Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of CNTO 136 (sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Anti-TNF Therapy

Summary

EudraCT number	2010-022243-38
Trial protocol	LT DE GB AT ES PT BE IT NL
Global end of trial date	12 January 2016

Results information

Result version number	v1 (current)
This version publication date	05 January 2017
First version publication date	05 January 2017

Trial information

Trial identification

Sponsor protocol code	CNTO136ARA3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01606761
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to assess the efficacy of sirukumab as measured by the reduction of the signs and symptoms of rheumatoid arthritis (RA) in subjects with moderately to severely active RA who were refractory or intolerant to anti-tumor necrosis factor (anti-TNF) agents.

Protection of trial subjects:

The safety assessments included adverse events, laboratory measurements (hematology, serum chemistry, and urinalysis), vital sign measurements, and physical examinations. Adverse events were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 19
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 116
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Lithuania: 16
Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 76
Country: Number of subjects enrolled	Puerto Rico: 8

Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	United States: 445
Worldwide total number of subjects	878
EEA total number of subjects	181

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)	684
From 65 to 84 years	194
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 878 subjects (placebo [n=294], sirukumab 50 mg every 4 week (q4w) [n=292], and sirukumab 100 mg every 2 week q2w [n=292]) were randomized and included in the study.

Period 1

Period 1 title	Placebo Controlled Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received matching placebo every 2 week (q2w) until either early escape (EE) at Week 18, or crossover (CO) at Week 24.

Arm type	Experimental
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:

Subjects received matching placebo subcutaneously (SC) q2w until either early escape (EE) at Week 18, or crossover (CO) at Week 24.

Arm title	Sirukumab 50 mg

Arm description:

Subjects received Sirukumab 50 mg SC at Week 0, 4 and q4w up to Week 24.

Arm type	Experimental
Investigational medicinal product name	Sirukumab 50 milligram (mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received Sirukumab 50 mg SC Week 0, 4 and q4w up to Week 24.

Arm title	Sirukumab 100 mg

Arm description:

Subjects received Sirukumab 100 mg SC at Week 0, 2 and q2w up to Week 24.

Arm type	Experimental
Investigational medicinal product name	Sirukumab 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received Sirukumab 100 mg SC at Week 0, 2 and q2w up to Week 24.

Number of subjects in period 1	Placebo	Sirukumab 50 mg	Sirukumab 100 mg
Started	294	292	292
Completed	252	237	246
Not completed	42	55	46
Consent withdrawn by subject	12	9	9
Physician decision	-	3	1
Adverse events	11	19	21
Other	3	7	5
Lost to follow-up	1	3	2
Lack of efficacy	15	14	8

Period 2

Period 2 title	Active Controlled Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo to 50 mg q4w due to EE or CO

Arm description:

Subjects who received matching placebo in the placebo controlled period were re-randomized (due to early escape [EE] at Week 18 or crossed over [CO] at Week 24) to receive subcutaneous (SC) sirukumab 50 mg dose regimen q4w up to Week 52.

Arm type	Experimental
Investigational medicinal product name	Sirukumab 50 milligram (mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received sirukumab 50 mg SC injection every 4 week (q4w) up to Week 52.

Arm title	Sirukumab 50 mg

Arm description:	
Subjects continued to receive sirukumab 50 mg SC q4w from Week 24 up to Week 52.	
Arm type	Experimental
Investigational medicinal product name	Sirukumab 50 milligram (mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Subjects received sirukumab 50 mg SC injection every 4 week (q4w) from Week 24 up to Week 52.	
Arm title	Placebo to 100 mg q2w due to EE or CO
Arm description:	
Subjects who received matching placebo in the placebo controlled period were re-randomized (due to EE at Week 18 or CO at Week 24) to receive subcutaneous (SC) sirukumab 100 mg dose regimen q2w up to Week 52.	
Arm type	Experimental
Investigational medicinal product name	Sirukumab 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Subjects received Sirukumab 100 mg SC at q2w from Week 24 up to Week 52.	
Arm title	Sirukumab 100 mg q2w
Arm description:	
Subjects continued to receive sirukumab 100 mg SC q2w from Week 24 up to Week 52.	
Arm type	Experimental
Investigational medicinal product name	Sirukumab 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Subjects received Sirukumab 100 mg SC q2w from Week 24 up to Week 52.	

Number of subjects in period 2	Placebo to 50 mg q4w due to EE or CO	Sirukumab 50 mg	Placebo to 100 mg q2w due to EE or CO
Started	126	237	126
Completed	109	204	106
Not completed	17	88	20
Consent withdrawn by subject	-	16	-
Physician decision	-	4	-
Adverse events	3	29	15
Death	1	-	-
Other	2	8	2
Lost to follow-up	1	4	-

Lack of efficacy	10	27	3
Joined	0	55	0
Discontinued prior to Week 24	-	55	-

Number of subjects in period 2	Sirukumab 100 mg q2w
Started	246
Completed	212
Not completed	80
Consent withdrawn by subject	12
Physician decision	2
Adverse events	36
Death	2
Other	10
Lost to follow-up	3
Lack of efficacy	15
Joined	46
Discontinued prior to Week 24	46

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo every 2 week (q2w) until either early escape (EE) at Week 18, or crossover (CO) at Week 24.	
Reporting group title	Sirukumab 50 mg
Reporting group description:	
Subjects received Sirukumab 50 mg SC at Week 0, 4 and q4w up to Week 24.	
Reporting group title	Sirukumab 100 mg
Reporting group description:	
Subjects received Sirukumab 100 mg SC at Week 0, 2 and q2w up to Week 24.	

Reporting group values	Placebo	Sirukumab 50 mg	Sirukumab 100 mg
Number of subjects	294	292	292
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	228	225	230
From 65 to 84 years	66	67	62
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
arithmetic mean	55.4	55.8	55
standard deviation	± 12.28	± 11.89	± 12.31
Title for Gender			
Units: subjects			
Female	240	232	240
Male	54	60	52

Reporting group values	Total		
Number of subjects	878		
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	683		
From 65 to 84 years	195		
85 years and over	0		
Title for AgeContinuous			
Units: years			
arithmetic mean			
standard deviation	-		
Title for Gender			
Units: subjects			
Female	712		
Male	166		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo every 2 week (q2w) until either early escape (EE) at Week 18, or crossover (CO) at Week 24.	
Reporting group title	Sirukumab 50 mg
Reporting group description:	
Subjects received Sirukumab 50 mg SC at Week 0, 4 and q4w up to Week 24.	
Reporting group title	Sirukumab 100 mg
Reporting group description:	
Subjects received Sirukumab 100 mg SC at Week 0, 2 and q2w up to Week 24.	
Reporting group title	Placebo to 50 mg q4w due to EE or CO
Reporting group description:	
Subjects who received matching placebo in the placebo controlled period were re-randomized (due to early escape [EE] at Week 18 or crossed over [CO] at Week 24) to receive subcutaneous (SC) sirukumab 50 mg dose regimen q4w up to Week 52.	
Reporting group title	Sirukumab 50 mg
Reporting group description:	
Subjects continued to receive sirukumab 50 mg SC q4w from Week 24 up to Week 52.	
Reporting group title	Placebo to 100 mg q2w due to EE or CO
Reporting group description:	
Subjects who received matching placebo in the placebo controlled period were re-randomized (due to EE at Week 18 or CO at Week 24) to receive subcutaneous (SC) sirukumab 100 mg dose regimen q2w up to Week 52.	
Reporting group title	Sirukumab 100 mg q2w
Reporting group description:	
Subjects continued to receive sirukumab 100 mg SC q2w from Week 24 up to Week 52.	

Primary: Percentage of Subjects Achieving American College of Rheumatology (ACR)20 Response at Week 16

End point title	Percentage of Subjects Achieving American College of Rheumatology (ACR)20 Response at Week 16
End point description:	
The ACR 20 Response is defined as greater than or equal to (>=) 20 percent improvement in swollen joint count (66 joints) and tender joint count (68 joints) and >=20 percent improvement in 3 of following 5 assessments: patient's assessment of pain using Visual Analog Scale (VAS; 0-10 millimeter [mm], 0 mm=no pain and 10 mm=worst possible pain), patient's global assessment of disease activity by using VAS (the scale ranges from 0 mm to 100 mm, [0 mm=no pain to 100 mm=worst possible pain]), physician's global assessment of disease activity using VAS, participant's assessment of physical function measured by Health Assessment Questionnaire-Disability Index (HAQ-DI, defined as a 20-question instrument assessing 8 functional areas. The derived HAQ-DI ranges from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area) and serum C-Reactive Protein (CRP). Efficacy full analysis set included all subjects who were randomized into the study.	
End point type	Primary
End point timeframe:	
Week 16	

End point values	Placebo	Sirukumab 50 mg	Sirukumab 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294	292	292	
Units: Percentage of subjects				
number (not applicable)	24.1	40.1	45.2	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Sirukumab 50 mg
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.085
upper limit	0.232

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Sirukumab 100 mg
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.136
upper limit	0.285

Secondary: Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) Score at Week 24

End point title	Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) Score at Week 24

End point description:

The HAQ-DI is a 20-question instrument that assesses the degree of difficulty a person has in

accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping and activities of daily living). Responses in each functional area are scored from 0 to 3 (0=no difficulty and 3=inability to perform a task in that area). Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty. Here, 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this endpoint. Efficacy full analysis set included all subjects who were randomized into the study.

End point type	Secondary
End point timeframe:	
Week 24	

End point values	Placebo	Sirukumab 50 mg	Sirukumab 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294	291	292	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.12 (± 0.491)	-0.31 (± 0.543)	-0.33 (± 0.526)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Sirukumab 50 mg
Number of subjects included in analysis	585
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.251
upper limit	-0.088

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Sirukumab 100 mg
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.194

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.275
upper limit	-0.112

Secondary: Percentage of Subjects With Disease Activity Index Score 28 (CRP) Remission at Week 24

End point title	Percentage of Subjects With Disease Activity Index Score 28 (CRP) Remission at Week 24

End point description:

The Disease Activity Index Score 28 (DAS28) based on C-Reactive Protein (CRP) is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), CRP and patient's global assessment of disease activity. The set of 28 joint count is based on evaluation of the shoulder, elbow, wrist, metacarpophalangeal (MCP) MCP1 to MCP5, proximal interphalangeal (PIP) PIP1 to PIP5 joints of both the upper right extremity and the upper left extremity as well as the knee joints of lower right and lower left extremities. DAS28 (CRP) remission is defined as a DAS28 (CRP) value of less than (<) 2.6 at any study visit. Efficacy full analysis set included all subjects who were randomized into the study.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Sirukumab 50 mg	Sirukumab 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294	292	292	
Units: percentage of Subjects				
number (not applicable)	8.2	19.2	21.6	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Sirukumab 50 mg v Placebo
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.165

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Sirukumab 100 mg
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.134
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	0.191

Secondary: Percentage of Subjects Achieving American College of Rheumatology (ACR) 50 Response at Week 24

End point title	Percentage of Subjects Achieving American College of Rheumatology (ACR) 50 Response at Week 24

End point description:

The ACR 50 Response is defined as >=50 percent improvement in swollen joint count (66 joints) and tender joint count (68 joints) and >=50 percent improvement in 3 of following 5 assessments: patient's assessment of pain using VAS (0-10 mm, 0 mm=no pain and 10 mm=worst possible pain), patient's global assessment of disease activity by using VAS (the scale ranges from 0 mm to 100 mm, [0 mm=no pain to 100 mm=worst possible pain]), physician's global assessment of disease activity using VAS, participant's assessment of physical function measured by HAQ-DI and serum CRP. Efficacy full analysis set included all subjects who were randomized into the study.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Sirukumab 50 mg	Sirukumab 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294	292	292	
Units: percentage of subjects				
number (not applicable)	8.8	20.9	21.6	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Sirukumab 50 mg
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	0.177

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Sirukumab 100 mg
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.184

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 52

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Week (W) 24-Placebo

Reporting group description:

Subjects received matching placebo every 2 week (q2w) until either early escape (EE) at Week 18, or crossover (CO) at Week 24.

Reporting group title	W24-Placebo to 50 mg q4w due to EE or CO

Reporting group description:

Subjects who received matching placebo in the placebo controlled period and were re-randomized (due to early escape [EE] at Week 18 or crossed over [CO] at Week 24) to subcutaneous (SC) sirukumab 50 mg q4w dose regimen.

Reporting group title	W24-Sirukumab 50 mg q4w

Reporting group description:

Subjects received Sirukumab 50 mg SC at Week 0, 4 and q4w up to Week 24.

Reporting group title	W24-Placebo to 100 mg q2w due to EE or CO

Reporting group description:

Subjects who received matching placebo in the placebo controlled period and were re-randomized (due to early escape [EE] at Week 18 or crossed over [CO] at Week 24) to subcutaneous (SC) sirukumab 100 mg q2w dose regimen.

Reporting group title	W24-Sirukumab 100 mg q2w

Reporting group description:

Subjects received sirukumab 100 mg SC at Week 0, 2 and q2w up to Week 24.

Reporting group title	W52-Placebo to 50 mg q4w due to EE or CO

Reporting group description:

Subjects who received matching placebo in the placebo controlled period and were re-randomized (due to early escape [EE] at Week 18 or crossed over [CO] at Week 24) to receive subcutaneous (SC) sirukumab 50 mg q4w dose regimen up to Week 52.

Reporting group title	W52-Sirukumab 50 mg q4w

Reporting group description:

Subjects received Sirukumab 50 mg SC q4w up to Week 52.

Reporting group title	W52-Placebo to 100 mg q2w due to EE or CO

Reporting group description:

Subjects who received matching placebo in the placebo controlled period and were re-randomized (due to early escape [EE] at Week 18 or crossed over [CO] at Week 24) to receive subcutaneous (SC) sirukumab 100 mg q4w dose regimen up to Week 52.

Reporting group title	W52-Sirukumab 100 mg q2w

Reporting group description:

Subjects received Sirukumab 100 mg SC q2w up to Week 52.

Serious adverse events	Week (W) 24-Placebo	W24-Placebo to 50 mg q4w due to EE or CO	W24-Sirukumab 50 mg q4w
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 294 (5.10%)	0 / 46 (0.00%)	28 / 292 (9.59%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer Metastatic			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondroma			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Adenocarcinoma			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoproliferative Disorder			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal Squamous Cell Carcinoma			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Adenocarcinoma			

subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent Claudication			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosed Varicose Vein			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Missed			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Device Dislocation			

subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired Healing			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food Allergy			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical Dysplasia			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			

subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Interstitial Lung Disease			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Oedema			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal Discomfort			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Status Changes			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Enzyme Abnormal			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Function Test Abnormal			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Morganella Test Positive			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic Fracture			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon Rupture			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
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			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Coronary Artery Stenosis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Myocardial Infarction			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Nervous system disorders			
Carotid Artery Stenosis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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

Cerebrovascular Accident			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic Neuropathy			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Radiculopathy			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Normochromic Normocytic Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Pancytopenia			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal Fissure			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular Perforation			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum Intestinal			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Ulcer			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Duodenal Ulcer Perforation			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal Incontinence			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Gastric Ulcer			

subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Perforation			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis Erosive			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic Pseudocyst			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			

subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Eruption			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Ulcer			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Ureteric			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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

Calculus Urinary			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic Syndrome			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthrofibrosis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back Pain			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Foot Deformity			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
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 Chest Pain			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	2 / 292 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Osteonecrosis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Arthritis			

subjects affected / exposed	2 / 294 (0.68%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Nodule			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft Tissue Necrosis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Abscess			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess Jaw			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alpha Haemolytic Streptococcal Infection			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis Infective			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	2 / 292 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic Abscess			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Related Infection			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Empyema			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Sepsis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Herpes Zoster			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious Pleural Effusion			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Necrotising Fasciitis			

subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	4 / 292 (1.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	1 / 294 (0.34%)	0 / 46 (0.00%)	0 / 292 (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
Urosepsis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Infection Pseudomonas			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Hypokalaemia			
subjects affected / exposed	0 / 294 (0.00%)	0 / 46 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	W24-Placebo to 100 mg q2w due to EE or CO	W24-Sirukumab 100 mg q2w	W52-Placebo to 50 mg q4w due to EE or CO
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 48 (6.25%)	22 / 292 (7.53%)	7 / 124 (5.65%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer Metastatic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondroma			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Adenocarcinoma			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoproliferative Disorder			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Oropharyngeal Squamous Cell Carcinoma			

subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Adenocarcinoma			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent Claudication			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosed Varicose Vein			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Missed			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
General disorders and administration site conditions			
Chest Pain			

subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Dislocation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Impaired Healing			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food Allergy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical Dysplasia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Oedema			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal Discomfort			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Status Changes			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Enzyme Abnormal			
subjects affected / exposed	1 / 48 (2.08%)	0 / 292 (0.00%)	0 / 124 (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
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Function Test Abnormal			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Morganella Test Positive			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	0 / 48 (0.00%)	2 / 292 (0.68%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic Fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Tendon Rupture			

subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Coronary Artery Stenosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Carotid Artery Stenosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diabetic Neuropathy			
subjects affected / exposed	1 / 48 (2.08%)	0 / 292 (0.00%)	0 / 124 (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
Lumbar Radiculopathy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normochromic Normocytic Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal Fissure			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular Perforation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Diverticulum Intestinal			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Duodenal Ulcer			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Ulcer Perforation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Faecal Incontinence			

subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Perforation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis Erosive			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic Pseudocyst			

subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Cholelithiasis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Drug Eruption			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Ulcer			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Calculus Ureteric			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Urinary			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic Syndrome			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Renal Colic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	1 / 124 (0.81%)
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			
Arthralgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Arthrofibrosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthropathy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Deformity			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			

subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Rheumatoid Arthritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Nodule			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft Tissue Necrosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Abscess			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess Jaw			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alpha Haemolytic Streptococcal Infection			

subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Appendicitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis Infective			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Cellulitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 292 (0.00%)	0 / 124 (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
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Colonic Abscess			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Cystitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Device Related Infection			

subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Empyema			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Sepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious Pleural Effusion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising Fasciitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 292 (0.34%)	0 / 124 (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
Peritonitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	3 / 292 (1.03%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Infection Pseudomonas			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 292 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	W52-Sirukumab 50 mg q4w	W52-Placebo to 100 mg q2w due to EE or CO	W52-Sirukumab 100 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 292 (16.78%)	16 / 126 (12.70%)	37 / 292 (12.67%)
number of deaths (all causes)	1	1	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer Metastatic			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Chondroma			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Lung Adenocarcinoma			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoproliferative Disorder			

subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal Squamous Cell Carcinoma			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Adenocarcinoma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 292 (0.34%)	1 / 126 (0.79%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent Claudication			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Phlebitis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosed Varicose Vein			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Missed			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	2 / 292 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Dislocation			
subjects affected / exposed	2 / 292 (0.68%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired Healing			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Sudden Death			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Food Allergy			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Reproductive system and breast disorders			
Cervical Dysplasia			

subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Laryngeal Oedema			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Oropharyngeal Discomfort			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Pleural Effusion			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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

Mental Status Changes			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Hepatic Enzyme Abnormal			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Liver Function Test Abnormal			
subjects affected / exposed	1 / 292 (0.34%)	1 / 126 (0.79%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Morganella Test Positive			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	2 / 292 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic Fracture			

subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon Rupture			
subjects affected / exposed	2 / 292 (0.68%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Angina Unstable			
subjects affected / exposed	3 / 292 (1.03%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Coronary Artery Disease			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Stenosis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			

subjects affected / exposed	1 / 292 (0.34%)	1 / 126 (0.79%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Carotid Artery Stenosis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	2 / 292 (0.68%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic Neuropathy			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Lumbar Radiculopathy			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Transient Ischaemic Attack			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normochromic Normocytic Anaemia			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Thrombocytopenia			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Gastrointestinal disorders			
Anal Fissure			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular Perforation			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum Intestinal			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Ulcer			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Ulcer Perforation			

subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal Incontinence			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Gastric Ulcer Perforation			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis Erosive			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Intestinal Obstruction			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Large Intestine Polyp			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Gastrointestinal Haemorrhage			

subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Pancreatic Pseudocyst			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Eruption			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Ulcer			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
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			

Acute Kidney Injury			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Calculus Ureteric			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Calculus Urinary			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Nephrolithiasis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Nephrotic Syndrome			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
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 Colic			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthrofibrosis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Arthropathy			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Back Pain			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Deformity			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	2 / 292 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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 Chest Pain			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Osteoarthritis			
subjects affected / exposed	3 / 292 (1.03%)	1 / 126 (0.79%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			

subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
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	3 / 292 (1.03%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Nodule			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Soft Tissue Necrosis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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			
Abdominal Abscess			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Abscess Jaw			

subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Alpha Haemolytic Streptococcal Infection			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Arthritis Infective			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Bacteraemia			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 292 (0.68%)	2 / 126 (1.59%)	2 / 292 (0.68%)
occurrences causally related to treatment / all	1 / 2	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic Abscess			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			

subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Related Infection			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	2 / 292 (0.68%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Erysipelas			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Escherichia Sepsis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Gastroenteritis			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Herpes Zoster			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Infectious Pleural Effusion			

subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Influenza			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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
Necrotising Fasciitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Osteomyelitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	2 / 292 (0.68%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 292 (1.71%)	0 / 126 (0.00%)	5 / 292 (1.71%)
occurrences causally related to treatment / all	4 / 5	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Sepsis			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 292 (0.34%)	0 / 126 (0.00%)	0 / 292 (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
Wound Infection Pseudomonas			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 292 (0.00%)	0 / 126 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 292 (0.00%)	1 / 126 (0.79%)	0 / 292 (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: 5 %

Non-serious adverse events	Week (W) 24-Placebo	W24-Placebo to 50 mg q4w due to EE or CO	W24-Sirukumab 50 mg q4w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 294 (33.33%)	10 / 46 (21.74%)	109 / 292 (37.33%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	6 / 294 (2.04%)	1 / 46 (2.17%)	18 / 292 (6.16%)
occurrences (all)	6	1	18
Aspartate Aminotransferase Increased			
subjects affected / exposed	4 / 294 (1.36%)	1 / 46 (2.17%)	14 / 292 (4.79%)
occurrences (all)	4	1	14
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 294 (2.38%)	0 / 46 (0.00%)	9 / 292 (3.08%)
occurrences (all)	7	0	9
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	4 / 294 (1.36%)	2 / 46 (4.35%)	22 / 292 (7.53%)
occurrences (all)	4	2	22

Injection Site Pruritus			
subjects affected / exposed	2 / 294 (0.68%)	1 / 46 (2.17%)	5 / 292 (1.71%)
occurrences (all)	2	1	5
Injection Site Swelling			
subjects affected / exposed	0 / 294 (0.00%)	2 / 46 (4.35%)	3 / 292 (1.03%)
occurrences (all)	0	2	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 294 (0.68%)	0 / 46 (0.00%)	7 / 292 (2.40%)
occurrences (all)	2	0	7
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 294 (1.02%)	0 / 46 (0.00%)	6 / 292 (2.05%)
occurrences (all)	3	0	6
Musculoskeletal and connective tissue disorders			
Rheumatoid Arthritis			
subjects affected / exposed	28 / 294 (9.52%)	2 / 46 (4.35%)	13 / 292 (4.45%)
occurrences (all)	28	2	13
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 294 (1.70%)	0 / 46 (0.00%)	6 / 292 (2.05%)
occurrences (all)	5	0	6
Nasopharyngitis			
subjects affected / exposed	11 / 294 (3.74%)	0 / 46 (0.00%)	21 / 292 (7.19%)
occurrences (all)	11	0	21
Pharyngitis			
subjects affected / exposed	9 / 294 (3.06%)	3 / 46 (6.52%)	6 / 292 (2.05%)
occurrences (all)	9	3	6
Sinusitis			
subjects affected / exposed	8 / 294 (2.72%)	1 / 46 (2.17%)	11 / 292 (3.77%)
occurrences (all)	8	1	11
Upper Respiratory Tract Infection			
subjects affected / exposed	19 / 294 (6.46%)	0 / 46 (0.00%)	19 / 292 (6.51%)
occurrences (all)	19	0	19
Urinary Tract Infection			

subjects affected / exposed	11 / 294 (3.74%)	0 / 46 (0.00%)	4 / 292 (1.37%)
occurrences (all)	11	0	4

Non-serious adverse events	W24-Placebo to 100 mg q2w due to EE or CO	W24-Sirukumab 100 mg q2w	W52-Placebo to 50 mg q4w due to EE or CO
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 48 (12.50%)	135 / 292 (46.23%)	43 / 124 (34.68%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 48 (4.17%)	17 / 292 (5.82%)	12 / 124 (9.68%)
occurrences (all)	2	17	12
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 48 (2.08%)	12 / 292 (4.11%)	6 / 124 (4.84%)
occurrences (all)	1	12	6
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 48 (0.00%)	8 / 292 (2.74%)	3 / 124 (2.42%)
occurrences (all)	0	8	3
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	1 / 48 (2.08%)	41 / 292 (14.04%)	5 / 124 (4.03%)
occurrences (all)	1	41	5
Injection Site Pruritus			
subjects affected / exposed	0 / 48 (0.00%)	28 / 292 (9.59%)	4 / 124 (3.23%)
occurrences (all)	0	28	4
Injection Site Swelling			
subjects affected / exposed	1 / 48 (2.08%)	21 / 292 (7.19%)	2 / 124 (1.61%)
occurrences (all)	1	21	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 48 (0.00%)	13 / 292 (4.45%)	3 / 124 (2.42%)
occurrences (all)	0	13	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 48 (0.00%)	11 / 292 (3.77%)	2 / 124 (1.61%)
occurrences (all)	0	11	2
Musculoskeletal and connective tissue			

disorders			
Rheumatoid Arthritis			
subjects affected / exposed	1 / 48 (2.08%)	15 / 292 (5.14%)	12 / 124 (9.68%)
occurrences (all)	1	15	12
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 48 (0.00%)	11 / 292 (3.77%)	6 / 124 (4.84%)
occurrences (all)	0	11	6
Nasopharyngitis			
subjects affected / exposed	1 / 48 (2.08%)	15 / 292 (5.14%)	2 / 124 (1.61%)
occurrences (all)	1	15	2
Pharyngitis			
subjects affected / exposed	0 / 48 (0.00%)	5 / 292 (1.71%)	4 / 124 (3.23%)
occurrences (all)	0	5	4
Sinusitis			
subjects affected / exposed	0 / 48 (0.00%)	7 / 292 (2.40%)	4 / 124 (3.23%)
occurrences (all)	0	7	4
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 48 (0.00%)	12 / 292 (4.11%)	4 / 124 (3.23%)
occurrences (all)	0	12	4
Urinary Tract Infection			
subjects affected / exposed	0 / 48 (0.00%)	14 / 292 (4.79%)	1 / 124 (0.81%)
occurrences (all)	0	14	1

Non-serious adverse events	W52-Sirukumab 50 mg q4w	W52-Placebo to 100 mg q2w due to EE or CO	W52-Sirukumab 100 mg q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 292 (50.34%)	57 / 126 (45.24%)	162 / 292 (55.48%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	27 / 292 (9.25%)	8 / 126 (6.35%)	23 / 292 (7.88%)
occurrences (all)	27	8	23
Aspartate Aminotransferase Increased			
subjects affected / exposed	18 / 292 (6.16%)	5 / 126 (3.97%)	15 / 292 (5.14%)
occurrences (all)	18	5	15
Vascular disorders			

Hypertension			
subjects affected / exposed	17 / 292 (5.82%)	3 / 126 (2.38%)	15 / 292 (5.14%)
occurrences (all)	17	3	15
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	28 / 292 (9.59%)	19 / 126 (15.08%)	47 / 292 (16.10%)
occurrences (all)	28	19	47
Injection Site Pruritus			
subjects affected / exposed	8 / 292 (2.74%)	10 / 126 (7.94%)	31 / 292 (10.62%)
occurrences (all)	8	10	31
Injection Site Swelling			
subjects affected / exposed	4 / 292 (1.37%)	7 / 126 (5.56%)	24 / 292 (8.22%)
occurrences (all)	4	7	24
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 292 (4.45%)	4 / 126 (3.17%)	22 / 292 (7.53%)
occurrences (all)	13	4	22
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 292 (3.08%)	0 / 126 (0.00%)	15 / 292 (5.14%)
occurrences (all)	9	0	15
Musculoskeletal and connective tissue disorders			
Rheumatoid Arthritis			
subjects affected / exposed	30 / 292 (10.27%)	4 / 126 (3.17%)	30 / 292 (10.27%)
occurrences (all)	30	4	30
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 292 (4.45%)	4 / 126 (3.17%)	22 / 292 (7.53%)
occurrences (all)	13	4	22
Nasopharyngitis			
subjects affected / exposed	34 / 292 (11.64%)	7 / 126 (5.56%)	26 / 292 (8.90%)
occurrences (all)	34	7	26
Pharyngitis			
subjects affected / exposed	9 / 292 (3.08%)	3 / 126 (2.38%)	10 / 292 (3.42%)
occurrences (all)	9	3	10
Sinusitis			

subjects affected / exposed	14 / 292 (4.79%)	3 / 126 (2.38%)	15 / 292 (5.14%)
occurrences (all)	14	3	15
Upper Respiratory Tract Infection			
subjects affected / exposed	24 / 292 (8.22%)	9 / 126 (7.14%)	26 / 292 (8.90%)
occurrences (all)	24	9	26
Urinary Tract Infection			
subjects affected / exposed	13 / 292 (4.45%)	6 / 126 (4.76%)	19 / 292 (6.51%)
occurrences (all)	13	6	19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2012	Clarification on the status of contraception of sexually active women; Clarification on the requirements for QuantiFERON-TB Gold test or purified protein derivative (PPD) test; Clarification of the exclusion criterion regarding the use of etanercept or yisaipu within 6 weeks of first study agent administration; Clarification that in the event of clinically significant decreases in neutrophils or platelet counts, methotrexate (MTX) should be temporarily or permanently discontinued; Clarification on the time period during which intra-articular (IA) steroid injections are allowed; Clarification on the training requirements for the independent joint assessor (IJA) and backup IJA was made; Questions added to the WLQ were removed; All events that met liver chemistry stopping criteria had to be reported as a serious adverse event (SAE); Text describing interruption of study agent administration was added; Clarification of hepatitis B virus (HBV) monitoring for subjects without detectable HBV deoxyribonucleic acid (DNA) at screening were made.
26 September 2013	Deletion of selected study site visits and allowance of subjects to self-administer study agent at home; Addition of the erythrocyte sedimentation rate (ESR) evaluation to the Screening visit assessments; Inclusion criterion was revised to: subjects must have a screening CRP level .8.00 mg/L or ESR .28 mm/hr; Retesting and rescreening procedures were revised to allow retesting of laboratory values or study entry procedure once; Exclusion criteria were modified to allow for shorter washout periods for a biologic prior to study entry, to clarify the procedure for detection of the M1 metabolite of leflunomide, if applicable; Clarification that subjects who have received the Bacille Calmette-Guerin vaccine within 12 months of screening were ineligible for the study; Clarification to Prohibitions and Restrictions that a woman must not donate eggs (ova,oocytes) for the purposes of assisted reproduction during the study and for 4 months after receiving the last dose of study agent; Clarification on the self-administration of study agent; Clarification on treatment compliance was added due to allowance of self-administration of study agent; Tofacitinib (XELJANZR) and any other biologic agent for the treatment of RA have been added to the list of prohibited medications; Clinic visits and self-administration schedules have been revised; The schedule for the collection of blood samples has been revised to match the revised studysite visit schedule; Clarification was made that all initial product quality complaints (PQCs) must be reported tothe Sponsor by the investigational staff within 24 hours after being made aware of the event; Clarifications on the transportation, storage, and administration of study agent by subjects who are able to self-administer the study agent at home were made; Clarification of HBV monitoring for subjects without detectable HBV DNA at screening was made.

18 February 2014	The total number of subjects to be enrolled was decreased from 990 to 840 subjects; The subject's name and date of birth were removed from the study card; Clarifications on the criteria for the planned statistical analyses of clinical laboratory data were made.
09 May 2014	Golimumab intravenous (IV) was added to list of anti-TNF agents that require a washout period prior to the first administration of study agent; Per data monitoring committee (DMC) recommendation, GI perforation and acute diverticulitis were added to the list of conditions that would result in the permanent discontinuation of study agent administrations; Introductory text was added and contents of the study card have been updated; Clarification was made that subject would be eligible for enrollment in the long term extension (LTE) provided a participating site is available to them; Clarification for subjects who do not participate in the LTE study was made; Clarification on the definition of end of study was made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported