6 choices per item using Likert-type responses. Summations of item scores give the subscale scores, which range from 0 to 100; zero= worst HRQL, 100=best HRQL. Higher scores indicate better health and well-being. LS mean and SE at Week 24 by MMRM with treatment,region,number of previous anti TNFs,visit,and treatment-by-visit interaction as fixed effects and baseline SF-36 PCS as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with SF-36 PCS assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	123	134	
Units: units on a scale				
least squares mean (standard error)	4.4 (± 0.692)	7.65 (± 0.653)	8.48 (± 0.63)	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [17]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	5.049

Notes:

[17] - Threshold for significance at 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	4.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.305
upper limit	5.846

Notes:

[18] - Threshold for significance at 0.025 level

Secondary: Change From Baseline in SF-36 MCS at Week 24

End point title	Change From Baseline in SF-36 MCS at Week 24

End point description:

SF-36 is 36-item questionnaire measuring HRQL covering PCS and MCS. The SF-36 is of 8 subscales. The PCS is represented by 4 subscales: physical function, role limitations due to physical problems, pain, and general health perception. The MCS is represented by 4 subscales: vitality, social function, role limitations due to emotional problems, and mental health. Subjects self-report on items in a subscale that have between 2-6 choices per item using Likert-type responses. Summations of item scores of the same subscale give the subscale scores, which range from 0to100; zero= worst HRQL, 100=best HRQL. Higher scores indicate better health and well-being. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs,visit and treatment-by-visit interaction as fixed effects and baseline SF-36 MCS as a covariate. Analysis was performed on ITT population. Number of subjects analyzed=subjects with SF-36 MCS assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	123	134	
Units: units on a scale				
least squares mean (standard error)	4.74 (± 0.902)	6.26 (± 0.848)	6.76 (± 0.817)	

Statistical analyses

Statistical analysis title	Placebo q2w vs Sarilumab 150 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 150 mg q2w
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2026 [19]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	1.515
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.818
upper limit	3.848

Notes:

[19] - Threshold for significance at 0.025 level

Statistical analysis title	Placebo q2w vs Sarilumab 200 mg q2w

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo q2w v Sarilumab 200 mg q2w
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0854 [20]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	2.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.282
upper limit	4.309

Notes:

[20] - Threshold for significance at 0.025 level

Secondary: Change From Baseline in the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-fatigue) Score at Week 24

End point title	Change From Baseline in the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-fatigue) Score at Week 24

End point description:

The FACIT-Fatigue is a 13-item questionnaire assessing fatigue where subjects scored each item on a 5-point scale (0-4): 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much. A total score ranging from 0 to 52. A higher score corresponded to a lower level of fatigue. A positive change from baseline score indicates an improvement. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline FACIT-fatigue as a covariate. Analysis was performed on ITT population. Number of Subjects analyzed = number of subjects with FACIT-fatigue score assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	126	136	
Units: units on a scale				
least squares mean (standard error)	6.82 (± 0.863)	9.86 (± 0.802)	10.06 (± 0.778)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning Stiffness VAS at Week 24

End point title	Change From Baseline in Morning Stiffness VAS at Week 24

End point description:

RA is associated with stiffness of joints, especially in the morning after prolonged stationery state. The degree of stiffness can be an indicator of disease severity. The severity of morning stiffness was assessed on a VAS scale from 0 mm (no problem) to 100 mm (major problem). LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline Morning Stiffness as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = number of subjects with morning stiffness VAS assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	127	136	
Units: units on a scale				
least squares mean (standard error)	-21.66 (± 2.39)	-32.3 (± 2.213)	-33.79 (± 2.148)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity Survey - Rheumatoid Arthritis (WPS-RA) at Week 24: Work Days Missed Due to RA

End point title	Change From Baseline in Work Productivity Survey - Rheumatoid Arthritis (WPS-RA) at Week 24: Work Days Missed Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of work days missed in the last month by the subject was reported. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	43	45	
Units: days				
least squares mean (standard error)	-2.01 (± 0.458)	-2.87 (± 0.438)	-3.19 (± 0.447)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 24: Days With Work Productivity Reduced by ≥ 50% Due to RA

End point title	Change From Baseline in WPS-RA at Week 24: Days With Work Productivity Reduced by ≥ 50% Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of work days with reduced productivity by ≥ 50% in the last month by the subject was reported. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed=subjects with WPS-RA individual items assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	43	45	
Units: days				
least squares mean (standard error)	-3.64 (± 0.589)	-4.26 (± 0.521)	-4.34 (± 0.535)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 24: Rate of RA Interference With Work Productivity

End point title	Change From Baseline in WPS-RA at Week 24: Rate of RA Interference With Work Productivity

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer administered and

was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Interference in the last month with work productivity is measured on a scale that ranges from 0 (no interference) to 10 (complete interference). LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	42	45	
Units: units on a scale				
least squares mean (standard error)	-16.32 (± 4.186)	-24.22 (± 3.719)	-27.27 (± 3.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 24: House Work Days Missed Due to RA

End point title	Change From Baseline in WPS-RA at Week 24: House Work Days Missed Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of days with no household work in the last month by the subject was reported. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	126	133	
Units: days				
least squares mean (standard error)	-3.5 (± 0.59)	-6.13 (± 0.551)	-6.18 (± 0.537)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 24: Days With Household Work Productivity Reduced by ≥ 50% Due to RA

End point title	Change From Baseline in WPS-RA at Week 24: Days With Household Work Productivity Reduced by ≥ 50% Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of days with reduced household work productivity by ≥ 50% in the last month by the subject was reported. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	125	133	
Units: days				
least squares mean (standard error)	-3.36 (± 0.632)	-4.6 (± 0.591)	-4.88 (± 0.574)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 24: Days With Family/Social/Leisure Activities Missed Due to RA

End point title	Change From Baseline in WPS-RA at Week 24: Days With Family/Social/Leisure Activities Missed Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of days missed of family/social/leisure activities in the last month by the subject was reported. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and

treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate.Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	127	133	
Units: days				
least squares mean (standard error)	-1.97 (± 0.479)	-3.51 (± 0.446)	-4.12 (± 0.435)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 24: Days With Outside Help Hired Due to RA

End point title	Change From Baseline in WPS-RA at Week 24: Days With Outside Help Hired Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of days with outside help hired in the last month by the subject was reported. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate.Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	126	133	
Units: days				
least squares mean (standard error)	-1.6 (± 0.567)	-3.87 (± 0.536)	-3.86 (± 0.523)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 24: Rate of RA Interference With Household Work Productivity

End point title	Change From Baseline in WPS-RA at Week 24: Rate of RA Interference With Household Work Productivity

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). The RA interference in the last month with household work productivity was measured on a scale that ranges from 0 (no interference) to 10 (complete interference). LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	126	132	
Units: units on a scale				
least squares mean (standard error)	-19.7 (± 2.438)	-30.96 (± 2.238)	-32.69 (± 2.186)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Rheumatoid Arthritis Impact of Disease (RAID) Scores at Week 24

End point title	Change From Baseline in Rheumatoid Arthritis Impact of Disease (RAID) Scores at Week 24

End point description:

RAID is a composite measure of the impact of RA on subjects that takes into account 7 domains: pain, functional disability, fatigue, physical and emotional well being, quality of sleep, and coping. The RAID is calculated based on 7 numerical rating scales (NRS) questions. Range of the final RAID value is 0-10 where 0= not affected, very good and 10 = most affected weighted and calculated with a total score range of 0 (not affected, very good) to 10 (most affected). A higher RAID value indicate worse status and lower indicate not affected. LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline RAID as a covariate. Analysis was performed ITT population. Number of subjects analyzed = number of subjects with RAID score assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	126	136	
Units: units on a scale				
least squares mean (standard error)	-1.8 (± 0.203)	-2.55 (± 0.189)	-2.8 (± 0.183)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life-5 Dimension 3 Level (EQ-5D-3L) VAS Scores at Week 24

End point title	Change From Baseline in European Quality of Life-5 Dimension 3 Level (EQ-5D-3L) VAS Scores at Week 24

End point description:

The EQ-5D-3L is a standardized, generic measure of health outcome. EQ-5D was designed for self-completion by subjects. The EQ-5D was specifically included to address concerns regarding the health economic impact of RA. The EQ-5D-3L comprises 5 questions on mobility, self-care, pain, usual activities, and psychological status with 3 possible answers for each item (1=no problem, 2=moderate problems, 3=severe problems) and a vertical VAS that allows the subjects to indicate their health state today that can range from 0 (worst imaginable) to 100 (best imaginable). LS mean and SE at Week 24 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline EQ-5D-3L Scores as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = number of subjects with EQ-5D-3L score assessment at both baseline and Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	126	133	
Units: units on a scale				
least squares mean (standard error)	14.85 (± 2.098)	20.06 (± 1.891)	18.4 (± 1.842)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving ACR20, ACR50 and ACR70 Criteria at

Week 12

End point title	Percentage of Subjects Achieving ACR20, ACR50 and ACR70 Criteria at Week 12

End point description:

ACR responses were assessed with a composite rating scale of the American College of Rheumatology that includes 7 variables: TJC; SJC; levels of an acute phase reactant (CRP level); subject's assessment of pain; subject's global assessment of disease activity; physician's global assessment of disease activity; subject's assessment of physical function (HAQ-DI). ACR20 is defined as achieving at least 20% improvement in both TJC and SJC, and at least 20% improvement in at least 3 of the 5 other assessments of the ACR. ACR50 is defined as achieving at least 50% improvement in both TJC and SJC, and at least 50% improvement in at least 3 of the 5 other assessments of the ACR. ACR70 is defined as achieving at least 70% improvement in both TJC and SJC, and at least 70% improvement in at least 3 of the 5 other assessments of the ACR. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	181	184	
Units: percentage of subjects				
number (not applicable)				
ACR20	37.6	54.1	62.5	
ACR50	13.3	30.4	33.2	
ACR70	2.2	13.8	14.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Disease Activity Score (DAS) 28 at Week 12

End point title	Changes From Baseline in Disease Activity Score (DAS) 28 at Week 12

End point description:

DAS28 is a composite score that includes 4 variables: TJC (based on 28 joints); SJC (based on 28 joints); GH by the subject assessed from the ACR rheumatoid arthritis core set questionnaire (subject global assessment) in 100 mm VAS; marker of inflammation assessed by hs-CRP in mg/L. The DAS28 provides a number indicating the current activity of the RA. DAS28 total score ranges from 2-10. A DAS28 score above 5.1 means high disease activity, whereas a DAS28 score below 3.2 indicates low disease activity and a DAS28 score below 2.6 means disease remission. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline DAS score as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = number of subjects with DAS28- Score assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168	163	169	
Units: : units on a scale				
least squares mean (standard error)	-0.97 (± 0.104)	-2.13 (± 0.105)	-2.45 (± 0.103)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Clinical Remission Score (DAS28--CRP) <2.6 at Week 12

End point title	Percentage of Subjects Achieving Clinical Remission Score (DAS28--CRP) <2.6 at Week 12

End point description:

DAS28 was a composite score that includes 4 variables: TJC (based on 28 joints); SJC (based on 28 joints); GH by the subject assessed from the ACR rheumatoid arthritis core set questionnaire (subject global assessment) in 100 mm VAS; marker of inflammation assessed by hs-CRP in mg/L. The DAS28 provides a number indicating the current activity of the RA. DAS28 total score ranges from 2-10. A DAS28 score above 5.1 means high disease activity, whereas a DAS28 score below 3.2 indicates low disease activity and a DAS28 score below 2.6 means disease remission. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	181	184	
Units: percentage of subjects				
number (not applicable)	3.9	17.1	17.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SF-36 at Week 12

End point title	Change From Baseline in SF-36 at Week 12

End point description:

SF-36 a 36-item questionnaire measuring health-related quality of life (HRQL) covering 2 summary measures: PCS and mental component summary (MCS). The SF-36 consists of 8 subscales. The PCS had 4 subscales: physical function, role limitations due to physical problems, pain, and general health perception. The MCS had 4 subscales: vitality, social function, role limitations due to emotional problems, and mental health. Reporting on subscale that have between 2-6 choices per item using Likert-type responses. Summations of item scores give the subscale scores, which range from 0 to 100; zero= worst HRQL, 100=best HRQL. Higher scores indicate better health and well-being. LS mean and

SE at Week 12 by MMRM with treatment,region,number of previous anti TNFs,visit,and treatment-by-visit interaction as fixed effects and baseline SF-36 (PCS) as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with SF-36 PCS assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169	160	165	
Units: units on a scale				
least squares mean (standard error)				
PCS Score at Week 12	3.74 (± 0.582)	6.93 (± 0.596)	6.84 (± 0.584)	
MCS Score at Week 12	3.5 (± 0.738)	5.14 (± 0.758)	6.47 (± 0.741)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 12: Work Days Missed Due to RA

End point title	Change From Baseline in WPS-RA at Week 12: Work Days Missed Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of work days missed in the last month by the subject was reported. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	54	56	
Units: days				
least squares mean (standard error)	-1.2 (± 0.581)	-1.97 (± 0.571)	-2.98 (± 0.585)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 12: Days With Work Productivity Reduced by ≥ 50% Due to RA

End point title	Change From Baseline in WPS-RA at Week 12: Days With Work Productivity Reduced by ≥ 50% Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of work days with reduced productivity by ≥ 50% in the last month by the subject was reported. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	54	56	
Units: days				
least squares mean (standard error)	-1.69 (± 0.784)	-4.24 (± 0.773)	-3.2 (± 0.785)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 12: Rate of RA Interference With Work Productivity

End point title	Change From Baseline in WPS-RA at Week 12: Rate of RA Interference With Work Productivity

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Interference in the last month with work productivity was measured on a scale that ranges from 0 (no interference) to 10 (complete interference). LS mean and SE at Week 12 were obtained from a MMRM with treatment,

region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	54	56	
Units: units on a scale				
least squares mean (standard error)	-10.43 (± 3.803)	-19.24 (± 3.742)	-18.73 (± 3.764)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 12: House Work Days Missed Due to RA

End point title	Change From Baseline in WPS-RA at Week 12: House Work Days Missed Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of days with no household work in the last month by the subject was reported. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	164	169	
Units: days				
least squares mean (standard error)	-2.1 (± 0.551)	-5.52 (± 0.563)	-5.54 (± 0.553)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 12: Days With Household Work Productivity Reduced by ≥ 50% Due to RA

End point title	Change From Baseline in WPS-RA at Week 12: Days With Household Work Productivity Reduced by ≥ 50% Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of days with reduced household work productivity by ≥ 50% in the last month by the subject was reported. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169	163	169	
Units: days				
least squares mean (standard error)	-2.6 (± 0.576)	-3.97 (± 0.587)	-3.98 (± 0.575)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 12: Days With Family/Social/Leisure Activities Missed Due to RA

End point title	Change From Baseline in WPS-RA at Week 12: Days With Family/Social/Leisure Activities Missed Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of days missed of family/social/leisure activities in the last month in the last month by the subject was reported. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	164	169	
Units: days				
least squares mean (standard error)	-2.23 (± 0.433)	-2.53 (± 0.442)	-3.26 (± 0.434)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 12: Days With Outside Help Hired Due to RA

End point title	Change From Baseline in WPS-RA at Week 12: Days With Outside Help Hired Due to RA

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Number of days with outside help hired in the last month by the subject was reported. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	164	169	
Units: days				
least squares mean (standard error)	-0.77 (± 0.558)	-3.07 (± 0.57)	-2.94 (± 0.56)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Week 12: Rate of RA Interference With Household Work Productivity

End point title	Change From Baseline in WPS-RA at Week 12: Rate of RA Interference With Household Work Productivity

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). The RA interference in the last month with household work productivity was measured on a scale that ranges from 0 (no interference) to 10 (complete interference). LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline WPS-RA as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = subjects with WPS-RA individual items assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169	164	167	
Units: units on a scale				
least squares mean (standard error)	-12.1 (± 2.428)	-27.72 (± 2.474)	-24.04 (± 2.443)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the FACIT-fatigue at Week 12

End point title	Change From Baseline in the FACIT-fatigue at Week 12

End point description:

The FACIT-Fatigue is a 13-item questionnaire assessing fatigue where subjects scored each item on a 5-point scale (0-4): 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much. A total score ranging from 0 to 52. A higher score corresponded to a lower level of fatigue. A positive change from baseline score indicates an improvement. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline FACIT-fatigue as a covariate. Analysis was performed on ITT population. Number of Subjects analyzed = number of subjects with FACIT-fatigue score assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169	165	172	
Units: units on a scale				
least squares mean (standard error)	5.56 (± 0.721)	8.02 (± 0.729)	9.45 (± 0.714)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ-5D-3L VAS Scores at Week 12

End point title	Change From Baseline in EQ-5D-3L VAS Scores at Week 12

End point description:

The EQ-5D-3L is a standardized, generic measure of health outcome. EQ-5D was designed for self-completion by subjects. The EQ-5D was specifically included to address concerns regarding the health economic impact of RA. The EQ-5D-3L comprises 5 questions on mobility, self-care, pain, usual activities, and psychological status with 3 possible answers for each item (1=no problem, 2=moderate problems, 3=severe problems) and a vertical VAS that allows the subjects to indicate their health state today that can range from 0 (worst imaginable) to 100 (best imaginable). LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline EQ-5D-3L Scores as a covariate. Analysis was performed on ITT population. Number of subjects analyzed = number of subjects with EQ-5D-3L score assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	163	171	
Units: units on a scale				
least squares mean (standard error)	8.39 (± 1.699)	17.16 (± 1.72)	15.23 (± 1.68)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in RAID Scores at Week 12

End point title	Change From Baseline in RAID Scores at Week 12

End point description:

RAID is a composite measure of the impact of RA on subjects that takes into account 7 domains: pain, functional disability, fatigue, physical and emotional well being, quality of sleep, and coping. The RAID is calculated based on 7 NRS questions. Range of the final RAID value is 0-10 where 0= not affected, very good and 10 = most affected weighted and calculated with a total score range of 0 (not affected, very good) to 10 (most affected). A higher RAID value indicate worse status and lower indicate not affected. LS mean and SE at Week 12 were obtained from a MMRM with treatment, region, number of previous

anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline RAID as a covariate. Analysis was performed ITT population. Number of subjects analyzed = number of subjects with RAID score assessment at both baseline and Week 12.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	162	171	
Units: units on a scale				
least squares mean (standard error)	-1.34 (± 0.163)	-2.27 (± 0.165)	-2.47 (± 0.161)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Each Individual ACR Component at Week 12 and Week 24

End point title	Change From Baseline in Each Individual ACR Component at Week 12 and Week 24

End point description:

ACR components were:TJC,SJC,physician global VAS,subject global VAS,pain VAS,HAQ-DI & CRP. TJC& SJC scored by tenderness assessed by pressure.Increase in number of tender/swollen joints indicates severity. Physician global VAS & subject global VAS was done by 100 mm non-anchored VAS,from no arthritis(0) to maximal arthritis(100). Pain VAS by 100 mm VAS from no pain to unbearable pain.HAQ-DI for quality of life score,0-1 shows mild to moderate difficulty,1-2 moderate to severe disability&2-3 severe to very severe disability.CRP was clinical marker in ACR scoring reduction shows improvement in RA.LS mean and SE at Week 12 & 24 by MMRM with treatment,region,number of previous anti-TNFs,visit,and treatment-by-visit interaction as fixed effects and baseline ACR components as a covariate.No. of subjects analyzed=No.of subjects with individual ACR assessment at both baseline and specified time points.Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Placebo q2w	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	181	181	184	
Units: units on a scale				
least squares mean (standard error)				
TJC at Week 12 (n=172,165,172)	-8.55 (± 0.959)	-13.74 (± 0.975)	-14.87 (± 0.954)	
SJC at Week 12 (n=172,165,172)	-6.75 (± 0.687)	-10.54 (± 0.698)	-10.59 (± 0.684)	

Pain VAS at Week 12 (n=172,165,172)	-15.13 (± 1.908)	-26.93 (± 1.933)	-30.56 (± 1.901)	
Physician global VAS at Week 12 (n=172,165,172	-22.74 (± 1.744)	-33.64 (± 1.775)	-35.44 (± 1.74)	
Subject global VAS at Week 12 (n=172,165,172)	-13.75 (± 1.807)	-25.28 (± 1.836)	-27.38 (± 1.803)	
HAQ-DI at Week 12 (n=170,165,171)	-0.26 (± 0.043)	-0.46 (± 0.044)	-0.47 (± 0.043)	
CRP at Week 12 (n=168,165,170)	-3.63 (± 1.436)	-15.08 (± 1.452)	-22.98 (± 1.432)	
TJC at Week 24 (n=101,127,137)	10.55 (± 1.06)	-14.44 (± 1.017)	-16.95 (± 0.992)	
SJC at Week 24 (n=101,127,137)	-8.19 (± 0.721)	-11.56 (± 0.691)	-11.94 (± 0.674)	
Pain VAS at Week 24 (n=98,127,135)	-21.27 (± 2.25)	-31.9 (± 2.086)	-33.65 (± 2.037)	
Physician global VAS at Week 24 (n=101,127,137)	-28.55 (± 1.806)	-40.65 (± 1.695)	-43.22 (± 1.646)	
Subject global VAS at Week 24 (n=100,127,136)	-19.76 (± 2.171)	-29.59 (± 2.046)	-31.28 (± 1.997)	
HAQ-DI at Week 24 (n=101,127,136)	-0.34 (± 0.051)	-0.52 (± 0.049)	-0.58 (± 0.048)	
CRP at Week 24 (n=100,126,137)	-3.6 (± 1.556)	-15.24 (± 1.457)	-23.27 (± 1.421)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 30) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment emergent adverse events that is AEs that developed/worsened and death during 'on treatment period' (time from the first dose injection of study drug to the end of follow up period). Safety population included all subjects from randomized population who received at least 1 dose or part of a dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo q2w

Reporting group description:

Placebo matched to sarilumab q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.

Reporting group title	Sarilumab 200 mg q2w

Reporting group description:

Sarilumab 200 mg q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.

Reporting group title	Sarilumab 150 mg q2w

Reporting group description:

Sarilumab 150 mg q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.

Serious adverse events	Placebo q2w	Sarilumab 200 mg q2w	Sarilumab 150 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 181 (3.31%)	10 / 184 (5.43%)	6 / 181 (3.31%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (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
Transaminases Increased			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Ureteric Cancer			
subjects affected / exposed	1 / 181 (0.55%)	0 / 184 (0.00%)	0 / 181 (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
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 184 (0.00%)	0 / 181 (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
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			
subjects affected / exposed	1 / 181 (0.55%)	0 / 184 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Venous Thrombosis Limb			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block Second Degree			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (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
Endocarditis Noninfective			

subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic Stroke			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 181 (0.00%)	0 / 184 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 184 (0.00%)	0 / 181 (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
Neutropenia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 181 (0.00%)	0 / 184 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Mixed Liver Injury			

subjects affected / exposed	1 / 181 (0.55%)	0 / 184 (0.00%)	0 / 181 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	0 / 181 (0.00%)	0 / 184 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 181 (0.00%)	0 / 184 (0.00%)	1 / 181 (0.55%)
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	1 / 181 (0.55%)	0 / 184 (0.00%)	0 / 181 (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
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 184 (0.00%)	0 / 181 (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
Bronchitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 184 (0.00%)	0 / 181 (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
Cellulitis			

subjects affected / exposed	1 / 181 (0.55%)	1 / 184 (0.54%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 181 (0.00%)	0 / 184 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 184 (0.54%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	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 q2w	Sarilumab 200 mg q2w	Sarilumab 150 mg q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 181 (14.36%)	57 / 184 (30.98%)	60 / 181 (33.15%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 181 (1.10%)	10 / 184 (5.43%)	5 / 181 (2.76%)
occurrences (all)	2	10	5
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 181 (1.10%)	22 / 184 (11.96%)	23 / 181 (12.71%)
occurrences (all)	2	31	32
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	0 / 181 (0.00%)	7 / 184 (3.80%)	11 / 181 (6.08%)
occurrences (all)	0	17	33
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 181 (4.97%)	7 / 184 (3.80%)	11 / 181 (6.08%)
occurrences (all)	9	7	12
Urinary Tract Infection			

subjects affected / exposed occurrences (all)	12 / 181 (6.63%) 13	13 / 184 (7.07%) 16	6 / 181 (3.31%) 6
Metabolism and nutrition disorders Hypertriglyceridaemia subjects affected / exposed occurrences (all)	3 / 181 (1.66%) 3	5 / 184 (2.72%) 5	11 / 181 (6.08%) 12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2012	• To implement new safety measures to prevent the administration of sarilumab to subjects at risk for development of severe thrombocytopenia (<100 000/mm3) and grade 3/grade 4 neutropenia (based on NCI Common Terminology Criteria for Adverse Events [CTCAE]). • To delete the Visit 3 (Week2) sampling time point for "genetic RNA" or "RNA for sequencing" . • To remove the open-label rescue therapy arm within this study (EFC10832) and give subject qualifying for rescue therapy the opportunity to directly enroll into the parallel ongoing long-term safety study (LTS11210) to receive open-label rescue therapy with sarilumab. • To replace the partial EQ-5D-3L (EuroQol) instrument with the original complete instrument • To add an additional exclusion criterion related to interstitial lung disease. • To clarify instructions that for any occurrence of a serious adverse event (SAE) and for any occurrence of an adverse event of special interest (AESI) with immediate notification, investigators must report such events to the monitoring team within 24 hours of knowledge of them, and send any follow up data related to the event to the monitoring team also within 24 hours of knowledge. • To clarify in the Clinical Trial Summary and text related to categorical safety analyses, cardiovascular (CV) events, and analyses of the laboratory data, vital signs data and electrocardiogram data.
03 April 2013	• To update text related to dosage regimen of methotrexate in the Clinical Trial Summary. • To clarify the general accepted adult age limit and treatment related to dyslipidemia. • To update study medication storage conditions. • Updated text relating to treatment accountability and compliance and treatment kit disposal. • To remove text related to description of an open treatment arm with sarilumab that is no longer part of the study design in relevant sections. • To update text related to handling of subject for temporary and permanent treatment discontinuation. • To update safety reporting instructions in relevant sections.
29 October 2014	• To modify the analyses for the co-primary endpoint related to change in physical function as measured by the HAQ-DI and replace the co-primary endpoint related to change in physical function as measured by the HAQ-DI from the "average of change from baseline in the HAQ-DI from week 8 to Week 24" to the co-primary endpoint of "the change from baseline in the HAQ-DI at Week 12" This was done to ensure a robust analysis was performed at a time point where the amount of missing data was minimal and where there was a sufficiently long period of treatment with study drug to permit a correct assessment of effect on physical function. • To remove the reference related to the Committee for Medicinal Products for Human Use (CHMP) guidelines for blood pressure measurement as the current instructions in the protocol for blood pressure measurement primarily reflected practical considerations and were to serve as generic guidance to ensure consistency. • To replace the acronym "ANC (absolute neutrophil count)" with "neutrophil count," in relevant sections. • To remove references to the bioanalytical assay and related analyses for "serum sarilumab-IL-6Rα complex (bound sarilumab)" as this assay was not performed for this study population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported