Clinical trial results:
A Multi-center, Uncontrolled Extension Study Evaluating Efficacy and Safety of SAR153191 in Patients With Active Rheumatoid Arthritis (RA)

Summary

EudraCT number	2010-019262-86
Trial protocol	ES FI EE HU NL DE GR NO LT CZ IT AT PT SK GB BE SE
Global end of trial date	31 December 2020

Results information

Result version number	v2 (current)
This version publication date	06 January 2023
First version publication date	11 January 2022
Version creation reason	• Correction of full data set Updated safety optional field

Trial information

Trial identification

Sponsor protocol code	LTS11210

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01146652
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly Mazarin Cedex, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of sarilumab in subjects with RA.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Subjects who completed any of the initial studies EFC11072 (2009-016266-90), ACT11575 (2010-021020-94), EFC10832 (2011-003538-16), SFY13370 (2012-003536-23), EFC13752 (2013-002790-22) were enrolled in study LTS11210.

Evidence for comparator: -

Actual start date of recruitment	21 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Belarus: 11
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Colombia: 61
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Chile: 123
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	Mexico: 223
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	New Zealand: 18
Country: Number of subjects enrolled	Poland: 224
Country: Number of subjects enrolled	Thailand: 2

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Peru: 43
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Brazil: 65
Country: Number of subjects enrolled	Czechia: 31
Country: Number of subjects enrolled	Estonia: 36
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Philippines: 6
Country: Number of subjects enrolled	Ukraine: 60
Country: Number of subjects enrolled	South Africa: 85
Country: Number of subjects enrolled	Argentina: 182
Country: Number of subjects enrolled	Guatemala: 12
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Romania: 46
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	Hungary: 70
Country: Number of subjects enrolled	Russian Federation: 228
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United States: 284
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Ecuador: 11
Country: Number of subjects enrolled	Lithuania: 12
Worldwide total number of subjects	2023
EEA total number of subjects	514

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)	1732
From 65 to 84 years	290
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

2023 subjects who completed any of studies EFC11072, ACT11575, EFC10832, SFY13370, EFC13752 were eligible and enrolled in study LTS11210 between 21-Jun-2010 and 04-May-2015. From Week 24 of LTS11210, willing subjects were enrolled in a 12-week sub-study (part of main study only) to assess usability of pre-filled syringe with safety system (PFS-S).

Pre-assignment

Screening details:

Exposure to sarilumab: for 12 weeks (W) if they were initially randomised (R) in EFC11072 Part A or ACT11575; up to 52 W if initially R in EFC11072 Part B; up to 24 W if initially R in EFC10832; or for 24 W if initially R in SFY13370 or EFC13752. Subject's end-of-treatment visit in initial study corresponded to initial visit in study LTS11210.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)

Arm description:

Subjects who completed any of initial studies:Part A or B of EFC11072, ACT11575, EFC10832 or SFY13370 were enrolled in LTS11210 and received sarilumab 150 milligrams (mg) subcutaneously (SC) once weekly (qw). Dose could be reduced to 150 mg every 2 weeks (q2w) due to neutropenia, thrombocytopenia or increase in liver enzymes (alanine aminotransferase [ALT]). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), subjects already receiving 150 mg qw were switched to sarilumab 200 mg q2w. Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks). Subjects who were already taking concomitant non-biologic DMARDs in initial study continued stable dose of one or combination of conventional synthetic DMARDs they were taking.

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

Dosage and administration details:

Sarilumab 150 mg, SC injection qw. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), 150 mg qw was switched to sarilumab 200 mg q2w.

Arm title	Sarilumab monotherapy

Arm description:

Subjects who completed study EFC13752 were enrolled in LTS11210 and received sarilumab 200 mg q2w. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks).

Arm type	Experimental

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

Dosage and administration details:

Sarilumab 150 mg, SC injection qw. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), 150 mg qw was switched to sarilumab 200 mg q2w.

Number of subjects in period 1	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy
Started	1912	111
Treated	1910	111
Enrolled in the sub-study	110 [1]	14 [2]
Discontinued from the sub-study	1 [3]	2 [4]
Switched back to main study	108 [5]	13 [6]
Completed	961	66
Not completed	951	45
Adverse event, non-fatal	506	15
Poor compliance to protocol	38	1
Other unspecified reasons	314	22
Enrolled but not treated	2	-
Lack of efficacy	91	7

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects who were eligible and entered sub-study from Week 24 of main study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects who were eligible and entered sub-study from Week 24 of main study.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Sub-study discontinued subjects were included in the discontinuation count of the main study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Sub-study discontinued subjects were included in the discontinuation count of the main study.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects who were willing to switch back to the main study regardless of if they completed the sub-study.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects who were willing to switch back to the main study regardless of if they completed the sub-study.

Baseline characteristics

Reporting groups

Reporting group title	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)

Reporting group description:

Subjects who completed any of initial studies:Part A or B of EFC11072, ACT11575, EFC10832 or SFY13370 were enrolled in LTS11210 and received sarilumab 150 milligrams (mg) subcutaneously (SC) once weekly (qw). Dose could be reduced to 150 mg every 2 weeks (q2w) due to neutropenia, thrombocytopenia or increase in liver enzymes (alanine aminotransferase [ALT]). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), subjects already receiving 150 mg qw were switched to sarilumab 200 mg q2w. Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks). Subjects who were already taking concomitant non-biologic DMARDs in initial study continued stable dose of one or combination of conventional synthetic DMARDs they were taking.

Reporting group title	Sarilumab monotherapy

Reporting group description:

Subjects who completed study EFC13752 were enrolled in LTS11210 and received sarilumab 200 mg q2w. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks).

Reporting group values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy	Total
Number of subjects	1912	111	2023
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 52.1 ± 11.8	 52.9 ± 13.1	 -
Gender categorical Units: Subjects			
Female	1550	88	1638
Male	362	23	385
Race/Ethnicity, Customized Units: Subjects			
Caucasian/White	1639	108	1747
Black	48	1	49
Asian/Oriental	69	1	70
Other	156	1	157

End points reporting groups

Reporting group title	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)

Reporting group description:

Subjects who completed any of initial studies:Part A or B of EFC11072, ACT11575, EFC10832 or SFY13370 were enrolled in LTS11210 and received sarilumab 150 milligrams (mg) subcutaneously (SC) once weekly (qw). Dose could be reduced to 150 mg every 2 weeks (q2w) due to neutropenia, thrombocytopenia or increase in liver enzymes (alanine aminotransferase [ALT]). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), subjects already receiving 150 mg qw were switched to sarilumab 200 mg q2w. Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks). Subjects who were already taking concomitant non-biologic DMARDs in initial study continued stable dose of one or combination of conventional synthetic DMARDs they were taking.

Reporting group title	Sarilumab monotherapy

Reporting group description:

Subjects who completed study EFC13752 were enrolled in LTS11210 and received sarilumab 200 mg q2w. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks).

Subject analysis set title	Sarilumab + DMARD: EFC11072 Part B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who completed EFC11072 Part B were enrolled in LTS11210 and received sarilumab 150 mg SC qw. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), subjects already receiving 150 mg qw were switched to sarilumab 200 mg q2w. Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks). Subjects who were already taking concomitant non-biologic DMARDs in initial study continued stable dose of one or combination of conventional synthetic DMARDs they were taking.

Subject analysis set title	Sarilumab + DMARD: EFC11072, ACT11575 and EFC10832
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who completed any of the initial studies: Part A or Part B of EFC11072, ACT11575, and EFC10832 were enrolled in LTS11210 and received sarilumab 150 mg SC qw. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), subjects already receiving 150 mg qw were switched to sarilumab 200 mg q2w. Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks). Subjects who were already taking concomitant non-biologic DMARDs in initial study continued stable dose of one or combination of conventional synthetic DMARDs they were taking.

Subject analysis set title	Sarilumab + DMARD: EFC11072, and ACT11575
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who completed any of the initial studies: Part A or Part B of EFC11072, and ACT11575 were enrolled in LTS11210 and received sarilumab 150 mg SC qw. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), subjects already receiving 150 mg qw were switched to sarilumab 200 mg q2w. Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks). Subjects who were already taking concomitant non-biologic DMARDs in initial study continued stable dose of one or combination of conventional synthetic DMARDs they were taking.

Subject analysis set title	Sarilumab + DMARD: EFC10832

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who completed study EFC10832 were enrolled in LTS11210 and received sarilumab 150 mg SC qw. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), subjects already receiving 150 mg qw were switched to sarilumab 200 mg q2w. Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks). Subjects who were already taking concomitant non-biologic DMARDs in initial study continued stable dose of one or combination of conventional synthetic DMARDs they were taking.

Subject analysis set title	PFS-S Sarilumab 150 mg q2w
Subject analysis set type	Sub-group analysis

Subject analysis set description:

From Week 24 of main study, eligible subjects entered sub-study and received sarilumab 150 mg SC q2w for 12 weeks (i.e., from main study Week 24 to Week 36) using PFS-S.

Subject analysis set title	PFS-S Sarilumab 200 mg q2w
Subject analysis set type	Sub-group analysis

Subject analysis set description:

From Week 24 of main study, eligible subjects entered sub-study and received sarilumab 200 mg SC q2w for 12 weeks (i.e., from main study Week 24 to Week 36) using PFS-S.

Subject analysis set title	PFS-S Sarilumab 200 to 150 mg q2w
Subject analysis set type	Sub-group analysis

Subject analysis set description:

From Week 24 of main study, eligible subjects entered sub-study and received sarilumab 200 mg SC q2w for 12 weeks (i.e., from main study Week 24 to Week 36) using PF-S. The dose might be reduced to 150 mg q2w due to neutropenia, thrombocytopenia, or an increase in liver enzymes.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical study subject administered a medicinal product and which did not necessarily have to have a causal relationship with the treatment. An SAE was any untoward medical occurrence at any dose that: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were AEs that developed or worsened or became serious during the TEAE period (defined as the time from the first dose of the investigational medicinal product (IMP) in study LTS11210 to the last dose of the IMP +60 days). Analysis was performed on safety population which included all enrolled subjects who had received at least one dose of the study treatment in LTS11210.

End point type	Primary

End point timeframe:

From first dose (i.e., Day 1 of study LTS11210) up to 60 days after last dose (maximum duration: up to 523 weeks)

Notes:

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

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1910	111		
Units: subjects				

Any TEAE	1760	98		
Any TE SAE	617	27		

Statistical analyses

No statistical analyses for this end point

Primary: Sub-study: Number of Subjects Reported Product Technical Complaints (PTC), Product Technical Failures (PTF) and/or Failed Drug Deliveries (FDD) With Pre-filled Syringe With Safety System

End point title	Sub-study: Number of Subjects Reported Product Technical Complaints (PTC), Product Technical Failures (PTF) and/or Failed Drug Deliveries (FDD) With Pre-filled Syringe With Safety System[2]

End point description:

A PTF was defined as any product technical complaint (PTC) related to the use of the PFS-S that had a validated technical cause. FDD was defined as subject's failure to administer the full dose at a given attempt. A PTC was defined as any subject- or healthcare provider-reported complaint regarding the use of the PFS-S syringe and collected via the completion of the injection diary. The injection diary comprised specific questions: 1. Were you able to remove the cap? 2. Was the needle safety system activated?, 3. Did the safety system entirely cover the needle, and 4. Was the person who performed the injection the person who was trained by the site staff?, where each question was given the option yes/no. Subjects who answered "no" for any of the questions of PTC, had PTF and/or FDD were reported in this endpoint. Analysis was performed on all subjects who were enrolled in the sub-study.

End point type	Primary

End point timeframe:

From Week 24 to 36

Notes:

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

End point values	PFS-S Sarilumab 150 mg q2w	PFS-S Sarilumab 200 mg q2w	PFS-S Sarilumab 200 to 150 mg q2w	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	98	1	
Units: subjects				
PFS-S-associated PTF	0	0	0	
PFS-S-associated FDD	0	5	0	
PFS-S-associated PTC	0	5	0	

Statistical analyses

No statistical analyses for this end point

Primary: Sub-study: Number of Product Technical Complaints - Product Technical Failures With Pre-filled Syringe With Safety System

End point title	Sub-study: Number of Product Technical Complaints - Product Technical Failures With Pre-filled Syringe With Safety System[3]

End point description:

A PTF was defined as any PTC (defined as any subject- or healthcare provider-reported complaint regarding the use of the PFS-S syringe and collected via the completion of the injection diary) related to the use of the PFS-S that had a validated technical cause. Number of PTF in the subjects enrolled in sub-study were reported in this endpoint. Analysis was performed on all subjects who were enrolled in the sub-study.

End point type	Primary

End point timeframe:

From Week 24 to 36

Notes:

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

End point values	PFS-S Sarilumab 150 mg q2w	PFS-S Sarilumab 200 mg q2w	PFS-S Sarilumab 200 to 150 mg q2w	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	98	1	
Units: PTF	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Sub-study: Number of Failed Drug Deliveries Associated With Pre-filled Syringe With Safety System

End point title	Sub-study: Number of Failed Drug Deliveries Associated With Pre-filled Syringe With Safety System[4]

End point description:

FDD was defined as subject’s failure to administer the full dose at a given attempt. Number of FDD in the subjects enrolled in sub-study were reported in this endpoint. Analysis was performed on all subjects who were enrolled in the sub-study.

End point type	Primary

End point timeframe:

From Week 24 to 36

Notes:

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

End point values	PFS-S Sarilumab 150 mg q2w	PFS-S Sarilumab 200 mg q2w	PFS-S Sarilumab 200 to 150 mg q2w	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	98	1	
Units: FDD	0	5	0	

Statistical analyses

No statistical analyses for this end point

Primary: Sub-study: Number of Product Technical Complaints With Pre-filled Syringe With Safety System

End point title	Sub-study: Number of Product Technical Complaints With Pre-filled Syringe With Safety System[5]

End point description:

A PTC was defined as any subject- or healthcare provider-reported complaint regarding the use of the PFS-S syringe and collected via the completion of the injection diary. The injection diary comprised specific questions: 1. Were you able to remove the cap? 2. Was the needle safety system activated?, 3. Did the safety system entirely cover the needle, and 4. Was the person who performed the injection the person who was trained by the site staff?, where each question was given the option yes/no. Number of PTC (based on subject's answer to "no" for any of the questions of PTC) in the subjects enrolled in sub-study were reported in this endpoint. Analysis was performed on all subjects who were enrolled in the sub-study.

End point type	Primary

End point timeframe:

From Week 24 to 36

Notes:

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

End point values	PFS-S Sarilumab 150 mg q2w	PFS-S Sarilumab 200 mg q2w	PFS-S Sarilumab 200 to 150 mg q2w	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	98	1	
Units: PTC	0	5	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 20 (ACR20) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 20 (ACR20) Response

End point description:

ACR20 response: greater than or equal to (>=) 20% improvement in both tender joint count and swollen joint count and >=20% improvement in at least 3 of 5 remaining ACR core measures assessments: C-reactive protein [CRP] level (mg/litre [mg/L]); subject's assessment of pain (measured on 0 [no pain] to 100 mm [worst pain] visual analog scale [VAS]); subject's global assessment of disease activity (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS); physician's global assessment of disease activity (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS); subject's assessment of physical function (measured by health assessment questionnaire disability index, with scoring range of 0 [better physical function] to 3 [worst physical function]). Higher score = worse outcomes. Safety population: subjects who had at least 1 dose of study treatment in LTS11210. Here, number of subjects analysed=subjects evaluable and n=subjects with data.

End point type	Secondary

End point timeframe:

At Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1898	111		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 0 (1898, 111)	69.4 (67.3 to 71.5)	82.0 (73.6 to 88.6)		
Week 4 (n=1885, 106)	77.8 (75.8 to 79.6)	85.8 (77.7 to 91.9)		
Week 8 (n=1852, 106)	80.2 (78.3 to 82.0)	92.5 (85.7 to 96.7)		
Week 12 (n=1829, 109)	80.3 (78.4 to 82.1)	91.7 (84.9 to 96.2)		
Week 24 (n=1787, 109)	82.9 (81.1 to 84.6)	88.1 (80.5 to 93.5)		
Week 36 (n= 1730, 109)	82.8 (80.9 to 84.5)	91.7 (84.9 to 96.2)		
Week 48 (n=1670, 107)	82.9 (81.0 to 84.7)	85.0 (76.9 to 91.2)		
Week 60 (n=1618, 103)	84.6 (82.8 to 86.3)	93.2 (86.5 to 97.2)		
Week 72 (n=1586, 101)	84.4 (82.5 to 86.1)	94.1 (87.5 to 97.8)		
Week 84 (n=1550, 95)	84.5 (82.6 to 86.2)	94.7 (88.1 to 98.3)		
Week 96 (n=1510, 92)	85.2 (83.3 to 87.0)	91.3 (83.6 to 96.2)		
Week 120 (n=1456, 88)	84.9 (82.9 to 86.7)	90.9 (82.9 to 96.0)		
Week 144 (n=1389, 83)	86.4 (84.5 to 88.2)	94.0 (86.5 to 98.0)		
Week 168 (n=1322,81)	86.0 (84.0 to 87.8)	90.1 (81.5 to 95.6)		
Week 192 (n=1263, 75)	85.7 (83.7 to 87.6)	89.3 (80.1 to 95.3)		
Week 216 (n=1189, 74)	87.1 (85.1 to 89.0)	89.2 (79.8 to 95.2)		
Week 240 (n=1125, 74)	86.4 (84.3 to 88.4)	91.9 (83.2 to 97.0)		
Week 264 (n=1049, 61)	88.5 (86.4 to 90.3)	90.2 (79.8 to 96.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 50 (ACR50) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 50 (ACR50) Response

End point description:

ACR50 response: >=50% improvement in both TJC and SJC, and >=50% improvement in at least 3 of the 5 remaining ACR core measures assessments: CRP level (in mg/L); subject's assessment of pain (measured on 0 [no pain] to 100 mm [worst pain] VAS); subject's global assessment of disease activity (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS); physician's global assessment of disease activity (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS); subject's assessment of physical function (measured by HAQ-DI, with scoring range of 0 [better physical function] to 3 [worst physical function]). Higher score indicated worse outcomes. Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

At Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1897	111		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 0 (n=1897, 111)	43.4 (41.2 to 45.7)	58.6 (48.8 to 67.8)		
Week 4 (n=1884, 108)	51.3 (49.0 to 53.6)	59.3 (49.4 to 68.6)		
Week 8 (n=1850, 105)	55.1 (52.8 to 57.4)	59.0 (49.0 to 68.5)		
Week 12 (n=1830, 108)	58.1 (55.8 to 60.4)	66.7 (56.9 to 75.4)		
Week 24 (n=1782, 109)	60.5 (58.2 to 62.8)	64.2 (54.5 to 73.2)		
Week 36 (n=1729, 109)	62.1 (59.8 to 64.4)	64.2 (54.5 to 73.2)		
Week 48 (n=1669, 107)	62.4 (60.0 to 64.7)	69.2 (59.5 to 77.7)		
Week 60 (n=1620, 103)	63.2 (60.8 to 65.6)	68.9 (59.1 to 77.7)		
Week 72 (n=1585, 101)	64.8 (62.4 to 67.1)	71.3 (61.4 to 79.9)		
Week 84 (n=1546, 94)	63.6 (61.2 to 66.1)	73.4 (63.3 to 82.0)		
Week 96 (n=1511, 92)	65.3 (62.8 to 67.7)	71.7 (61.4 to 80.6)		
Week 120 (n=1455, 87)	65.6 (63.1 to 68.0)	73.6 (63.0 to 82.4)		
Week 144 (n=1385, 84)	65.7 (63.1 to 68.2)	70.2 (59.3 to 79.7)		
Week 168 (n=1320, 80)	66.2 (63.6 to 68.8)	70.0 (58.7 to 79.7)		
Week 192 (n=1257, 75)	68.4 (65.8 to 71.0)	70.7 (59.0 to 80.6)		

Week 216 (n=1189, 74)	69.0 (66.3 to 71.7)	75.7 (64.3 to 84.9)		
Week 240 (n=1125, 74)	68.3 (65.5 to 71.0)	79.7 (68.8 to 88.2)		
Week 264 (n=1040, 60)	69.6 (66.7 to 72.4)	71.7 (58.6 to 82.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 70 (ACR70) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 70 (ACR70) Response

End point description:

ACR70 response: >=70% improvement in both TJC and SJC, and >=70% improvement in at least 3 of the 5 remaining ACR core measures assessments: CRP level (in mg/L); subject's assessment of pain (measured on 0 [no pain] to 100 mm [worst pain] VAS); subject's global assessment of disease activity (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS); physician's global assessment of disease activity (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS); subject's assessment of physical function (measured by HAQ-DI, with scoring range of 0 [better physical function] to 3 [worst physical function]). Higher score indicated worse outcomes. Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and 'n' = subject with available data for each specified category.

End point type	Secondary

End point timeframe:

At Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1901	111		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 0 (n=1901, 111)	22.9 (21.0 to 24.8)	32.4 (23.9 to 42.0)		
Week 4 (n=1879, 108)	27.8 (25.8 to 29.9)	31.5 (22.9 to 41.1)		
Week 8 (n=1854, 105)	32.1 (30.0 to 34.3)	36.2 (27.0 to 46.1)		
Week 12 (n=1829, 107)	34.1 (31.9 to 36.3)	43.0 (33.5 to 52.9)		
Week 24 (n=1781, 107)	38.7 (36.4 to 41.0)	37.4 (28.2 to 47.3)		
Week 36 (n=1726, 109)	40.2 (37.9 to 42.6)	40.4 (31.1 to 50.2)		
Week 48 (n=1666, 105)	40.6 (38.3 to 43.0)	43.8 (34.1 to 53.8)		

Week 60 (n=1618, 103)	41.6 (39.2 to 44.0)	45.6 (35.8 to 55.7)		
Week 72 (n=1585, 100)	42.1 (39.6 to 44.6)	49.0 (38.9 to 59.2)		
Week 84 (n=1541, 94)	41.8 (39.3 to 44.3)	52.1 (41.6 to 62.5)		
Week 96 (n=1510, 92)	43.4 (40.9 to 45.9)	55.4 (44.7 to 65.8)		
Week 120 (n=1449, 88)	42.9 (40.3 to 45.5)	56.8 (45.8 to 67.3)		
Week 144 (n=1386, 84)	44.7 (42.0 to 47.3)	50.0 (38.9 to 61.1)		
Week 168 (n=1317, 80)	45.6 (42.9 to 48.4)	51.3 (39.8 to 62.6)		
Week 192 (n=1262, 76)	47.9 (45.1 to 50.7)	53.9 (42.1 to 65.5)		
Week 216 (n=1186, 71)	46.8 (43.9 to 49.7)	62.0 (49.7 to 73.2)		
Week 240 (n=1123, 74)	47.9 (44.9 to 50.9)	60.8 (48.8 to 72.0)		
Week 264 (n=1030, 60)	48.8 (45.7 to 51.9)	58.3 (44.9 to 70.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Activity Score for 28 Joints (DAS28) Remission

End point title	Percentage of Subjects With Disease Activity Score for 28 Joints (DAS28) Remission

End point description:

Disease activity score based on 28 joints and C-reactive protein (DAS28-CRP) was a composite score which included 4 components: TJC with 28 joints assessed; SJC with 28 joints assessed; high-sensitivity CRP (in mg/L) and general health assessment by the subject using subject global assessment (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS). DAS28-CRP total score ranges from 0 to 10, where higher scores indicated greater disease activity. Percentage of subjects with DAS28 remission were reported. Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and n' = subject with available data for each specified category and "99999" was used as space filler which indicates that data was not planned to be collected and analysed for the specified time-points in the respective groups.

End point type	Secondary

End point timeframe:

At Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1873	110		

Units: percentage of subjects				
number (confidence interval 95%)				
Week 0 (n=1873, 110)	30.4 (28.3 to 32.5)	46.4 (36.8 to 56.1)		
Week 4 (n=1867, 106)	39.2 (36.9 to 41.4)	51.9 (42.0 to 61.7)		
Week 8 (n=1804, 105)	44.6 (42.3 to 46.9)	49.5 (39.6 to 59.5)		
Week 12 (n=1819, 109)	47.9 (45.6 to 50.3)	55.0 (45.2 to 64.6)		
Week 24 (n=1778, 109)	50.6 (48.2 to 52.9)	59.6 (49.8 to 68.9)		
Week 36 (n=1721, 109)	51.7 (49.3 to 54.1)	59.6 (49.8 to 68.9)		
Week 48 (n=1661, 107)	53.7 (51.3 to 56.1)	56.1 (46.1 to 65.7)		
Week 60 (n=1608, 102)	56.5 (54.1 to 59.0)	61.8 (51.6 to 71.2)		
Week 72 (n=1580, 101)	55.8 (53.3 to 58.3)	68.3 (58.3 to 77.2)		
Week 84 (n=1537, 95)	55.8 (53.2 to 58.3)	70.5 (60.3 to 79.4)		
Week 96 (n=1506, 92)	57.0 (54.5 to 59.6)	71.7 (61.4 to 80.6)		
Week 120 (n=1444, 88)	59.2 (56.6 to 61.8)	73.9 (63.4 to 82.7)		
Week 144 (n=1381, 83)	59.3 (56.7 to 61.9)	72.3 (61.4 to 81.6)		
Week 168 (n=1309, 81)	59.7 (56.9 to 62.3)	70.4 (59.2 to 80.0)		
Week 192 (n=1250, 76)	62.1 (59.3 to 64.8)	67.1 (55.4 to 77.5)		
Week 216 (n=1175, 73)	63.6 (60.7 to 66.3)	71.2 (59.4 to 81.2)		
Week 240 (n=1118, 73)	61.6 (58.7 to 64.5)	82.2 (71.5 to 90.2)		
Week 264 (n=1036, 62)	64.4 (61.4 to 67.3)	75.8 (63.3 to 85.8)		
Week 288 (n=715, 26)	68.7 (65.1 to 72.1)	73.1 (52.2 to 88.4)		
Week 312 (n=655, 7)	69.0 (65.3 to 72.5)	85.7 (42.1 to 99.6)		
Week 336 (n=540, 0)	72.2 (68.2 to 76.0)	99999 (99999 to 99999)		
Week 360 (n=424, 0)	71.7 (67.2 to 75.9)	99999 (99999 to 99999)		
Week 384 (n=334, 0)	71.6 (66.4 to 76.3)	99999 (99999 to 99999)		
Week 408 (n=199, 0)	69.8 (63.0 to 76.1)	99999 (99999 to 99999)		
Week 432 (n=106, 0)	76.4 (67.2 to 84.1)	99999 (99999 to 99999)		
Week 456 (n=55, 0)	72.7 (59.0 to 83.9)	99999 (99999 to 99999)		
Week 480 (n=39, 0)	76.9 (60.7 to 88.9)	99999 (99999 to 99999)		
Week 504 (n=26, 0)	73.1 (52.2 to 88.4)	99999 (99999 to 99999)		
Week 516 (n=2, 0)	50.0 (1.3 to 98.7)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects achieving Good Response, Moderate Response or Non-response Using the European League Against Rheumatism (EULAR) Response Criteria

End point title	Percentage of Subjects achieving Good Response, Moderate Response or Non-response Using the European League Against Rheumatism (EULAR) Response Criteria

End point description:

DAS28-based EULAR response criteria measured individual response as none, good or moderate, depending on extent of change from baseline and level of disease activity reached. EULAR response criteria were defined as: Good response=change from baseline of >1.2 and present DAS28-CRP score <=3.2. Moderate response=change from baseline of >0.6 to <=1.2 and present DAS28-CRP score <=5.1, or, change from baseline of >1.2 and present DAS28-CRP score >3.2. Non-response=change from baseline of <=0.6 or change from baseline of >0.6 to <=1.2 and present DAS28-CRP score >5.1. Scores of good and moderate=therapeutic response. DAS28-CRP: composite score which had 4 components: TJC with 28 joints assessed; SJC with 28 joints assessed; high-sensitivity CRP (in mg/L) and general health assessment by subject using subject global assessment (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS. Safety population. number of subjects=subjects evaluable and n=subjects with data.

End point type	Secondary

End point timeframe:

At Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1872	110		
Units: percentage of subjects				
number (not applicable)				
Week 0: Good response (n=1872,110)	44.7	60.9		
Week 0: Moderate response (n=1872, 110)	40.3	30.9		
Week 0: None response (n=1872, 110)	15.0	8.2		
Week 4: Good response (n=1866,106)	57.2	69.8		
Week 4: Moderate response (n=1866,106)	36.2	26.4		
Week 4:None response (n=1866,106)	6.6	3.8		
Week 8: Good response (n=1803, 105)	62.3	68.6		
Week 8: Moderate response (n=1803, 105)	31.7	27.6		
Week 8: None response (n=1803, 105)	6.0	3.8		

Week 12: Good response (n=1818, 109)	64.1	74.3		
Week 12: Moderate response (n=1818, 109)	30.6	22.9		
Week 12: None response (n=1818, 109)	5.2	2.8		
Week 24: Good response (n=1777, 109)	66.6	73.4		
Week 24: Moderate response (n=1777, 109)	28.9	24.8		
Week 24: None response (n=1777, 109)	4.5	1.8		
Week 36: Good response (n=1720, 109)	67.9	71.6		
Week 36: Moderate response (n=1720, 109)	27.0	24.8		
Week 36: None response (n=1720, 109)	5.1	3.7		
Week 48: Good response (n=1660, 107)	68.1	72.0		
Week 48: Moderate response (n=1660, 107)	27.4	24.3		
Week 48: None response (n=1660, 107)	4.5	3.7		
Week 60: Good response (n=1607, 102)	71.1	68.6		
Week 60: Moderate response (n=1607, 102)	24.6	29.4		
Week 60: None response (n=1607, 102)	4.2	2.0		
Week 72: Good response (n=1579, 101)	70.0	81.2		
Week 72: Moderate response (n=1579, 101)	26.0	16.8		
Week 72: None response (n=1579, 101)	4.0	2.0		
Week 84: Good response (n=1536, 95)	71.3	84.2		
Week 84: Moderate response (n=1536, 95)	24.2	14.7		
Week 84: None response (n=1536, 95)	4.6	1.1		
Week 96: Good response (n=1505, 92)	72.6	76.1		
Week 96: Moderate response (n=1505, 92)	23.3	21.7		
Week 96: None response (n=1505, 92)	4.1	2.2		
Week 120: Good response (n=1443, 88)	73.5	80.7		
Week 120: Moderate response (n=1443, 88)	22.3	17.0		
Week 120: None response (n=1443, 88)	4.2	2.3		
Week 144: Good response (n=1381, 83)	73.3	86.7		
Week 144: Moderate response (n=1381, 83)	22.8	13.3		
Week 144: None response (n=1381, 83)	3.9	0		
Week 168: Good response (n=1309, 81)	74.5	84.0		
Week 168: Moderate response (n=1309, 81)	20.6	16.0		
Week 168: None response (n=1309, 81)	4.9	0		
Week 192: Good response (n=1250, 76)	75.6	81.6		
Week 192: Moderate response (n=1250, 76)	20.6	13.2		
Week 192: None response (n=1250, 76)	3.8	5.3		

Week 216: Good response (n=1175, 73)	75.9	80.8		
Week 216: Moderate response (n=1175, 73)	20.5	17.8		
Week 216: None response (n=1175, 73)	3.6	1.4		
Week 240: Good response (n=1118, 73)	78.6	89.0		
Week 240: Moderate response (n=1118, 73)	17.5	9.6		
Week 240: None response (n=1118, 73)	3.8	1.4		
Week 264: Good response (n=1036, 62)	76.7	83.9		
Week 264: Moderate response (n=1036, 62)	20.2	16.1		
Week 264: None response (n=1036, 62)	3.1	0		
Week 288: Good response (n=715, 26)	82.4	80.8		
Week 288: Moderate response (n=715, 26)	15.2	19.2		
Week 288: None response (n=715, 26)	2.4	0		
Week 312: Good response (n=655, 7)	81.5	100		
Week 312: Moderate response (n=655, 7)	16.3	0		
Week 312: None response (n=655, 7)	2.1	0		
Week 336: Good response (n=540, 0)	83.0	99999		
Week 336: Moderate response (n=540, 0)	14.6	99999		
Week 336: None response (n=540, 0)	2.4	99999		
Week 360: Good response (n=424, 0)	83.3	99999		
Week 360: Moderate response (n=424, 0)	15.1	99999		
Week 360: None response (n=424, 0)	1.7	99999		
Week 384: Good response (n=334, 0)	86.2	99999		
Week 384: Moderate response (n=334, 0)	12.9	99999		
Week 384: None response (n=334, 0)	0.9	99999		
Week 408: Good response (n=199, 0)	81.9	99999		
Week 408: Moderate response (n=199, 0)	16.1	99999		
Week 408: None response (n=199, 0)	2.0	99999		
Week 432: Good response (n=106, 0)	85.8	99999		
Week 432: Moderate response (n=106, 0)	14.2	99999		
Week 432: None response (n=106, 0)	0	99999		
Week 456: Good response (n=55, 0)	87.3	99999		
Week 456: Moderate response (n=55, 0)	12.7	99999		
Week 456: None response (n=55, 0)	0	99999		
Week 480: Good response (n=39, 0)	79.5	99999		
Week 480: Moderate response (n=39, 0)	17.9	99999		
Week 480: None response (n=39, 0)	2.6	99999		
Week 504: Good response (n=26, 0)	92.3	99999		
Week 504: Moderate response (n=26, 0)	7.7	99999		
Week 504: None response (n=26, 0)	0	99999		
Week 516: Good response (n=2, 0)	100	99999		
Week 516: Moderate response (n=2, 0)	0	99999		

Week 516: None response (n=2, 0)	0	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in DAS28-CRP Score at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point title	Change From Baseline in DAS28-CRP Score at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point description:

DAS28-CRP is a composite score which included 4 components: TJC with 28 joints assessed; SJC with 28 joints assessed; high-sensitivity CRP (in mg/L) and general health assessment by the subject using subject global assessment (measured on 0 [no arthritis activity] to 100 mm [maximal arthritis activity] VAS). DAS28-CRP total score ranges from 0 to 10, where higher scores indicated greater disease activity. Here, Baseline refers to the Baseline of initial studies (EFC11072, ACT11575, EFC10832, SFY13370 and EFC13752). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and 'n' = subjects with available data for each specified category and "99999" was used as space filler which indicates that data was not planned to be collected and analysed for the specified time-points in the respective groups.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1872	110		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=1872, 110)	-2.50 (± 1.52)	-2.99 (± 1.42)		
Week 4 (n=1866, 106)	-2.98 (± 1.38)	-3.18 (± 1.31)		
Week 8 (n=1803, 105)	-3.12 (± 1.41)	-3.21 (± 1.26)		
Week 12 (n=1818, 109)	-3.19 (± 1.41)	-3.28 (± 1.29)		
Week 24 (n=1777, 109)	-3.28 (± 1.41)	-3.43 (± 1.21)		
Week 36 (n=1720, 109)	-3.31 (± 1.43)	-3.35 (± 1.23)		
Week 48 (n=1660, 107)	-3.35 (± 1.42)	-3.36 (± 1.35)		
Week 60 (n=1607, 102)	-3.41 (± 1.41)	-3.50 (± 1.28)		
Week 72 (n=1579, 101)	-3.41 (± 1.42)	-3.61 (± 1.24)		
Week 84 (n=1536, 95)	-3.40 (± 1.45)	-3.70 (± 1.19)		
Week 96 (n=1505, 92)	-3.46 (± 1.43)	-3.59 (± 1.32)		

Week 120 (n=1443, 88)	-3.49 (± 1.45)	-3.72 (± 1.20)		
Week 144 (n=1381, 83)	-3.51 (± 1.41)	-3.79 (± 1.29)		
Week 168 (n=1309, 81)	-3.52 (± 1.45)	-3.66 (± 1.30)		
Week 192 (n=1250, 76)	-3.55 (± 1.43)	-3.61 (± 1.48)		
Week 216 (n=1175, 73)	-3.59 (± 1.43)	-3.71 (± 1.24)		
Week 240 (n=1118, 73)	-3.57 (± 1.44)	-3.90 (± 1.35)		
Week 264 (n=1036, 62)	-3.64 (± 1.39)	-3.92 (± 1.36)		
Week 288 (n=715, 26)	-3.80 (± 1.38)	-4.38 (± 1.33)		
Week 312 (n=655, 7)	-3.86 (± 1.34)	-5.62 (± 0.86)		
Week 336 (n=540, 0)	-3.86 (± 1.34)	99999 (± 99999)		
Week 360 (n=424, 0)	-3.93 (± 1.34)	99999 (± 99999)		
Week 384 (n=334, 0)	-3.99 (± 1.36)	99999 (± 99999)		
Week 408 (n=199, 0)	-3.85 (± 1.44)	99999 (± 99999)		
Week 432 (n=106, 0)	-4.11 (± 1.35)	99999 (± 99999)		
Week 456 (n=55, 0)	-4.01 (± 1.14)	99999 (± 99999)		
Week 480 (n=39, 0)	-3.69 (± 1.47)	99999 (± 99999)		
Week 504 (n=26, 0)	-3.76 (± 1.24)	99999 (± 99999)		
Week 516 (n=2, 0)	-3.76 (± 2.32)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Scores at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point title	Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Scores at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point description:

HAQ-DI: standardised questionnaire used to assess degree of difficulty a subject has experienced during past week in 8 domains of daily living activities: dressing/grooming; arising; eating; walking; hygiene; reach; grip and activities. Total of 30 items distributed in these 8 domains. Each item was scored on 4-point scale from 0 to 3, where 0=no difficulty in physical function; 1=some difficulty in physical function; 2=much difficulty in physical function; 3=unable to do. Overall score was computed as sum of domain scores and divided by number of domains answered. Total possible score range 0 (least difficulty in physical function) to 3 (extreme difficulty in physical function), where higher scores=more difficulty while performing daily living activities. Baseline refers to Baseline of initial studies (EFC11072, ACT11575, EFC10832, SFY13370 and EFC13752). Safety population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and 'n' = subjects with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1895	111		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=1895, 111)	-0.56 (± 0.63)	-0.58 (± 0.59)		
Week 4 (n=1882, 109)	-0.59 (± 0.62)	-0.57 (± 0.52)		
Week 8 (n=1858, 106)	-0.63 (± 0.63)	-0.63 (± 0.53)		
Week 12 (n=1826, 109)	-0.65 (± 0.64)	-0.65 (± 0.57)		
Week 24 (n=1787, 109)	-0.69 (± 0.65)	-0.63 (± 0.60)		
Week 36 (n=1728, 109)	-0.70 (± 0.66)	-0.67 (± 0.61)		
Week 48 (n=1667, 107)	-0.70 (± 0.66)	-0.63 (± 0.60)		
Week 60 (n=1625, 103)	-0.70 (± 0.67)	-0.67 (± 0.50)		
Week 72 (n=1586, 101)	-0.71 (± 0.66)	-0.67 (± 0.59)		
Week 84 (n=1551, 95)	-0.71 (± 0.68)	-0.68 (± 0.59)		
Week 96 (n=1509, 92)	-0.72 (± 0.67)	-0.69 (± 0.58)		
Week 120 (n=1458, 89)	-0.74 (± 0.69)	-0.67 (± 0.55)		
Week 144 (n=1386, 84)	-0.73 (± 0.70)	-0.64 (± 0.61)		
Week 168 (n=1327, 81)	-0.74 (± 0.70)	-0.61 (± 0.59)		
Week 192 (n=1268, 77)	-0.74 (± 0.71)	-0.65 (± 0.65)		
Week 216 (n=1185, 70)	-0.75 (± 0.71)	-0.62 (± 0.69)		
Week 240 (n=1127, 74)	-0.74 (± 0.72)	-0.61 (± 0.64)		
Week 264 (n=998 , 57)	-0.76 (± 0.71)	-0.54 (± 0.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Van Der Heijde Modified Total Sharp Score (mTSS) at Week 0 and Week 48 of LTS11210: Campaign 1 X-ray Data - Subjects From EFC11072 Part B

End point title	Change From Baseline in Van Der Heijde Modified Total Sharp Score (mTSS) at Week 0 and Week 48 of LTS11210: Campaign 1 X-ray Data - Subjects From EFC11072 Part B

End point description:

Van der Heijde modified Sharp method is composite X-ray scoring system used to assess structural (joint) disease progression (DP) in RA. The method evaluates both joint erosions (JE) for 44 joints and joint space narrowing (JSN) for 42 joints in bilateral hand and foot joints. Total mTSS: sum of the scores from both erosion score and joint space narrowing score and ranged from 0 (normal, no progression) to 448 (worst possible total score). An increase in total score represents progression of structural damage. Here, Baseline refers to the Baseline of initial study (EFC11072 Part B). In this endpoint, change from initial study baseline (CFISB) in 2 years X-ray data at Week 0 and 48 of LTS11210 were reported. Here, 'number of subjects analysed' = subjects from studies EFC11072 Part B evaluable for this endpoint and 'n'=subjects with available data. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Week 0 and 48 of LTS11210

End point values	Sarilumab + DMARD: EFC11072 Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	856			
Units: score on scale				
arithmetic mean (standard deviation)				
Change at Week 0 (n=856)	1.05 (± 4.61)			
Change at Week 48 (n=848)	1.34 (± 5.31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Van Der Heijde Modified Total Sharp Score (mTSS) at Week 48 and Week 96 of LTS11210: Campaign 2 X-ray Data - Subjects From EFC11072 Part B

End point title	Change From Baseline in Van Der Heijde Modified Total Sharp Score (mTSS) at Week 48 and Week 96 of LTS11210: Campaign 2 X-ray Data - Subjects From EFC11072 Part B

End point description:

Van der Heijde modified Sharp method:composite X-ray scoring system to assess structural (joint) disease progression in RA. Method evaluates both JE for 44 joints and JSN for 42 joints in bilateral hand and foot joints. Total mTSS:sum of scores from both erosion score and joint space narrowing score and ranged from 0 (normal, no progression) to 448 (worst possible total score). Increase in total score=progression of structural damage. Baseline=Baseline of initial study (EFC11072 Part B). In this endpoint, CFISB in 3 years X-ray data (subjects with study duration of more than 48 weeks in LTS11210) at Week 48 and 96 from Campaign 2 were reported. Analysed on subset of subjects who previously completed study EFC11072, Part B with end of treatment X-ray evaluation. Number of subject analysed=subjects from study EFC11072 Part B evaluable for this endpoint and 'n'=subjects with available data. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Baseline, Week 48 and 96 of LTS11210

End point values	Sarilumab + DMARD: EFC11072 Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	756			
Units: score on scale				
arithmetic mean (standard deviation)				

Change at Week 48 (n=756)	1.60 (± 5.96)			
Change at Week 96 (n=755)	2.14 (± 7.20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Van Der Heijde Modified Total Sharp Score (mTSS) at Week 96, 144 and Week 192 of LTS11210: Campaign 3 X-ray Data - Subjects From EFC11072 Part B

End point title	Change From Baseline in Van Der Heijde Modified Total Sharp Score (mTSS) at Week 96, 144 and Week 192 of LTS11210: Campaign 3 X-ray Data - Subjects From EFC11072 Part B

End point description:

Van der Heijde modified Sharp method:composite X-ray scoring system to assess structural (joint) disease progression in RA. Method evaluates both JE for 44 joints and JSN for 42 joints in bilateral hand and foot joints. Total mTSS:sum of scores from both erosion score and joint space narrowing score and ranged from 0 (normal, no progression) to 448 (worst possible total score). Increase in total score=progression of structural damage. Baseline=Baseline of initial study (EFC11072 Part B). In this endpoint, CFISB in 5 years X-ray data (subjects with study duration of more than 96 weeks in LTS11210) at Week 96, 144 and 192 from Campaign 3 were reported. Analysed on subset of subjects who previously completed study EFC11072, Part B with end of treatment X-ray evaluation. Number of subjects analysed=subjects from studies EFC11072 Part B evaluable for this endpoint and 'n'=subjects with data. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Baseline, Week 96, 144 and 192 of LTS11210

End point values	Sarilumab + DMARD: EFC11072 Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	699			
Units: score on scale				
arithmetic mean (standard deviation)				
Change at Week 96 (n=699)	1.83 (± 7.76)			
Change at Week 144 (n=689)	2.24 (± 8.43)			
Change at Week 192 (n=656)	2.83 (± 9.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With no Radiographic Progression of the Van Der Heijde Modified Total Sharp Score at Week 0 and 48 of LTS11210: Campaign 1 X-ray Data - Subjects From EFC11072 Part B

End point title	Percentage of Subjects With no Radiographic Progression of the Van Der Heijde Modified Total Sharp Score at Week 0 and 48 of LTS11210: Campaign 1 X-ray Data - Subjects From EFC11072 Part B

End point description:

Radiographic no progression: defined as a change from Baseline in Van der Heijde mTSS <= 0. Van der Heijde modified Sharp method is composite X-ray scoring system to assess structural (joint) disease progression in RA. Method evaluates both JE for 44 joints and JSN for 42 joints in bilateral hand and foot joints. Total mTSS = sum of scores from both erosion score and joint space narrowing score, ranged from 0 (normal, no progression) to 448 (worst possible total score). Increase in total score = progression of structural damage. In this endpoint, percentage (%) of subjects with no radiographic progression at Week 48 of LTS11210 from Campaign 1 X-ray data were reported. Analysed on subset of subjects who previously completed study EFC11072, Part B with end of treatment X-ray evaluation. Here, 'number of subjects analysed'=subjects from studies EFC11072 Part B evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Week 0 (post-dose) and 48 of LTS11210

End point values	Sarilumab + DMARD: EFC11072 Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	889			
Units: percentage of subjects				
number (not applicable)				
Week 0	51.9			
Week 48	51.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With no Radiographic Progression of the Van Der Heijde Modified Total Sharp Score at Week 48 and 96 of LTS11210: Campaign 2 X-ray Data - Subjects From EFC11072 Part B

End point title	Percentage of Subjects With no Radiographic Progression of the Van Der Heijde Modified Total Sharp Score at Week 48 and 96 of LTS11210: Campaign 2 X-ray Data - Subjects From EFC11072 Part B

End point description:

Radiographic no progression:defined as change from Baseline in Van der Heijde mTSS <=0. Van der Heijde modified Sharp method:composite X-ray scoring system to assess structural (joint) DP in RA. Method evaluates both JE for 44 joints and JSN for 42 joints in bilateral hand and foot joints. Total mTSS=sum of scores from erosion score and joint space narrowing score, ranged from 0(normal, no progression) to 448(worst possible total score). Increase in total score=progression of structural damage. In this endpoint, % of subjects with no radiographic progression at Week 48 and 96 of LTS11210 from Campaign 2 X-ray data (subjects with study duration of more than 48 weeks in LTS11210) were reported. Analysed on subset of subjects who previously completed study EFC11072, Part B with end of treatment X-ray evaluation. Number of subjects analysed=subjects from study EFC11072 Part B evaluable for this endpoint. Data for this endpoint was not planned to be collected for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Week 48 and 96 of LTS11210

End point values	Sarilumab + DMARD: EFC11072 Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	796			
Units: percentage of subjects				
number (not applicable)				
Week 48	46.6			
Week 96	44.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With no Radiographic Progression of the Van Der Heijde Modified Total Sharp Score at Week 96, 144 and 192 of LTS11210: Campaign 3 X-ray Data - Subjects From EFC11072 Part B

End point title	Percentage of Subjects With no Radiographic Progression of the Van Der Heijde Modified Total Sharp Score at Week 96, 144 and 192 of LTS11210: Campaign 3 X-ray Data - Subjects From EFC11072 Part B

End point description:

Radiographic no progression:defined as change from Baseline in Van der Heijde mTSS <=0. Van der Heijde modified Sharp method:composite X-ray scoring system used to assess structural (joint) DP in RA. Method evaluates both JE for 44 joints and JSN for 42 joints in bilateral hand and foot joints. Total mTSS:sum of scores from erosion score and joint space narrowing score, ranged:0(normal, no progression) to 448(worst possible total score). Increase in total score=progression of structural damage. In this endpoint % of subjects with no radiographic progression at Week 96, 144 and 192 from Campaign 3 X-ray data (subjects with study duration more than 96 weeks in LTS11210) were reported. Analysed on subset of subjects who previously completed study EFC11072, Part B with end of treatment X-ray evaluation. Number of subjects analysed=subjects from studies EFC11072 Part B evaluable for endpoint. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Week 96, 144 and 192 of LTS11210

End point values	Sarilumab + DMARD: EFC11072 Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	732			
Units: percentage of subjects				
number (not applicable)				

Week 96	48.6			
Week 144	46.0			
Week 192	41.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Tender Joint Count (TJC) at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point title	Change From Baseline in Tender Joint Count (TJC) at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point description:

TJC is the sum of all tender joints based on examination of the 68 joints of the fingers, elbows, hips, knees, ankles, and toes. Total TJC ranged from 0 (best) to 68 (worst), where higher score = more severity. Change from Baseline in TJC was reported in the endpoint. Here, Baseline refers to Baseline of initial study (EFC11072, ACT11575, EFC10832, SFY13370 and EFC13752). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and 'n' = subjects with available data for each specified category and "99999" was used as space filler which indicates that data was not planned to be collected and analysed for the specified time-points in the respective groups.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1904	111		
Units: joints				
arithmetic mean (standard deviation)				
Week 0 (n=1904, 111)	-16.67 (± 14.05)	-19.86 (± 12.43)		
Week 4 (n=1891, 109)	-18.97 (± 13.81)	-20.13 (± 12.64)		
Week 8 (n=1867, 106)	-19.72 (± 13.61)	-20.09 (± 11.73)		
Week 12 (n=1837, 109)	-20.20 (± 13.89)	-20.05 (± 12.99)		
Week 24 (n=1791, 109)	-20.67 (± 14.09)	-21.19 (± 12.55)		
Week 36 (n=1733, 109)	-20.68 (± 14.39)	-20.60 (± 12.19)		
Week 48 (n=1674, 107)	-20.95 (± 14.04)	-20.27 (± 13.54)		

Week 60 (n=1625, 103)	-21.29 (± 14.06)	-20.95 (± 12.66)		
Week 72 (n=1589, 101)	-21.41 (± 13.98)	-21.67 (± 12.65)		
Week 84 (n=1553, 95)	-21.53 (± 14.17)	-21.36 (± 13.04)		
Week 96 (n=1514, 92)	-21.65 (± 14.08)	-20.89 (± 13.50)		
Week 120 (n=1459, 88)	-21.92 (± 14.20)	-20.18 (± 12.73)		
Week 144 (n=1394, 83)	-22.13 (± 14.01)	-22.52 (± 13.41)		
Week 168 (n=1331, 81)	-22.35 (± 14.26)	-22.42 (± 13.34)		
Week 192 (n=1269, 78)	-22.62 (± 14.20)	-21.83 (± 13.79)		
Week 216 (n=1211, 76)	-22.69 (± 14.28)	-22.33 (± 13.29)		
Week 240 (n=1136, 74)	-22.89 (± 14.47)	-23.07 (± 14.24)		
Week 264 (n=1072, 62)	-23.09 (± 14.08)	-23.66 (± 15.02)		
Week 288 (n=788, 26)	-22.59 (± 15.70)	-28.95 (± 14.79)		
Week 312 (n=713, 7)	-23.47 (± 15.23)	-43.71 (± 12.12)		
Week 336 (n=556, 0)	-23.37 (± 15.24)	99999 (± 99999)		
Week 360 (n=442, 0)	-24.12 (± 14.89)	99999 (± 99999)		
Week 384 (n=358, 0)	-24.73 (± 15.14)	99999 (± 99999)		
Week 408 (n=226, 0)	-24.58 (± 14.97)	99999 (± 99999)		
Week 432 (n=109, 0)	-25.33 (± 15.05)	99999 (± 99999)		
Week 456 (n=59, 0)	-24.21 (± 14.37)	99999 (± 99999)		
Week 480 (n=45, 0)	-21.23 (± 14.66)	99999 (± 99999)		
Week 504 (n=27, 0)	-23.62 (± 13.63)	99999 (± 99999)		
Week 516 (n=2, 0)	-24.00 (± 12.73)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swollen Joint Count (SJC) at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point title	Change From Baseline in Swollen Joint Count (SJC) at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point description:

SJC is the sum of all swollen joints based on examination of the fingers, elbows, knees and toes. Total

SJC ranged from 0 (best) to 66 (worst), where higher score = more severity. Change from Baseline in SJC was reported in the endpoint. Here, Baseline refers to the Baseline of initial studies (EFC11072, ACT11575, EFC10832, SFY13370 and EFC13752). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and 'n' = subject with available data for each specified category and "99999" was used as space filler which indicates that data was not planned to be collected and analysed for the specified time-points in the respective groups.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1904	111		
Units: joints				
arithmetic mean (standard deviation)				
Week 0 (n=1904, 111)	-11.36 (± 9.96)	-14.06 (± 9.65)		
Week 4 (n=1891, 109)	-12.81 (± 9.77)	-14.55 (± 9.19)		
Week 8 (n=1867, 106)	-13.43 (± 9.82)	-14.60 (± 9.30)		
Week 12 (n=1837, 109)	-13.77 (± 10.13)	-14.58 (± 9.31)		
Week 24 (n=1791, 109)	-14.28 (± 10.09)	-14.83 (± 9.64)		
Week 36 (n=1733, 109)	-14.37 (± 9.99)	-14.51 (± 9.70)		
Week 48 (n=1674, 107)	-14.53 (± 9.97)	-14.96 (± 9.22)		
Week 60 (n=1625, 103)	-14.75 (± 10.20)	-15.54 (± 9.49)		
Week 72 (n=1589, 101)	-14.76 (± 10.12)	-15.43 (± 9.67)		
Week 84 (n=1553, 95)	-14.84 (± 10.16)	-15.83 (± 9.50)		
Week 96 (n=1514, 92)	-15.03 (± 10.20)	-15.51 (± 10.24)		
Week 120 (n=1459, 88)	-15.09 (± 10.17)	-15.77 (± 9.95)		
Week 144 (n=1394, 83)	-15.18 (± 10.20)	-15.90 (± 8.57)		
Week 168 (n=1331, 81)	-15.16 (± 10.30)	-15.47 (± 8.91)		
Week 192 (n=1269, 78)	-15.26 (± 10.09)	-15.01 (± 9.17)		
Week 216 (n=1211, 76)	-15.25 (± 9.97)	-15.72 (± 8.65)		
Week 240 (n=1135, 74)	-15.43 (± 10.34)	-15.59 (± 9.08)		
Week 264 (n=1072, 62)	-15.50 (± 9.79)	-16.59 (± 9.53)		

Week 288 (n=788, 26)	-14.67 (± 10.98)	-18.65 (± 8.90)		
Week 312 (n=713, 7)	-15.38 (± 10.71)	-23.57 (± 9.83)		
Week 336 (n=556, 0)	-15.51 (± 10.48)	99999 (± 99999)		
Week 360 (n=442, 0)	-15.96 (± 10.76)	99999 (± 99999)		
Week 384 (n=358, 0)	-16.42 (± 10.76)	99999 (± 99999)		
Week 408 (n=226, 0)	-16.30 (± 11.47)	99999 (± 99999)		
Week 432 (n=109, 0)	-16.62 (± 11.51)	99999 (± 99999)		
Week 456 (n=59, 0)	-15.64 (± 10.65)	99999 (± 99999)		
Week 480 (n=45, 0)	-15.43 (± 10.67)	99999 (± 99999)		
Week 504 (n=27, 0)	-16.21 (± 10.94)	99999 (± 99999)		
Week 516 (n=2, 0)	-13.00 (± 2.83)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physician’s Global Assessments of Disease Activity Visual Analogue Scale (VAS) Score at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, and 264 of LTS11210

End point title	Change From Baseline in Physician’s Global Assessments of Disease Activity Visual Analogue Scale (VAS) Score at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, and 264 of LTS11210

End point description:

Physician global assessment of disease activity was measured on a 100 millimetres (mm) horizontal VAS, ranging from 0 (best disease activity) to 100 (worst disease activity), where lower score = less disease activity and higher score = more disease activity. Here, Baseline refers to Baseline of initial studies (EFC11072, ACT11575, EFC10832, SFY13370 and EFC13752). Analysis was performed on safety population. Here, 'number of subjects analysed’ = subjects evaluable for endpoint and ‘n’ = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, and 264 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1903	110		

Units: millimetres				
arithmetic mean (standard deviation)				
Week 0 (n=1903, 110)	-40.51 (± 23.82)	-46.38 (± 19.17)		
Week 4 (n=1888, 109)	-43.98 (± 22.03)	-47.94 (± 19.16)		
Week 8 (n=1863, 106)	-45.79 (± 22.06)	-49.27 (± 18.80)		
Week 12 (n=1832, 109)	-47.02 (± 22.03)	-50.20 (± 19.74)		
Week 24 (n=1786, 109)	-48.39 (± 21.94)	-50.82 (± 19.99)		
Week 36 (n=1730, 109)	-48.94 (± 21.72)	-51.12 (± 19.87)		
Week 48 (n=1675, 107)	-49.36 (± 21.68)	-50.58 (± 21.38)		
Week 60 (n=1624, 103)	-49.98 (± 21.62)	-51.40 (± 20.51)		
Week 72 (n=1586, 101)	-49.91 (± 21.72)	-52.90 (± 19.40)		
Week 84 (n=1551, 94)	-50.28 (± 21.42)	-55.84 (± 17.39)		
Week 96 (n=1512, 92)	-50.73 (± 21.62)	-54.14 (± 18.97)		
Week 120 (n=1458, 88)	-50.43 (± 21.39)	-54.33 (± 19.41)		
Week 144 (n=1390, 84)	-50.84 (± 21.13)	-55.73 (± 18.04)		
Week 168 (n=1329, 81)	-50.49 (± 21.65)	-53.21 (± 21.36)		
Week 192 (n=1264, 78)	-50.32 (± 22.00)	-52.22 (± 22.44)		
Week 216 (n=1209, 76)	-51.49 (± 21.57)	-54.67 (± 18.30)		
Week 240 (n=1133, 74)	-51.00 (± 21.57)	-55.16 (± 18.82)		
Week 264 (n=1055, 63)	-51.18 (± 21.24)	-55.27 (± 21.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject Global Assessment of Disease Activity Visual Analogue Scale Score at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point title	Change From Baseline in Subject Global Assessment of Disease Activity Visual Analogue Scale Score at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point description:

Subject global assessment of disease activity was measured on a 100 mm horizontal VAS, ranging from 0 (best disease activity) to 100 (worst disease activity), where lower score = less disease activity and higher score = more disease activity. Here, Baseline refers to the Baseline of initial studies (EFC11072, ACT11575, EFC10832, SFY13370 and EFC13752). Analysis was performed on safety population. Here, number of subjects analysed' = subjects evaluable for endpoint and 'n' = subject with available data for

each specified category and "99999" was used as space filler which indicates that data was not planned to be collected and analysed for the specified time-points in the respective groups.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 516 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1904	111		
Units: millimetres				
arithmetic mean (standard deviation)				
Week 0 (n=1904, 111)	-30.51 (± 26.78)	-32.30 (± 27.55)		
Week 4 (n=1887, 109)	-32.87 (± 25.60)	-33.63 (± 25.86)		
Week 8 (n=1863, 106)	-34.65 (± 26.25)	-34.25 (± 25.90)		
Week 12 (n=1830, 109)	-35.60 (± 26.77)	-34.24 (± 28.38)		
Week 24 (n=1785, 109)	-36.91 (± 26.50)	-36.12 (± 27.82)		
Week 36 (n=1729, 109)	-37.08 (± 27.18)	-37.13 (± 24.73)		
Week 48 (n=1674, 107)	-37.28 (± 26.93)	-35.98 (± 28.18)		
Week 60 (n=1622, 103)	-37.79 (± 27.38)	-37.82 (± 25.40)		
Week 72 (n=1589, 101)	-37.90 (± 27.26)	-37.95 (± 26.53)		
Week 84 (n=1552, 95)	-37.45 (± 27.82)	-40.52 (± 26.69)		
Week 96 (n=1512, 92)	-38.34 (± 27.34)	-41.46 (± 26.57)		
Week 120 (n=1459, 89)	-38.41 (± 27.43)	-41.67 (± 26.43)		
Week 144 (n=1394, 84)	-38.91 (± 27.52)	-38.52 (± 26.40)		
Week 168 (n=1328, 81)	-38.22 (± 28.26)	-37.27 (± 27.46)		
Week 192 (n=1267, 76)	-39.26 (± 28.16)	-37.79 (± 32.12)		
Week 216 (n=1191, 74)	-39.96 (± 27.72)	-38.72 (± 32.76)		
Week 240 (n=1133, 74)	-39.54 (± 27.79)	-41.64 (± 30.13)		
Week 264 (n=1061, 62)	-39.87 (± 27.31)	-37.84 (± 32.94)		
Week 288 (n=727, 26)	-43.68 (± 25.55)	-48.00 (± 33.87)		
Week 312 (n=671, 7)	-44.05 (± 26.40)	-65.71 (± 21.40)		

Week 336 (n=543, 0)	-43.42 (± 26.95)	99999 (± 99999)		
Week 360 (n=445, 0)	-44.56 (± 26.59)	99999 (± 99999)		
Week 384 (n=349, 0)	-47.19 (± 26.25)	99999 (± 99999)		
Week 408 (n=214, 0)	-44.97 (± 29.16)	99999 (± 99999)		
Week 432 (n=109, 0)	-49.77 (± 25.95)	99999 (± 99999)		
Week 456 (n=58, 0)	-50.40 (± 24.27)	99999 (± 99999)		
Week 480 (n=43, 0)	-46.65 (± 29.66)	99999 (± 99999)		
Week 504 (n=27, 0)	-48.89 (± 28.83)	99999 (± 99999)		
Week 516 (n=2,0)	-40.50 (± 36.06)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject's Assessment of Pain Visual Analogue Scale Score at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, and 264 of LTS11210

End point title	Change From Baseline in Subject's Assessment of Pain Visual Analogue Scale Score at Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, and 264 of LTS11210

End point description:

Subjects were requested to indicate their pain intensity due to their RA on a 100 mm horizontal VAS, ranging from 0 (no pain) to 100 (worst pain), where a higher score represented more pain due to RA. Here, Baseline refers to the Baseline of initial studies (EFC11072, ACT11575, EFC10832, SFY13370 and EFC13752). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240, and 264 of LTS11210

End point values	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1897	111		
Units: millimetres				
arithmetic mean (standard deviation)				
Week 0 (n=1897, 111)	-31.08 (± 27.45)	-37.01 (± 28.73)		
Week 4 (n=1885, 109)	-34.04 (± 26.52)	-37.53 (± 27.28)		

Week 8 (n=1859, 106)	-35.79 (± 26.88)	-38.14 (± 27.16)		
Week 12 (n=1827, 109)	-36.46 (± 27.46)	-39.08 (± 26.79)		
Week 24 (n=1784, 109)	-37.87 (± 27.07)	-38.75 (± 28.12)		
Week 36 (n=1725, 109)	-37.60 (± 27.97)	-39.56 (± 25.72)		
Week 48 (n=1671, 107)	-38.07 (± 28.33)	-39.41 (± 30.12)		
Week 60 (n=1621, 103)	-38.46 (± 28.18)	-40.79 (± 26.20)		
Week 72 (n=1587, 101)	-38.00 (± 28.54)	-42.62 (± 27.33)		
Week 84 (n=1547, 95)	-38.37 (± 28.79)	-42.38 (± 28.69)		
Week 96 (n=1510, 92)	-38.62 (± 28.57)	-43.73 (± 27.59)		
Week 120 (n=1457, 89)	-39.29 (± 28.44)	-44.11 (± 25.69)		
Week 144 (n=1392, 84)	-39.19 (± 28.21)	-41.42 (± 27.31)		
Week 168 (n=1325, 81)	-39.47 (± 28.84)	-38.86 (± 29.46)		
Week 192 (n=1266, 76)	-40.17 (± 28.98)	-41.25 (± 30.44)		
Week 216 (n=1185, 70)	-40.25 (± 28.56)	-44.01 (± 30.27)		
Week 240 (n=1129, 74)	-40.28 (± 28.44)	-43.59 (± 29.22)		
Week 264 (n=1044, 62)	-41.02 (± 28.09)	-40.71 (± 29.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 (SF-36; Version 2) Physical Component Summary (PCS) Score at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, ACT11575 and EFC10832 Only

End point title	Change From Baseline in Short Form 36 (SF-36; Version 2) Physical Component Summary (PCS) Score at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, ACT11575 and EFC10832 Only

End point description:

SF-36 is a generic 36-item questionnaire consisting of 8 domains, measuring quality of life (QoL) covering 2 summary measures: PCS and mental component summary (MCS). PCS with 4 domains: physical functioning, role limitations due to physical problems, bodily pain, and general health; and MCS with 4 domains: vitality, social functioning, role limitations due to emotional problems, and mental health. Each domain is scored by summing individual items, which are transformed into a score range from 0 to 100; where 0=worst QoL to 100=best QoL. PCS total score ranged from 0 to 100 with higher scores = better physical health. Here, Baseline refers to Baseline of initial studies (EFC11072, ACT11575 and EFC10832). Here, 'number of subjects analysed'=subjects from studies EFC11072, ACT11575 and EFC10832 evaluable for this endpoint and 'n'=subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC11072, ACT11575 and EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	1367			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=1301)	7.95 (± 8.29)			
Week 12 (n=1367)	8.84 (± 8.45)			
Week 24 (n=1339)	9.25 (± 8.59)			
Week 36 (n=1303)	9.72 (± 8.85)			
Week 48 (n=1269)	9.43 (± 8.89)			
Week 60 (n=1231)	9.64 (± 8.53)			
Week 72 (n=1213)	9.62 (± 8.78)			
Week 84 (n=1179)	9.95 (± 8.97)			
Week 96 (n=1143)	9.90 (± 8.90)			
Week 120 (n=1111)	10.18 (± 9.12)			
Week 144 (n=1065)	10.15 (± 9.18)			
Week 168 (n=1018)	10.24 (± 9.24)			
Week 192 (n=967)	10.34 (± 9.52)			
Week 216 (n=908)	10.15 (± 9.45)			
Week 240 (n=848)	10.38 (± 9.21)			
Week 264 (n=754)	10.32 (± 9.38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 (SF-36; Version 2) Mental Component Summary Score at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, ACT11575 and EFC10832 Only

End point title	Change From Baseline in Short Form 36 (SF-36; Version 2) Mental Component Summary Score at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, ACT11575 and EFC10832 Only

End point description:

SF-36 is a generic 36-item questionnaire consisting of 8 domains, measuring QoL covering 2 summary measures: PCS and MCS. PCS with 4 domains: physical functioning, role limitations due to physical problems, bodily pain and general health; and MCS with 4 domains: vitality, social functioning, role limitations due to emotional problems and mental health. Each domain is scored by summing the individual items, which are transformed into a score range from 0 to 100; 0 = worst QoL to 100 = best QoL. MCS total score ranged from 0 to 100 with higher scores = better physical and mental health. Here, Baseline refers to the Baseline of initial studies (EFC11072, ACT11575 and EFC10832). Analysed

on safety population. Here, 'number of subjects analysed'=subjects from studies EFC11072, ACT11575 and EFC10832 evaluable for this endpoint and 'n'=subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC11072, ACT11575 and EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	1367			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=1301)	6.43 (± 10.80)			
Week 12 (n=1367)	7.15 (± 11.03)			
Week 24 (n=1339)	7.43 (± 11.15)			
Week 36 (n=1303)	7.20 (± 11.31)			
Week 48 (n=1269)	7.48 (± 11.15)			
Week 60 (n=1231)	7.43 (± 11.21)			
Week 72 (n=1213)	7.25 (± 11.24)			
Week 84 (n=1179)	7.29 (± 11.20)			
Week 96 (n=1143)	7.47 (± 11.52)			
Week 120 (n=1111)	7.69 (± 11.62)			
Week 144 (n=1065)	7.22 (± 11.60)			
Week 168 (n=1018)	7.29 (± 11.52)			
Week 192 (n=967)	7.10 (± 11.51)			
Week 216 (n=908)	7.20 (± 11.91)			
Week 240 (n=848)	7.23 (± 12.03)			
Week 264 (n=754)	7.32 (± 12.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-fatigue) Total Score at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, ACT11575 and EFC10832 only

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-fatigue) Total Score at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, ACT11575 and EFC10832 only

End point description:

The FACIT-F is a 13-item questionnaire assessing fatigue where subjects scored each item on a 5-point scale (0 to 4): 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much. The sum of all

responses resulted in the FACIT-Fatigue total score ranged from 0 to 52, where higher score = lower level of fatigue and indicates better QoL. A positive change from baseline score indicates an improvement. Here, Baseline refers to the Baseline of initial studies (EFC11072, ACT11575, and EFC10832). Here, 'number of subjects analysed' = subjects from studies EFC11072, ACT11575 and EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC11072, ACT11575 and EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	1651			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=1342)	9.20 (± 10.05)			
Week 12 (n=1651)	10.26 (± 10.10)			
Week 24 (n=1621)	10.94 (± 10.31)			
Week 36 (n=1570)	10.91 (± 10.67)			
Week 48 (n=1520)	10.86 (± 10.64)			
Week 60 (n=1474)	10.97 (± 10.50)			
Week 72 (n=1444)	10.84 (± 10.68)			
Week 84 (n=1411)	10.75 (± 10.88)			
Week 96 (n=1372)	11.09 (± 10.85)			
Week 120 (n=1323)	11.18 (± 10.74)			
Week 144 (n=1262)	11.14 (± 10.86)			
Week 168 (n=1197)	11.00 (± 11.27)			
Week 192 (n=1141)	10.80 (± 11.10)			
Week 216 (n=1062)	11.12 (± 11.25)			
Week 240 (n=1013)	11.15 (± 11.21)			
Week 264 (n=910)	10.99 (± 11.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sleep Visual Analogue Scale Score at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, and ACT11575 only

End point title	Change From Baseline in Sleep Visual Analogue Scale Score at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, and ACT11575 only

End point description:

Rheumatoid arthritis (RA), like other chronic illness, is associated with sleep disturbances and is linked to pain, mood, and disease activity. The effect of sarilumab on sleep was assessed on a on 100 mm horizontal VAS scale, ranging from 0 (sleep is not a problem) to 100 (sleep is a major problem), where higher score = more sleep disturbances. Here, Baseline refers to the Baseline of initial studies (EFC11072, and ACT11575). Analysis was performed on safety population. Here, 'number of subjects analyed' = subjects from studies EFC11072, and ACT11575 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC11072, and ACT11575			
Subject group type	Subject analysis set			
Number of subjects analysed	1231			
Units: millimetres				
arithmetic mean (standard deviation)				
Week 0 (n=894)	-24.58 (± 30.96)			
Week 12 (n=1231)	-26.11 (± 30.59)			
Week 24 (n=1206)	-26.44 (± 30.94)			
Week 36 (n=1164)	-27.37 (± 31.52)			
Week 48 (n=1132)	-26.15 (± 31.37)			
Week 60 (n=1098)	-26.98 (± 31.24)			
Week 72 (n=1075)	-26.85 (± 32.16)			
Week 84 (n=1051)	-25.81 (± 31.90)			
Week 96 (n=1024)	-26.91 (± 31.63)			
Week 120 (n=983)	-27.63 (± 32.26)			
Week 144 (n=940)	-26.90 (± 31.54)			
Week 168 (n=892)	-27.33 (± 33.25)			
Week 192 (n=853)	-26.87 (± 32.03)			

Week 216 (n=802)	-28.58 (± 31.46)			
Week 240 (n=755)	-27.72 (± 33.07)			
Week 264 (n=705)	-27.71 (± 32.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity and Activity Impairment (WPAI): Percent Work Time Missed due to RA at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072 and ACT11575 only

End point title	Change From Baseline in Work Productivity and Activity Impairment (WPAI): Percent Work Time Missed due to RA at Week 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072 and ACT11575 only

End point description:

WPAI assesses work productivity and impairment. It is 6-item questionnaire to assess degree to which RA affected work productivity and regular activities over past 7 days. Questions were: Q1=currently employed; Q2=hours missed due to RA; Q3=hours missed due to other reasons; Q4=hours actually worked; Q5=RA affected productivity while working (0-10 scale, with higher numbers=less productivity); Q6=RA affected regular activities (0-10 scale, higher numbers=greater impairment). Percent work time missed due to RA was subscale and calculated: 100*Q2/(Q2+Q4) for those who were currently employed. Subscale score was expressed as impairment percentage (range:0 to 100%) where higher numbers=greater impairment and less productivity. Baseline=Baseline of initial studies (EFC11072 and ACT11575). Safety population. Number of subjects analysed=subjects from studies EFC11072 and ACT11575 evaluable for this endpoint & 'n'=with data. Data was not planned to be collected for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Baseline, Week 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC11072, and ACT11575			
Subject group type	Subject analysis set			
Number of subjects analysed	267			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=191)	-10.82 (± 30.64)			
Week 12 (n=267)	-8.62 (± 28.67)			
Week 24 (n=255)	-11.92 (± 29.33)			
Week 36 (n=251)	-9.62 (± 30.08)			
Week 48 (n=243)	-11.39 (± 29.92)			

Week 60 (n=236)	-10.03 (± 25.74)			
Week 72 (n=216)	-9.10 (± 28.14)			
Week 84 (n=206)	-8.20 (± 27.06)			
Week 96 (n=209)	-11.32 (± 30.28)			
Week 120 (n=189)	-8.62 (± 32.95)			
Week 144 (n=183)	-9.01 (± 30.16)			
Week 168 (n=176)	-10.38 (± 31.48)			
Week 192 (n=166)	-8.99 (± 29.24)			
Week 216 (n=147)	-11.17 (± 29.35)			
Week 240 (n=147)	-8.57 (± 26.11)			
Week 264 (n=133)	-13.40 (± 30.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity and Activity Impairment: Percent Impairment While Working due to RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, and ACT11575 only

End point title	Change From Baseline in Work Productivity and Activity Impairment: Percent Impairment While Working due to RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, and ACT11575 only

End point description:

WPAI assesses work productivity & impairment. It is 6-item questionnaire to assess degree to which RA affected work productivity & regular activities over past 7 days. Questions: Q1=currently employed; Q2=hours(hrs) missed due to RA; Q3=hrs missed due to other reasons; Q4=hrs actually worked; Q5=RA affected productivity while working (0-10 scale, higher numbers=less productivity); Q6=RA affected regular activities (0-10 scale, higher numbers=greater impairment). Percent impairment while working was subscale and calculated: 10*Q5 for those who were currently employed & actually worked in past 7 days. Subscale score=expressed as impairment percentage (range:0-100%), where higher numbers=greater impairment and less productivity. Baseline:Baseline of initial studies (EFC11072 & ACT11575). Safety population. Number of subjects analysed=subjects from studies EFC11072 & ACT11575 evaluable for this endpoint and 'n'=with data. Data was not planned to be collected for Sarilumab monotherapy arm.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC11072, and ACT11575			
Subject group type	Subject analysis set			
Number of subjects analysed	273			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=194)	-21.65 (± 27.74)			
Week 12 (n=273)	-22.16 (± 26.53)			
Week 24 (n=258)	-23.45 (± 26.70)			
Week 36 (n=254)	-27.01 (± 27.11)			
Week 48 (n=252)	-24.76 (± 26.05)			
Week 60 (n=240)	-25.17 (± 25.12)			
Week 72 (n=224)	-24.33 (± 27.57)			
Week 84 (n=214)	-24.02 (± 27.09)			
Week 96 (n=212)	-26.42 (± 27.11)			
Week 120 (n=189)	-24.02 (± 27.63)			
Week 144 (n=184)	-24.67 (± 28.20)			
Week 168 (n=181)	-24.25 (± 28.46)			
Week 192 (n=168)	-25.24 (± 26.60)			
Week 216 (n=147)	-24.56 (± 27.28)			
Week 240 (n=155)	-24.39 (± 26.48)			
Week 264 (n=135)	-25.26 (± 27.40)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity and Activity Impairment: Percent Overall Work Impairment due to RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, and ACT11575 only

End point title	Change From Baseline in Work Productivity and Activity Impairment: Percent Overall Work Impairment due to RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, and ACT11575 only

End point description:

WPAI assesses work productivity and impairment. It is 6-item questionnaire to assess degree to which RA affected work productivity & regular activities over past 7 days. Questions were: Q1=currently employed; Q2=hrs missed due to RA; Q3=hrs missed due to other reasons;Q4=hrs actually worked;

Q5=RA affected productivity while working (0-10 scale, higher numbers=less productivity); Q6=RA affected regular activities (0-10 scale, higher numbers=greater impairment). Percent overall work impairment due to RA was subscale and calculated: 100*Q2/(Q2+Q4)+100*[(1-Q2/(Q2+Q4))*(Q5/10)] for those who were currently employed . Subscale score=expressed as impairment percentage (range:0-100%) where higher numbers=greater impairment. Baseline: Baseline of initial studies (EFC11072 and ACT11575). Safety population. Number of subjects analysed=subjects from studies EFC11072, and ACT11575 evaluable for this endpoint and 'n'=with data. Data was not planned to be collected for Sarilumab monotherapy arm.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC11072, and ACT11575			
Subject group type	Subject analysis set			
Number of subjects analysed	246			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=172)	-22.84 (± 30.73)			
Week 12 (n=246)	-23.13 (± 27.98)			
Week 24 (n=232)	-25.39 (± 28.84)			
Week 36 (n=230)	-28.13 (± 29.01)			
Week 48 (n=223)	-24.72 (± 29.38)			
Week 60 (n=222)	-26.44 (± 28.03)			
Week 72 (n=200)	-25.06 (± 29.84)			
Week 84 (n=193)	-23.62 (± 29.25)			
Week 96 (n=193)	-27.06 (± 30.60)			
Week 120 (n=172)	-24.15 (± 31.14)			
Week 144 (n=168)	-23.97 (± 32.05)			
Week 168 (n=162)	-24.59 (± 31.16)			
Week 192 (n=155)	-24.77 (± 29.63)			
Week 216 (n=136)	-24.54 (± 31.55)			
Week 240 (n=140)	-25.05 (± 29.26)			
Week 264 (n=122)	-27.10 (± 28.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity and Activity Impairment: Percent Activity Impairment due to RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, and ACT11575 only

End point title	Change From Baseline in Work Productivity and Activity Impairment: Percent Activity Impairment due to RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210 - Subjects From EFC11072, and ACT11575 only

End point description:

WPAI assesses work productivity and impairment. It is 6-item questionnaire to assess degree to which RA affected work productivity & regular activities over past 7 days. Questions: Q1=currently employed; Q2=hrs missed due to RA; Q3=hrs missed due to other reasons; Q4=hrs actually worked; Q5=RA affected productivity while working (0 to 10 scale, with higher numbers indicated less productivity); Q6 = RA affected regular activities (0-10 scale, with higher numbers=greater impairment). Percent activity impairment due to RA was a subscale and calculated as: 10*Q6 for all respondents. Subscale score=expressed as impairment percentage (range: 0-100%) where higher numbers indicate greater impairment. Here, Baseline: Baseline of initial studies (EFC11072 and ACT11575). Safety population. Here, 'number of subjects analysed'=subjects from studies EFC11072, and ACT11575 evaluable for this endpoint and 'n'=subjects with data. Data was not planned to be collected for Sarilumab Monotherapy arm.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC11072, and ACT11575			
Subject group type	Subject analysis set			
Number of subjects analysed	1157			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=846)	-26.47 (± 29.30)			
Week 12 (n=1157)	-28.02 (± 27.44)			
Week 24 (n=1121)	-28.76 (± 27.62)			
Week 36 (n=1095)	-29.71 (± 28.03)			
Week 48 (n=1061)	-29.11 (± 28.28)			
Week 60 (n=1034)	-29.81 (± 27.78)			
Week 72 (n=1013)	-29.61 (± 29.02)			
Week 84 (n=985)	-30.28 (± 29.53)			
Week 96 (n=954)	-30.28 (± 28.32)			
Week 120 (n=924)	-30.42 (± 28.78)			

Week 144 (n=883)	-30.29 (± 28.90)			
Week 168 (n=840)	-30.64 (± 29.30)			
Week 192 (n=804)	-30.88 (± 29.36)			
Week 216 (n=753)	-30.36 (± 29.34)			
Week 240 0 (n=722)	-31.12 (± 29.63)			
Week 264 (n=645)	-31.97 (± 28.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity Survey - Rheumatoid Arthritis (WPS-RA) at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Work Days Missed Due to Arthritis - Subjects From EFC10832 Only

End point title	Change From Baseline in Work Productivity Survey - Rheumatoid Arthritis (WPS-RA) at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Work Days Missed Due to Arthritis - Subjects From EFC10832 Only

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with arthritis over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Change from Baseline in number of work days missed in the last month due to arthritis by the subject was reported in the endpoint. Here, Baseline refers to the Baseline of initial study (EFC10832). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects from study EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	145			
Units: days				
arithmetic mean (standard deviation)				
Week 0 (n=145)	-2.72 (± 6.38)			
Week 12 (n=127)	-3.66 (± 6.80)			
Week 24 (n=125)	-3.70 (± 6.85)			
Week 36 (n=121)	-3.73 (± 7.08)			

Week 48 (n=116)	-3.37 (± 7.18)			
Week 60 (n=114)	-3.55 (± 6.93)			
Week 72 (n=111)	-3.58 (± 7.07)			
Week 84 (n=106)	-3.11 (± 8.49)			
Week 96 (n=101)	-3.47 (± 7.57)			
Week 120 (n=101)	-3.54 (± 7.56)			
Week 144 (n=94)	-3.51 (± 6.84)			
Week 168 (n=88)	-3.73 (± 7.37)			
Week 192 (n=80)	-3.76 (± 7.21)			
Week 216 (n=74)	-3.51 (± 7.30)			
Week 240 (n=73)	-2.44 (± 6.70)			
Week 264 (n=66)	-2.86 (± 5.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Days With Work Productivity Reduced by >=50% Due to Arthritis - Subjects From EFC10832 Only

End point title	Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Days With Work Productivity Reduced by >=50% Due to Arthritis - Subjects From EFC10832 Only

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subjects self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Change from Baseline in number of work days with work productivity reduced by >= 50% by the subjects was reported in the endpoint. Here, Baseline refers to the Baseline of initial study (EFC10832). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects from study EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	145			
Units: days				
arithmetic mean (standard deviation)				
Week 0 (n=145)	-3.47 (± 7.64)			
Week 12 (n=126)	-4.93 (± 9.22)			
Week 24 (n=123)	-5.14 (± 7.67)			
Week 36 (n=122)	-5.47 (± 8.41)			

Week 48 (n=115)	-5.75 (± 8.14)			
Week 60 (n=114)	-5.16 (± 7.96)			
Week 72 (n=110)	-5.21 (± 7.74)			
Week 84 (n=105)	-4.40 (± 8.27)			
Week 96 (n=101)	-5.03 (± 6.91)			
Week 120 (n=101)	-4.63 (± 7.47)			
Week 144 (n=94)	-4.88 (± 7.53)			
Week 168 (n=88)	-4.67 (± 7.06)			
Week 192 (n=80)	-4.55 (± 7.25)			
Week 216 (n=74)	-4.42 (± 8.01)			
Week 240 (n=73)	-3.48 (± 7.56)			
Week 264 (n=66)	-3.97 (± 5.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Arthritis Interference With Work Productivity - Subjects From EFC10832 Only

End point title	Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Arthritis Interference With Work Productivity - Subjects From EFC10832 Only

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subejct self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Interference in the last month with work productivity was measured on a scale that ranges from 0 (no interference) to 10 (complete interference), where higher scores indicated more interference. Here, Baseline refers to the Baseline of initial study (EFC10832). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects from study EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	144			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=144)	-20.83 (± 30.51)			
Week 12 (n=127)	-27.95 (± 58.67)			

Week 24 (n=124)	-35.16 (± 31.45)			
Week 36 (n=123)	-37.48 (± 33.72)			
Week 48 (n=115)	-36.78 (± 31.58)			
Week 60 (n=115)	-40.35 (± 33.19)			
Week 72 (n=111)	-38.74 (± 32.73)			
Week 84 (n=106)	-39.62 (± 41.56)			
Week 96 (n=102)	-42.35 (± 32.19)			
Week 120 (n=102)	-37.84 (± 32.32)			
Week 144 (n=95)	-39.16 (± 32.28)			
Week 168 (n=90)	-38.11 (± 32.25)			
Week 192 (n=81)	-40.74 (± 34.96)			
Week 216 (n=74)	-39.19 (± 37.00)			
Week 240 0 (n=73)	-38.22 (± 38.24)			
Week 264 (n=66)	-39.24 (± 36.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: House Work Days Missed due to Arthritis - Subjects From EFC10832 Only

End point title	Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: House Work Days Missed due to Arthritis - Subjects From EFC10832 Only

End point description:

'The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Change from baseline in number of days with no household work//household work missed in the last month by the subjects was reported. Here, Baseline refers to the Baseline of initial study (EFC10832). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects from study EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.
'

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	446			
Units: days				
arithmetic mean (standard deviation)				
Week 0 (n=446)	-4.65 (± 9.44)			
Week 12 (n=401)	-6.17 (± 10.29)			
Week 24 4 (n=397)	-6.55 (± 9.92)			
Week 36 (n=388)	-6.65 (± 10.36)			
Week 48 (n=373)	-6.61 (± 10.57)			
Week 60 (n=364)	-6.84 (± 10.47)			
Week 72 (n=355)	-6.50 (± 10.72)			
Week 84 (n=343)	-6.56 (± 10.63)			
Week 96 (n=336)	-6.80 (± 10.32)			
Week 120 (n=323)	-6.81 (± 10.31)			
Week 144 (n=309)	-6.78 (± 10.67)			
Week 168 (n=283)	-7.04 (± 10.13)			
Week 192 (n=274)	-6.74 (± 10.51)			
Week 216 (n=261)	-6.78 (± 10.07)			
Week 240 (n=243)	-6.82 (± 10.02)			
Week 264 (n=230)	-6.95 (± 10.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Days With Household Work Productivity Reduced by >=50% Due to Arthritis - Subjects From EFC10832 Only

End point title	Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Days With Household Work Productivity Reduced by >=50% Due to Arthritis - Subjects From EFC10832 Only

End point description:

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

was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Change from baseline in number of days with reduced household work productivity by >= 50% in the last month by the subjects was reported. Here, Baseline refers to the Baseline of initial study (EFC10832). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects from study EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	445			
Units: days				
arithmetic mean (standard deviation)				
Week 0 (n=445)	-4.08 (± 10.24)			
Week 12 (n=402)	-5.64 (± 10.93)			
Week 24 (n=395)	-6.01 (± 10.40)			
Week 36 (n=387)	-6.57 (± 10.29)			
Week 48 (n=372)	-7.06 (± 10.13)			
Week 60 (n=363)	-7.01 (± 10.30)			
Week 72 (n=353)	-6.70 (± 10.72)			
Week 84 (n=342)	-6.38 (± 10.79)			
Week 96 (n=334)	-7.05 (± 10.62)			
Week 120 (n=322)	-7.12 (± 10.37)			
Week 144 (n=308)	-6.58 (± 10.59)			
Week 168 (n=284)	-6.39 (± 10.28)			
Week 192 (n=274)	-6.01 (± 10.07)			
Week 216 (n=259)	-6.27 (± 10.30)			
Week 240 (n=241)	-6.31 (± 9.99)			
Week 264 (n=229)	-6.93 (± 9.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Days With Family/Social/Leisure Activities Missed Due to Arthritis - Subjects From EFC10832 Only

End point title	Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Days With Family/Social/Leisure Activities Missed Due to Arthritis - Subjects From EFC10832 Only

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Change from baseline in number of days missed of family/social/leisure activities in the last month by the subjects was reported. Here, Baseline refers to the Baseline of initial study (EFC10832). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects from study EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	447			
Units: days				
arithmetic mean (standard deviation)				
Week 0 (n=447)	-2.94 (± 8.34)			
Week 12 (n=401)	-4.16 (± 8.38)			
Week 24 (n=397)	-4.50 (± 8.42)			
Week 36 (n=388)	-4.38 (± 8.88)			
Week 48 (n=373)	-4.44 (± 8.51)			
Week 60 (n=364)	-4.46 (± 8.31)			
Week 72 (n=354)	-4.20 (± 8.52)			
Week 84 (n=343)	-4.31 (± 8.30)			
Week 96 (n=335)	-4.38 (± 8.03)			
Week 120 (n=323)	-4.43 (± 8.01)			
Week 144 (n=309)	-4.17 (± 7.90)			
Week 168 (n=285)	-4.12 (± 8.16)			
Week 192 (n=272)	-4.23 (± 8.17)			
Week 216 (n=261)	-3.93 (± 8.03)			
Week 240 (n=242)	-4.03 (± 8.26)			
Week 264 (n=230)	-3.85 (± 7.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Days With Outside Help Hired Due to Arthritis- Subjects From EFC10832 Only

End point title	Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Days With Outside Help Hired Due to Arthritis- Subjects From EFC10832 Only

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). Change from baseline in number of days with outside help hired in the last month by the subject was reported. Here, Baseline refers to the Baseline of initial study (EFC10832). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects from study EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	446			
Units: days				
arithmetic mean (standard deviation)				
Week 0 (n=446)	-2.92 (± 10.14)			
Week 12 (n=401)	-4.24 (± 10.16)			
Week 24 (n=397)	-4.12 (± 10.47)			
Week 36 (n=388)	-4.28 (± 10.27)			
Week 48 (n=373)	-4.58 (± 10.12)			
Week 60 (n=364)	-4.21 (± 10.16)			
Week 72 (n=354)	-4.00 (± 9.52)			
Week 84 (n=343)	-3.81 (± 9.67)			
Week 96 (n=335)	-3.90 (± 10.11)			
Week 120 (n=323)	-3.90 (± 9.62)			
Week 144 (n=309)	-3.91 (± 9.73)			
Week 168 (n=285)	-4.14 (± 10.00)			
Week 192 (n=273)	-3.93 (± 10.14)			
Week 216 (n=261)	-4.19 (± 9.84)			
Week 240 (n=242)	-4.12 (± 10.43)			

Week 264 (n=230)	-4.05 (± 9.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Arthritis Interference With Household Work Productivity - Subjects From EFC10832 Only

End point title	Change From Baseline in WPS-RA at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210: Arthritis Interference With Household Work Productivity - Subjects From EFC10832 Only

End point description:

The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and was based on subject self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items). The RA interference in the last month with household work productivity was measured on a scale that ranged from 0 (no interference) to 10 (complete interference), where higher scores indicated more interference. Here, Baseline refers to the Baseline of initial study (EFC10832). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects from study EFC10832 evaluable for this endpoint and 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for Sarilumab Monotherapy arm, as pre-specified in the protocol.

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 (post-dose), 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 240 and 264 of LTS11210

End point values	Sarilumab + DMARD: EFC10832			
Subject group type	Subject analysis set			
Number of subjects analysed	444			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=444)	-23.24 (± 35.09)			
Week 12 (n=401)	-33.49 (± 35.76)			
Week 24 (n=399)	-36.94 (± 36.75)			
Week 36 (n=388)	-36.42 (± 39.35)			
Week 48 (n=373)	-37.45 (± 34.85)			
Week 60 (n=365)	-38.19 (± 34.55)			
Week 72 (n=355)	-36.48 (± 35.37)			

Week 84 (n=344)	-35.61 (± 39.69)			
Week 96 (n=335)	-36.81 (± 36.04)			
Week 120 (n=324)	-38.86 (± 35.22)			
Week 144 (n=310)	-36.23 (± 37.52)			
Week 168 (n=286)	-36.01 (± 39.84)			
Week 192 (n=274)	-35.80 (± 40.99)			
Week 216 (n=260)	-38.54 (± 39.81)			
Week 240 (n=240)	-40.08 (± 35.68)			
Week 264 (n=228)	-38.07 (± 42.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sub-study: Number of subjects who Reported Adverse Events Related to Pre-filled Syringe With Safety System

End point title	Sub-study: Number of subjects who Reported Adverse Events Related to Pre-filled Syringe With Safety System

End point description:

AEs related to PFS-S included PTC-related AEs, device-related AEs, or AEs of injection site reaction. In this endpoint, only PTC-related AEs, device-related AEs, or AEs of injection site reaction assessed during the sub-study were reported. TEAEs and SAEs reported during the sub-study were included in the main study data and no separate data collection and analysis was performed, as pre-planned in the protocol. Analysis was performed on all subjects who were enrolled in the sub-study.

End point type	Secondary

End point timeframe:

From Week 24 to 36

End point values	PFS-S Sarilumab 150 mg q2w	PFS-S Sarilumab 200 mg q2w	PFS-S Sarilumab 200 to 150 mg q2w	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	98	1	
Units: subejcts				
PTC-related AEs	0	0	0	
Device-related AEs	0	0	0	
AEs of injection site reaction	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose (i.e., Day 1 of study LTS11210) of IMP to last dose of IMP + 60 days (maximum duration: up to 523 weeks)

Adverse event reporting additional description:

Reported AEs and deaths were TEAEs that developed/worsened in grade or became serious during TEAE period (defined as time from 1st dose of IMP to last dose of IMP + 60 days). As pre-specified and initially planned, TEAEs and SAEs reported during sub-study were included in the main study data and no separate analysis was done. Safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)

Reporting group description:

Subjects who completed any of initial studies:Part A or B of EFC11072, ACT11575, EFC10832 or SFY13370 were enrolled in LTS11210 and received sarilumab 150 milligrams (mg) subcutaneously (SC) once weekly (qw). Dose could be reduced to 150 mg every 2 weeks (q2w) due to neutropenia, thrombocytopenia or increase in liver enzymes (alanine aminotransferase [ALT]). After dose regimens selection for Phase 3 studies (150 mg q2w and 200 mg q2w), subjects already receiving 150 mg qw were switched to sarilumab 200 mg q2w. Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks). Subjects who were already taking concomitant non-biologic DMARDs in initial study continued stable dose of one or combination of conventional synthetic DMARDs they were taking.

Reporting group title	Sarilumab monotherapy

Reporting group description:

Subjects who completed study EFC13752 were enrolled in LTS11210 and received sarilumab 200 mg q2w. Dose could be reduced to 150 mg q2w due to neutropenia, thrombocytopenia or increase in liver enzymes (ALT). Treatment duration per subject was at least 264 weeks from first study drug administration in LTS11210. Subjects continued to be treated beyond 264 weeks until sarilumab was commercially available in their respective countries or until 2020, at the latest (maximum duration: 523 weeks).

Serious adverse events	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	617 / 1910 (32.30%)	27 / 111 (24.32%)	
number of deaths (all causes)	49	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Of Colon			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ameloblastoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Squamous Cell Carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-Cell Lymphoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 1910 (0.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Neoplasm Of Thyroid Gland			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Cancer Stage Ii			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Breast Cancer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer Stage Ii			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial Carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix Cancer Metastatic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cholesteatoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear Cell Renal Cell Carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal Adenocarcinoma			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal Cancer Metastatic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye Naevus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma Of Breast			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder Cancer Metastatic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Invasive Ductal Breast Carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung Adenocarcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lung Cancer Metastatic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Carcinoma Cell Type Unspecified Stage Iii			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm Malignant			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Melanoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Renal Cell Carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm Malignant			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-Small Cell Lung Cancer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian Cancer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Germ Cell Teratoma Benign			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary Thyroid Cancer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid Tumour Benign			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary Tumour Benign			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleomorphic Adenoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic Adenoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Cancer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory Anaemia With An Excess Of Blasts			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cell Carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serous Cystadenocarcinoma Ovary			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Cancer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestine Carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Skin			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of The Cervix			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 1910 (0.37%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated Hypertension			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Embolus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 1910 (0.42%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypotension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic Shock			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Iliac Artery Embolism			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Venous Thrombosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Occlusion			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Embolism			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Ischaemia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Venous Disease			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose Vein			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous Thrombosis Limb			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Missed			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion Spontaneous			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cardiac Death			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chills			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multiple Organ Dysfunction Syndrome			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Non-Cardiac Chest Pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 1910 (0.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Pregnancy Of Partner			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Acquired Hydrocele			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adnexa Uteri Cyst			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Prostatic Hyperplasia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Enlargement			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Hyperplasia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Dysplasia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Polyp			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Hyperplasia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menometrorrhagia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Menorrhagia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cyst			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Prolapse			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Prolapse			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute Respiratory Failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Asthma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial Hyperreactivity			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic Abnormal Relaxation			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic Pulmonary Fibrosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infiltration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural Effusion			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax Spontaneous			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	10 / 1910 (0.52%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	1 / 10	0 / 3	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pulmonary Fibrosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Hypertension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Mass			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep Apnoea Syndrome			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute Psychosis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol Abuse			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar Disorder			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion Disorder			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major Depression			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed Anxiety And Depressive Disorder			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Breakage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Dislocation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Loosening			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Malfunction			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 1910 (0.47%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	7 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal Test Positive			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiv Test False Positive			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen Saturation Decreased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases Increased			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal Injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental Overdose			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol Poisoning			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anaemia Postoperative			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bite			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral Injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocation Of Vertebra			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 1910 (0.42%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 1910 (0.37%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Foot Fracture				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Fractured Sacrum				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal Stoma Complication				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gun Shot Wound				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hip Fracture				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 5	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Humerus Fracture				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	5 / 1910 (0.26%)	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 5	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Incision Site Fibrosis				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional Hernia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Sprain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Limb Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Injuries			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Patella Fracture alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Fracture alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital Haematoma alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic Fracture alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic Osteolysis alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Fistula alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haematoma alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Shock			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdural Haematoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Rupture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal Burn			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity To Various Agents			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ulna Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Left Ventricular Failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute Myocardial Infarction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	11 / 1910 (0.58%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	3 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 1910 (0.47%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	2 / 11	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial Tachycardia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Complete			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac Failure Acute			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Tamponade			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary Failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Congestive Cardiomyopathy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary Artery Perforation				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Coronary Artery Stenosis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Left Ventricular Failure				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 1	0 / 1		
Microvascular Coronary Artery Disease				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Myocardial Infarction				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 5	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Myocardial Ischaemia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 4	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pericarditis				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Node Dysfunction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Asystole			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Fibrillation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal Tunnel Syndrome			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar Stroke			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haematoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular Insufficiency			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed Level Of Consciousness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epilepsy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage Intracranial			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic Stroke			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Transformation Stroke			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic Stroke			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Radiculopathy			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multifocal Motor Neuropathy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial Seizures			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Sensory Neuropathy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ruptured Cerebral Aneurysm				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	1 / 1	0 / 0		
Sciatica				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Seizure				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Subarachnoid Haemorrhage				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	2 / 3	0 / 0		
deaths causally related to treatment / all	1 / 2	0 / 0		
Syncope				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 4	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Transient Global Amnesia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Transient Ischaemic Attack				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	6 / 1910 (0.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Headache			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anaemia Megaloblastic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Loss Anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Marrow Failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron Deficiency Anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic Insufficiency			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	11 / 1910 (0.58%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	12 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombocytopenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Cataract			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central Vision Loss			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroiditis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry Age-Related Macular Degeneration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular Hole			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neovascular Age-Related Macular Degeneration			
alternative dictionary used:			

MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic Ischaemic Neuropathy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Vascular Thrombosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicolith			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Gastritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's Disease			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular Perforation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum Intestinal			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum Intestinal Haemorrhagic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Perforation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical Fistula			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Hernia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer Perforation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Inflammation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal Reflux Disease			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial Eventration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus Hernia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal Perforation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated Umbilical Hernia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory Bowel Disease			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Inguinal Hernia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intestinal Dilatation				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intestinal Obstruction				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Irritable Bowel Syndrome				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Large Intestine Perforation				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	1 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Noninfectious Peritonitis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pancreatic Necrosis				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Pseudocyst Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Necrotising			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal Adhesions			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Small Intestinal Obstruction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal Prolapse			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 1910 (0.47%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	3 / 1910 (0.16%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	24 / 1910 (1.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 24	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Chronic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis Obstructive			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portosplenomesenteric Venous Thrombosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cutaneous Lupus Erythematosus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus Ulcer			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatomyositis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema Multiforme			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Necrosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Ulcer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous Emphysema			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic Skin Eruption			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute Kidney Injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Urinary			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis Haemorrhagic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hydronephrosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 1910 (0.37%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Colic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral Stenosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Incontinence			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis Subacute			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ankle Deformity			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 1910 (0.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atlantoaxial Subluxation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Cyst			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Costochondritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fasciitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot Deformity			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	14 / 1910 (0.73%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 19	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Deformity			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Degeneration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Disorder			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Destruction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee Deformity			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Spinal Stenosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	45 / 1910 (2.36%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 52	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoporotic Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid Arthritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	32 / 1910 (1.68%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	3 / 33	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid Nodule			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator Cuff Syndrome			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Osteoarthritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Stenosis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	4 / 1910 (0.21%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist Deformity			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Limb			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 1910 (0.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Neck			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Oral			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Soft Tissue			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Sinusitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous Graft Site Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis Bacterial			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 1910 (0.31%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	5 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis Infective			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical Pneumonia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Dacryocystitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin's Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Tuberculosis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Fungal			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bullous Erysipelas			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis Infective			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	21 / 1910 (1.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	15 / 24	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis Staphylococcal			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Infective			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coccidioidomycosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue Fever			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea Infectious			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 1910 (0.37%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	2 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis Infectious			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epiglottitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 1910 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Urinary Tract Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gas Gangrene			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Bacterial			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Salmonella			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Ophthalmic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	5 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Histoplasmosis Disseminated			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infected Bite			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected Skin Ulcer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 1910 (0.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	5 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious Pleural Effusion			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infective Exacerbation Of Bronchiectasis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation Of Chronic Obstructive Airways Disease			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Infection			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leptospirosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme Disease			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical Device Site Joint Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Meningitis Viral			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis Herpetic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising Fasciitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising Soft Tissue Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic Herpes Zoster			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral Candidiasis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 1910 (0.31%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	3 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis Acute			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreas Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 1910 (0.37%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	52 / 1910 (2.72%)	1 / 111 (0.90%)		
occurrences causally related to treatment / all	25 / 55	0 / 1		
deaths causally related to treatment / all	1 / 5	0 / 0		
Pneumonia Chlamydial				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia Pneumococcal				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia Streptococcal				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia Viral				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	1 / 1	0 / 0		
Post Procedural Infection				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Postoperative Abscess				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary Tuberculosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	4 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Chronic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Relapsing Fever			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-Oophoritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	6 / 1910 (0.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Septic Arthritis Neisserial			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 1910 (0.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
Sialoadenitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Staphylococcal Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Skin Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 1910 (0.26%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-Ovarian Abscess			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 1910 (0.21%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Myositis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection Staphylococcal			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wound Sepsis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus Inadequate Control			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic Hyperosmolar Nonketotic Syndrome			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 1910 (0.10%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Latent Autoimmune Diabetes In Adults			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	3 / 1910 (0.16%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Lysis Syndrome			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 1910 (0.05%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sarilumab + Disease Modifying Anti-Rheumatic Drugs (DMARD)	Sarilumab monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1444 / 1910 (75.60%)	82 / 111 (73.87%)	
Investigations			
Alanine Aminotransferase Increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	201 / 1910 (10.52%)	4 / 111 (3.60%)	
occurrences (all)	287	4	
Injury, poisoning and procedural complications			
Accidental Overdose			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	330 / 1910 (17.28%)	20 / 111 (18.02%)	
occurrences (all)	496	22	
Fall			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	109 / 1910 (5.71%)	3 / 111 (2.70%)	
occurrences (all)	122	3	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	235 / 1910 (12.30%)	4 / 111 (3.60%)	
occurrences (all)	271	5	
Blood and lymphatic system disorders			
Leukopenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	101 / 1910 (5.29%)	4 / 111 (3.60%)	
occurrences (all)	181	5	
Neutropenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	348 / 1910 (18.22%)	18 / 111 (16.22%)	
occurrences (all)	786	64	
General disorders and administration site conditions			
Injection Site Erythema			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	111 / 1910 (5.81%)	0 / 111 (0.00%)	
occurrences (all)	751	0	
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	122 / 1910 (6.39%)	2 / 111 (1.80%)	
occurrences (all)	153	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	62 / 1910 (3.25%)	7 / 111 (6.31%)	
occurrences (all)	70	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	87 / 1910 (4.55%)	9 / 111 (8.11%)	
occurrences (all)	109	11	
Rheumatoid Arthritis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	227 / 1910 (11.88%)	16 / 111 (14.41%)	
occurrences (all)	357	31	
Back Pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	122 / 1910 (6.39%)	6 / 111 (5.41%)	
occurrences (all)	141	6	
Infections and infestations			
Bronchitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	215 / 1910 (11.26%)	12 / 111 (10.81%)	
occurrences (all)	301	19	
Influenza			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	124 / 1910 (6.49%)	3 / 111 (2.70%)	
occurrences (all)	160	4	
Pharyngitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	110 / 1910 (5.76%)	4 / 111 (3.60%)	
occurrences (all)	129	4	
Nasopharyngitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	249 / 1910 (13.04%)	14 / 111 (12.61%)	
occurrences (all)	390	26	
Upper Respiratory Tract Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	303 / 1910 (15.86%)	16 / 111 (14.41%)	
occurrences (all)	574	21	
Urinary Tract Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	264 / 1910 (13.82%)	14 / 111 (12.61%)	
occurrences (all)	428	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2011	Following changes were performed: • Included subjects in LTS11210 study population who were randomised into and completed treatment period of ACT11575. • Indicated that study name of LTS11210 is ABILITY (Monoclonal AntiBody anti-IL-6R extensiontrial in RA for safety purposes). • Added a section that described assessment of following subject-reported outcomes health questionnaires: Functional Assessment of Chronic Illness Therapy Fatigue (FACITFatigue), Work Productivity and Activities Impairment (WPAI), Sleep Visual Analog Scale (VAS), and the SF-36 Health Survey. • Clarified that an independent joint assessor (ie, a third party who is not involved in the conduct of the study at the investigational site) was not required to carry out efficacy assessments in LTS11210 study. • Clarified hypersensitivity reactions, referred to throughout protocol as systemic hypersensitivity reactions rather than local reactions. • Specified that thrombocytopenia was an indication to decrease study drug dose regimen from 150 mg SAR153191 (subcutaneous) weekly to 150 mg SAR153191 every other week. • Indicated that prior ACT11575 subject(s) enrolled in LTS11210 study were allowed to continue use of rescue treatment, for example, sulfasalazine or leflunomide, if use was ongoing at ACT11575 end-of-treatment visit. • Deleted sIL-6Rα measurements in LTS11210 study. • Revised exclusion criterion from female of childbearing potential with a positive pregnancy test to pregnant or breastfeeding women. • Deleted exclusion criterion - Men who were unwilling to utilise 2 forms of contraception: a condom and spermicidal agent. • Indicated that absolute neutrophil count of <500/mm3, lasting more than 5 days, was reported as serious adverse event. • Clarified within statistical section of LTS11210 study protocol. • Added RNA sample collection time points and modified biomarker collection time points in LTS11210 study protocol. • Provided minor clarifications to protocol.

26 May 2011	• Indicated that investigational drug product administered to subjects enrolled in LTS11210 was to be switched to new drug product, which consisted of new formulation made with different cell line, and with different drug concentrations compared to drug product that was currently in use in study. New drug product was to be packaged in prefilled syringe, compared to former drug product packaged in vial. • Clarified that after selection of Phase 3 pivotal dose(s) for program, it was intention of sponsor to switch currently enrolled subjects to highest of available selected dose regimens. All new subjects, subsequently enrolled were to be assigned to highest available selected dose regimen. Dosage switch procedure was instituted so that all enrolled subjects (preceding and proceeding pivotal dose selection) were on dose regimen with same benefit: risk ratio. • Clarified that step-down dose (due to safety issue) after selection of Phase 3 pivotal dose(s) was to be lowest available selected dose regimen. • Indicated that additional pharmaceutical form of SAR153191 (sarilumab) in amber glass vial at concentration of 100 mg/mL was to be administered to subjects enrolled into LTS11210. Use of this drug product was to be implemented, if at time of dose selection decision, selected pivotal dose regimen(s) included 200 mg dose, and/or 100 mg every other week dose. • Excluded subjects with latex hypersensitivity from enrolment because needle cap on prefilled syringe contained dry natural rubber latex particles that might cause allergic reactions. • Incorporated recently assigned International Non-proprietary Name of sarilumab. • Provided Sponsor’s guidance for medical follow-up of laboratory abnormality, by adding “Thrombocytopenia” appendix. • Removed text related to nonclinical studies of embryo-fetal development, pre-/postnatal development and fertility since final study results were now formally presented in updated Investigator’s Brochure. • Provided minor clarifications
24 January 2012	• Indicated that all enrolled subjects in LTS11210 were to be assigned to highest available sarilumab dose, 200 mg q2w dose and step-down dose (in case of specified safety issue) was to be 150 mg q2w. 150 mg and 200 mg q2w doses were selected based on analysis of completed and locked Part A study results. • Included subjects in LTS11210 population who were randomised into and completed treatment period of EFC10832. • Removed 7-day screening period from design and flowchart for subjects rolling over into LTS11210 that were previously randomised into EFC11072 Part B, Cohort 2 and EFC10832 and successfully completed treatment period. • Revised study name from ABILITY to SARIL-RA-EXTEND. • Added Week 10 visit blood samples for hematology and liver function tests (LFTs) to insure collection of hematology and LFTs every 2 weeks for initial 12 weeks of LTS11210, which mirrors schedule in EFC11072. • Provided summary of EFC11072, Part A results. • Indicated that Cardiovascular Adjudication Committee was to be established for LTS11210 to ensure that cardiovascular events were evaluated with consistent criteria and in unbiased manner. • Modified Exclusion criterion to bring consistency between exclusion criteria applied to study populations across all preceding study protocols (EFC11072, ACT11575 and EFC10832). • Added Permitted Concomitant Treatment list that needed dose adjustment following initiation of sarilumab. • Updated description of endpoints and statistical methodology for clarification purposes. • WPS-RA was added in LTS11210 because WPS-RA was included in EFC10832. • Added Subject Safety guidelines for reporting adverse events with prespecified monitoring to be consistent with guidance provided in upcoming Phase 3 sarilumab study protocols. • Provided Investigators set of clinical criteria for diagnosing anaphylaxis and Web link to National Heart, Lung and Blood Institute for reference to clinical management of lipid disorders. • Provided minor clarifications.

08 August 2012	The following changes were made: • Implemented new safety precautions to prevent administration of sarilumab to subjects at risk for thrombocytopenia <100 000/mm3 and/or grade 3/grade 4 neutropenia. These changes were to be implemented immediately • Provided additional safety information related to thrombocytopenia and neutropenia, and to infections.
31 October 2012	The following changes were made: • Modified to allow rollover of subjects from study SFY13370. • Modified the assessment schedule starting at 2 years from 12-week to 24-week intervals, with intervening 12-week IMP supply visits • Added yearly HIV testing starting at Week 48. • Revised scheduling of X-rays of hands and feet at EOT visit to have 14-day windows except Week 260. • Added DMARD concomitant medication restrictions. • Added FM30 latex-free formulation. • Updated IMP administration language. • Updated urine analysis language. • Updated safety language related to neurological event, anti-DNA antibodies, platelets, pregnancy and infections • Added chronic neurodegenerative disease to list of medically important events • Updated database lock language • Updated Appendix L language
17 July 2014	• Included subjects in LTS11210 who were randomised and completed monotherapy treatment period of EFC13752; sarilumab in LTS11210 was not administered with concomitant DMARDs in subjects of EFC13752. • Modified protocol title to remove 'on top of DMARDs' and modified other sections. • Modified Exclusion Criteria: - Deleted history of latex allergy (systemic hypersensitivity reaction to latex) except for subjects coming from EFC10832 or SFY13370'. - Women of childbearing potential was modified to be part of local informed consent in order to follow local guidelines - Deleted "Subjects with active or latent tuberculosis at last treatment visit in EFC11072, ACT11575, SFY13370 or EFC10832' as these subjects were to be permanently discontinued in initial studies. - Added "Subjects with temporary IMP discontinuation lasting >31 days at time of planned first dose in LTS11210 ' and "Subjects fulfilling protocol-defined criteria for permanent treatment discontinuation'. • Removed Phase 2 results and added Phase 3 results of EFC11072 Part B. • Conditions for any change in concomitant treatments including nonbiologic DMARDs, steroids, and nonsteroidal anti-inflammatory drugs and analgesics were adapted. • Modified temporary treatment discontinuation up to 3 missed doses (<=59 days). • 2 local amendments were incorporated in this global amendment. • Other minor changes: - Removed tuberculin skin test and serum QuantiFERON test at Week 260. - Replaced HIV yearly testing with HIV testing anytime during study when subject was at risk for this infection. - Added pharmacokinetic sampling to sampling time points for ADA beyond 2 years of study treatment to facilitate appropriate interpretation of the results. - Removed X-rays performed at Week 192 visit. - Updated total number of subjects and sites. - Improved wording throughout protocol and removed superseded text. - Modified safety section to harmonise with other ongoing sarilumab studies. - Corrected schedule inconsistencies.

31 August 2015	• Sarilumab treatment in LTS11210 was extended to 264 weeks in order to allow all subjects to be treated for approximately 5 calendar years from 1st sarilumab administration. • Subjects continued to be treated beyond 264 weeks if sarilumab was not commercially available in their country at Week 264.. • In the UK, duration of treatment was 264 weeks from 1st study drug administration in LTS11210 to provide finite duration of study treatment in accordance with local requirements. • Some assessments were not performed after Week 264 as per flowcharts, including health economics assessments, 12-lead ECG, and some DAS28 components of ACR core set (after Week 264, only TJC& SJC for 28 joints, subject´s global assessment of disease activity) • Week 192 X-ray was deleted in Amendment 8 and reinstated with Amendment 9. • PFS-S syringe was modified version of prefilled syringe that included needle safety shield to prevent needle stick injury. •12-week substudy was optional and was to be conducted at limited sites in selected countries. • Prior to this amendment, the protocol required permanent discontinuation of subject from study treatment in case of opportunistic infection or possible opportunistic infection per protocol. Definition of opportunistic infection had been modified. • To ensure continuity of treatment between last administration of IMP and 1st dose of commercial sarilumab, • PK: clarified analysis of bound sarilumab concentrations. After completion of EFC11072 Part B study, decision was made to only analyse functional sarilumab concentrations. • Deatiled Serum and RNA biomarkers samples long-term storage. • Corrected 2 secondary efficacy endpoints inconsistency. • Replaced “initial study” with “LTS11210”, where applicable, to clarify that treatment period of 264 weeks begins day of 1st dose of sarilumab in LTS11210. • Added active comparator to list of drugs subject might had been exposed to in prior study • Corrected minor grammatical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported