Clinical trial results:
A Randomized, Double-Blind, Double-Dummy Study Assessing the Safety and Tolerability of Sarilumab and Tocilizumab in Patients With Rheumatoid Arthritis who are Inadequate Responders to or Intolerant of TNF Antagonists

Summary

EudraCT number	2012-003536-23
Trial protocol	CZ BE HU ES IT SE EE NO FI NL GB PL
Global end of trial date	14 October 2014

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	SFY13370

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01768572
WHO universal trial number (UTN)	-

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	14 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of sarilumab and tocilizumab in subjects with rheumatoid arthritis (RA) who are inadequate responders to or intolerant of tumor necrosis factor (TNF) 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: -
Evidence for comparator: -

Actual start date of recruitment	25 March 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	Argentina: 30
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Estonia: 6

Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	202
EEA total number of subjects	89

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)	173
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 78 centers in 19 countries. A total of 389 subjects were screened between 25 March 2013 and 02 April 2014, 187 of whom were screen failures. Screen failures were mainly due to failure to meet inclusion and exclusion criteria.

Pre-assignment

Screening details:

Randomization of subjects were stratified by region and screening value of absolute neutrophil count. Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in 1:1:2 (sarilumab 150 mg q2w: sarilumab 200 mg q2w: tocilizumab q4w). 202 subjects were randomized.

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	Sarilumab 150 mg q2w

Arm description:

Sarilumab 150 mg once every 2 weeks (q2w) and placebo (for Tocilizumab) once every 4 weeks (q4w) was added to one or a combination of the non-biologic disease modifying anti-rheumatic drug (DMARD) for 24 weeks.

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 a subcutaneous (SC) injection in the abdomen, thigh or upper arm.

Investigational medicinal product name	Placebo (for Tocilizumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo (for Tocilizumab) as a 60-minute single intravenous (IV) infusion.

Arm title	Sarilumab 200 mg q2w

Arm description:

Sarilumab 200 mg q2w and placebo (for Tocilizumab) q4w 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, REGN88
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:	
Sarilumab as a SC injection in the abdomen, thigh or upper arm.	
Investigational medicinal product name	Placebo (for Tocilizumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Placebo (for Tocilizumab) as a 60-minute single IV infusion.	
Arm title	Tocilizumab q4w
Arm description:	
Tocilizumab 4 mg/kg or 8 mg/kg q4w and placebo (for Sarilumab) q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Tocilizumab as a 60-minute single IV infusion. Dose for tocilizumab could be up-titrated to 8 mg/kg or dose down-titrated to 4 mg/kg based on clinical response as per Investigator's discretion.	
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 a SC injection in the abdomen, thigh or upper arm.	

Number of subjects in period 1	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	Tocilizumab q4w
Started	49	51	102
Completed	40	39	96
Not completed	9	12	6
Other, not due to an adverse event	1	1	1
Adverse event	7	8	4
Lack of efficacy	1	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Sarilumab 150 mg q2w
Reporting group description:	
Sarilumab 150 mg once every 2 weeks (q2w) and placebo (for Tocilizumab) once every 4 weeks (q4w) was added to one or a combination of the non-biologic disease modifying anti-rheumatic drug (DMARD) for 24 weeks.	
Reporting group title	Sarilumab 200 mg q2w
Reporting group description:	
Sarilumab 200 mg q2w and placebo (for Tocilizumab) q4w was added to one or a combination of the non-biologic DMARD for 24 weeks.	
Reporting group title	Tocilizumab q4w
Reporting group description:	
Tocilizumab 4 mg/kg or 8 mg/kg q4w and placebo (for Sarilumab) q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.	

Reporting group values	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	Tocilizumab q4w
Number of subjects	49	51	102
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54.8	51.7	50.4
standard deviation	± 12.1	± 13.1	± 13
Gender categorical			
Units: Subjects			
Female	41	39	82
Male	8	12	20
RA Functional Class			
RA Class I subjects: completely able to perform usual activities of daily living (self-care, vocational and avocational); Class II subjects: able to perform usual self-care and vocational activities, but limited in avocational activities; Class III subjects: able to perform usual self-care activities, but limited in vocational and avocational activities; Class IV subjects: limited in ability to perform usual self-care, vocational and avocational activities.			
Units: Subjects			
Class I	10	4	16
Class II	25	33	62
Class III	14	14	24
Class IV	0	0	0
Duration of RA since diagnosis			
Units: years			
arithmetic mean	13.59	10.45	10.84
standard deviation	± 8.24	± 7.57	± 8.91
Health Assessment Questionnaire Disability Index (HAQ-DI)			
Subject-reported assessment of ability to perform tasks in 8 categories of daily living activities: HAQ-DI consists of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; activities rated on a 4-point scale where 0=best and 3=worst. Overall score was computed as the sum of domain scores and divided by the number of domains answered, ranging from 0 to 3, where 0 = no disability and 3 = very severe, high-dependency disability.			

Units: units on a scale			
arithmetic mean	1.63	1.71	1.78
standard deviation	± 0.66	± 0.6	± 0.63
Disease Activity Score for 28 Joints- C-reactive protein (DAS28-CRP)			
The DAS28-CRP is a composite score that contains 4 variables: Tender Joints Count (based on 28 joints), Swollen Joints Count (based on 28 joints), general health assessment and high sensitivity C-reactive protein (hs-CRP) in mg/L or erythrocyte sedimentation rate (ESR) in mm/hr. It ranges from 0-10 with a lower score indicating less disease activity. A DAS28-CRP above 5.1 indicates high disease activity, whereas a below 3.2 indicates low disease activity and below 2.6 as disease remission.			
Units: score on scale			
arithmetic mean	5.85	5.88	5.91
standard deviation	± 0.92	± 0.97	± 1.01

Reporting group values	Total		
Number of subjects	202		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	162		
Male	40		
RA Functional Class			
RA Class I subjects: completely able to perform usual activities of daily living (self-care, vocational and avocational); Class II subjects: able to perform usual self-care and vocational activities, but limited in avocational activities; Class III subjects: able to perform usual self-care activities, but limited in vocational and avocational activities; Class IV subjects: limited in ability to perform usual self-care, vocational and avocational activities.			
Units: Subjects			
Class I	30		
Class II	120		
Class III	52		
Class IV	0		
Duration of RA since diagnosis			
Units: years			
arithmetic mean			
standard deviation	-		
Health Assessment Questionnaire Disability Index (HAQ-DI)			
Subject-reported assessment of ability to perform tasks in 8 categories of daily living activities: HAQ-DI consists of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; activities rated on a 4-point scale where 0=best and 3=worst. Overall score was computed as the sum of domain scores and divided by the number of domains answered, ranging from 0 to 3, where 0 = no disability and 3 = very severe, high-dependency disability.			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Disease Activity Score for 28 Joints- C-reactive protein (DAS28-CRP)			
The DAS28-CRP is a composite score that contains 4 variables: Tender Joints Count (based on 28 joints), Swollen Joints Count (based on 28 joints), general health assessment and high sensitivity C-			

reactive protein (hs-CRP) in mg/L or erythrocyte sedimentation rate (ESR) in mm/hr. It ranges from 0-10 with a lower score indicating less disease activity. A DAS28-CRP above 5.1 indicates high disease activity, whereas a below 3.2 indicates low disease activity and below 2.6 as disease remission.			
Units: score on scale arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Sarilumab 150 mg q2w
Reporting group description:	
Sarilumab 150 mg once every 2 weeks (q2w) and placebo (for Tocilizumab) once every 4 weeks (q4w) was added to one or a combination of the non-biologic disease modifying anti-rheumatic drug (DMARD) for 24 weeks.	
Reporting group title	Sarilumab 200 mg q2w
Reporting group description:	
Sarilumab 200 mg q2w and placebo (for Tocilizumab) q4w was added to one or a combination of the non-biologic DMARD for 24 weeks.	
Reporting group title	Tocilizumab q4w
Reporting group description:	
Tocilizumab 4 mg/kg or 8 mg/kg q4w and placebo (for Sarilumab) q2w was added to one or a combination of the non-biologic DMARD for 24 weeks.	

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs)[1]
End point description:	
Adverse event (AE) was defined as any untoward medical occurrence in a subjects who received study drug and does not necessary had to have a causal relationship with treatment. All adverse events that occurred from the first dose of the study drug administration up to 60 days after the end of treatment visit were considered as TEAEs. Serious AE (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly or a medically important event. A summary of SAEs, all other non-serious AEs, regardless of causality, were reported in AE section. Safety population consisted of all randomized subjects who received at least 1 dose or a partial dose of study drug analyzed according to the treatment actually received.	
End point type	Primary
End point timeframe:	
Up to 211 days	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Sarilumab 150 mg q2w	Sarilumab 200 mg q2w	Tocilizumab q4w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	51	102	
Units: subjects				
Any TEAE	33	36	68	
Any treatment-emergent SAE	1	3	7	
Any TEAE leading to death	0	0	1	
Any TEAE leading to discontinuation	6	8	4	

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 (Day 211) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent that is AEs that developed/worsened that occurred during 'TEAE period' (first dose of study drug to last dose of study drug+60 days, last contact date, or the date of death, whichever came first). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Tocilizumab q4w

Reporting group description:

Tocilizumab 4 mg/kg or 8 mg/kg q4w and placebo (for 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 and placebo (for Tocilizumab) q4w 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 and placebo (for Tocilizumab) q4w was added to one or a combination of the non-biologic DMARD for 24 weeks.

Serious adverse events	Tocilizumab q4w	Sarilumab 200 mg q2w	Sarilumab 150 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 102 (6.86%)	3 / 51 (5.88%)	1 / 49 (2.04%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Investigations			
Transaminases Increased			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (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	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (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			
Tremor			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (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	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (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 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic Pulmonary Fibrosis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (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
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (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
Pseudarthrosis			

subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (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			
Erysipelas			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (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
Septic Shock			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tocilizumab q4w	Sarilumab 200 mg q2w	Sarilumab 150 mg q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 102 (64.71%)	36 / 51 (70.59%)	33 / 49 (67.35%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 102 (3.92%)	2 / 51 (3.92%)	0 / 49 (0.00%)
occurrences (all)	4	2	0
Vascular Fragility			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	1 / 102 (0.98%)	4 / 51 (7.84%)	4 / 49 (8.16%)
occurrences (all)	1	14	4
Device Dislocation			

subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Chills			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Injection Site Macule			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	2
Injection Site Nodule			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Injection Site Pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	2 / 102 (1.96%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	2	0	1
Injection Site Pruritus			
subjects affected / exposed	1 / 102 (0.98%)	1 / 51 (1.96%)	2 / 49 (4.08%)
occurrences (all)	1	8	5
Injection Site Rash			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Injection Site Papule			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Nodule			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Pain			

subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	2 / 102 (1.96%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	4	0	0
Reproductive system and breast disorders			
Menstruation Irregular			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Ovarian Cyst			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Bronchiectasis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Nasal Ulcer			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal Pain			
subjects affected / exposed	3 / 102 (2.94%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	3	0	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	5 / 102 (4.90%)	2 / 51 (3.92%)	1 / 49 (2.04%)
occurrences (all)	5	2	1
Blood Cholesterol Increased			
subjects affected / exposed	1 / 102 (0.98%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	1	1	0

Blood Pressure Increased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Glomerular Filtration Rate Increased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Neutrophil Count Increased			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Neutrophil Count Decreased			
subjects affected / exposed	3 / 102 (2.94%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	3	1	0
Liver Function Test Abnormal			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Transaminases Increased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	9 / 102 (8.82%)	3 / 51 (5.88%)	1 / 49 (2.04%)
occurrences (all)	11	5	1
Ankle Fracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Fall			
subjects affected / exposed	2 / 102 (1.96%)	1 / 51 (1.96%)	1 / 49 (2.04%)
occurrences (all)	2	1	1
Infusion Related Reaction			
subjects affected / exposed	1 / 102 (0.98%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	1	2	0
Overdose			

subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Muscle Strain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Joint Injury			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Post-Traumatic Pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Traumatic Haematoma			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Road Traffic Accident			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac Failure Chronic			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 102 (3.92%)	3 / 51 (5.88%)	1 / 49 (2.04%)
occurrences (all)	4	3	1
Cerebral Ischaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Carpal Tunnel Syndrome			
subjects affected / exposed	1 / 102 (0.98%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Dysgeusia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Headache			

subjects affected / exposed	5 / 102 (4.90%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	9	0	1
Sciatica			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Paraesthesia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia Of Chronic Disease			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Leukocytosis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Neutrophilia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	3 / 102 (2.94%)	8 / 51 (15.69%)	6 / 49 (12.24%)
occurrences (all)	3	12	15
Lymphadenopathy			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0

Normochromic Normocytic Anaemia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Eye disorders			
Ocular Hyperaemia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Dark Circles Under Eyes			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Ulcerative Keratitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Abdominal Pain Upper			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	0 / 102 (0.00%)	2 / 51 (3.92%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Gastric Ulcer			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			

subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	2 / 49 (4.08%)
occurrences (all)	1	0	2
Gastrointestinal Disorder			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Mouth Ulceration			
subjects affected / exposed	3 / 102 (2.94%)	2 / 51 (3.92%)	0 / 49 (0.00%)
occurrences (all)	4	3	0
Irritable Bowel Syndrome			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Loose Tooth			
subjects affected / exposed	1 / 102 (0.98%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Haematochezia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	7 / 102 (6.86%)	1 / 51 (1.96%)	1 / 49 (2.04%)
occurrences (all)	7	1	1
Stomatitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 102 (0.00%)	2 / 51 (3.92%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Dermatitis Allergic			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Pruritus Generalised			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	2 / 102 (1.96%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	2	0	1
Skin Ulcer			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Rash Pruritic			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Hydronephrosis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0

Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 102 (2.94%)	2 / 51 (3.92%)	0 / 49 (0.00%)
occurrences (all)	3	2	0
Arthralgia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Hand Deformity			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Muscle Spasms			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Muscle Haemorrhage			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	2 / 102 (1.96%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Osteoarthritis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Pain In Extremity			
subjects affected / exposed	2 / 102 (1.96%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	4	0	0
Spinal Osteoarthritis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Rheumatoid Nodule			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Rheumatoid Arthritis			

subjects affected / exposed	6 / 102 (5.88%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	15	0	1
Spinal Pain			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Synovial Cyst			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acute Sinusitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Bronchitis Viral			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Herpes Simplex			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	3 / 49 (6.12%)
occurrences (all)	1	0	3
Conjunctivitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	2 / 49 (4.08%)
occurrences (all)	0	0	2
Influenza			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0

Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Otitis Media			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Onychomycosis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Oral Herpes			
subjects affected / exposed	2 / 102 (1.96%)	0 / 51 (0.00%)	2 / 49 (4.08%)
occurrences (all)	2	0	2
Nasopharyngitis			
subjects affected / exposed	4 / 102 (3.92%)	3 / 51 (5.88%)	6 / 49 (12.24%)
occurrences (all)	4	4	7
Paronychia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Periodontitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Pharyngotonsillitis			
subjects affected / exposed	1 / 102 (0.98%)	1 / 51 (1.96%)	1 / 49 (2.04%)
occurrences (all)	1	1	1
Sinusitis			
subjects affected / exposed	2 / 102 (1.96%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Pyuria			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	2 / 49 (4.08%)
occurrences (all)	0	0	2

Skin Infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Tinea Pedis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Tinea Versicolour			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Tooth Infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Tracheitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 102 (6.86%)	1 / 51 (1.96%)	2 / 49 (4.08%)
occurrences (all)	7	1	2
Urinary Tract Infection			
subjects affected / exposed	6 / 102 (5.88%)	1 / 51 (1.96%)	4 / 49 (8.16%)
occurrences (all)	6	1	6
Vulvovaginitis Trichomonal			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Food Craving			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Hypercholesterolaemia			
subjects affected / exposed	6 / 102 (5.88%)	1 / 51 (1.96%)	2 / 49 (4.08%)
occurrences (all)	6	1	2
Hypertriglyceridaemia			

subjects affected / exposed	2 / 102 (1.96%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Dyslipidaemia			
subjects affected / exposed	4 / 102 (3.92%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	4	1	0
Hypoglycaemia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 51 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 102 (0.98%)	1 / 51 (1.96%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Vitamin D Deficiency			
subjects affected / exposed	0 / 102 (0.00%)	0 / 51 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2013	It included following changes: Guidance for female subjects of childbearing potential in this clinical trial was provided to comply with the Medicines and Healthcare products Regulatory Agency guidance's on contraceptive wording in Clinical Trials conducted in the United Kingdom.
10 September 2013	It included the following changes: - Added laboratory visits at Weeks 14, 18, and 22 for additional hematology assessments. - Inconsistencies were corrected within the protocol related to concomitant DMARD therapy. - Inconsistencies within the protocol were corrected related to blood sampling at Visit 2 (Day 1), Visit 9 (Day 113), and Visit 10 (Day 141); DNA blood sampling time for subjects; tocilizumab/placebo preparation; blood volumes to be drawn for DNA and protein biomarker samples; stratification at baseline during randomization period. - Updated the AEs of special interest with immediate notification section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported