

**Clinical trial results:****A Randomized, Double-blind, Parallel Group Study of the Safety and Effect on Clinical Outcome of Tocilizumab SC Versus Tocilizumab IV, in Combination With Traditional Disease Modifying Anti-rheumatic Drugs (DMARDs), in Patients With Moderate to Severe Active Rheumatoid Arthritis****Summary**

EudraCT number	2010-018375-22
Trial protocol	ES GB IT DE LT BG
Global end of trial date	19 August 2013

**Results information**

Result version number	v1 (current)
This version publication date	27 May 2016
First version publication date	27 May 2016

**Trial information****Trial identification**

Sponsor protocol code	WA22762
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01194414
WHO universal trial number (UTN)	-
Other trial identifiers	Other study name: SUMMACTA

Notes:

**Sponsors**

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
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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	19 August 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 August 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This randomised, double-blind, parallel group study compares the efficacy and safety of subcutaneous (sc) versus intravenous (iv) administration of tocilizumab (RoActemra/Actemra) in subjects with moderate to severe active rheumatoid arthritis. Subjects were randomised to receive either tocilizumab 162 mg sc weekly plus iv placebo every 4 weeks, or tocilizumab 8 mg/kg iv every 4 weeks plus sc placebo weekly during the double-blind period from baseline to Week 24. The double-blind period was followed by a 72-week open-label treatment with some switching of sc and iv administration. No placebo was administered in the open-label phase. Subjects continued on their stable dose of disease-modifying anti-rheumatic drugs (DMARDs) throughout the study. Anticipated time on study treatment was 2 years.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

Subjects will continue on their stable dose of disease-modifying anti-rheumatic drugs (DMARDs) throughout the study.

Evidence for comparator: -

Actual start date of recruitment	18 August 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	Argentina: 43
Country: Number of subjects enrolled	Australia: 40
Country: Number of subjects enrolled	Brazil: 70
Country: Number of subjects enrolled	Bulgaria: 40
Country: Number of subjects enrolled	Canada: 96
Country: Number of subjects enrolled	Colombia: 24
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 58
Country: Number of subjects enrolled	United Kingdom: 52
Country: Number of subjects enrolled	Guatemala: 14
Country: Number of subjects enrolled	Hong Kong: 20
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Lithuania: 32
Country: Number of subjects enrolled	Mexico: 135
Country: Number of subjects enrolled	New Zealand: 11
Country: Number of subjects enrolled	Peru: 24

Country: Number of subjects enrolled	Philippines: 24
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	South Africa: 30
Country: Number of subjects enrolled	Spain: 100
Country: Number of subjects enrolled	Thailand: 24
Country: Number of subjects enrolled	United States: 265
Worldwide total number of subjects	1262
EEA total number of subjects	397

Notes:

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### **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)	1041
From 65 to 84 years	219
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

A total of 1262 subjects at 209 centers in 25 countries were randomised into the study.

### Pre-assignment

Screening details:

Rheumatoid arthritis (RA) of  $\geq 6$  months' duration, diagnosed according to the revised 1987 American College of Rheumatology (ACR) criteria. Swollen joint count (SJC)  $\geq 4$  (66 joint count) and tender joint count (TJC)  $\geq 4$  (68 joint count) at screening and baseline and taking at least one non-biologic disease-modifying anti-rheumatic drug (DMARD).

### Period 1

Period 1 title	24 Weeks Double Blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Tocilizumab SC

Arm description:

Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Arm type	Experimental
Investigational medicinal product name	tocilizumab SC
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Tocilizumab supplied in a single-use pre-filled syringe, with a needle safety device, delivering 162 mg/0.9 mL solution for subcutaneous injection once a week.

Investigational medicinal product name	placebo to tocilizumab IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to tocilizumab IV supplied as a solution in 10 mL vials containing polysorbate 80 and sucrose in water for infusion every 4 weeks.

<b>Arm title</b>	Tocilizumab IV
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Arm description:

Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Arm type	Experimental
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Investigational medicinal product name	tocilizumab IV
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab supplied in vials as a sterile solution for 8 mg/kg intravenous infusion every 4 weeks.

Investigational medicinal product name	placebo to tocilizumab SC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo to tocilizumab SC supplied as a single-use pre-filled syringe with a needle safety device, delivering 0.9 mL sodium chloride for subcutaneous injection once a week.

<b>Number of subjects in period 1</b>	Tocilizumab SC	Tocilizumab IV
Started	631	631
Completed	572	564
Not completed	59	67
Adverse event, serious fatal	-	1
Subject/legal Guardian Decision	9	5
Adverse event, non-fatal	28	40
Other	-	1
Pregnancy	2	2
Physician Decision to Withdraw Subject	-	5
Anaphylaxis or Hypersensitivity Reaction	2	1
Lost to follow-up	2	1
Insufficient Therapeutic Response	11	8
Protocol deviation	5	3

**Period 2**

Period 2 title	72 Weeks Open Label Extension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Tocilizumab SC
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Arm description:

Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Arm type	Experimental
Investigational medicinal product name	tocilizumab SC
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Tocilizumab supplied in a single-use pre-filled syringe, with a needle safety device, delivering 162 mg/0.9 mL solution for subcutaneous injection once a week.

<b>Arm title</b>	Tocilizumab IV
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Arm description:

Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Arm type	Experimental
Investigational medicinal product name	tocilizumab IV
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab supplied in vials as a sterile solution for 8 mg/kg intravenous infusion every 4 weeks.

<b>Arm title</b>	Tocilizumab SC Then Tocilizumab IV
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Arm description:

Subjects who received tocilizumab 162 mg subcutaneous (SC) injection weekly and placebo to tocilizumab IV every 4 weeks for 24 weeks in double blind treatment period switched to tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Arm type	Experimental
Investigational medicinal product name	tocilizumab IV
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab supplied in vials as a sterile solution for 8 mg/kg intravenous infusion every 4 weeks.

<b>Arm title</b>	Tocilizumab IV Then Tocilizumab SC
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Arm description:

Subjects who received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC once a week in double blind treatment period switched to tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose will be continued throughout the study.

Arm type	Experimental
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Investigational medicinal product name	tocilizumab SC
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Tocilizumab supplied in a single-use pre-filled syringe, with a needle safety device, delivering 162 mg/0.9 mL solution for subcutaneous injection once a week.

Number of subjects in period 2 <sup>[1]</sup>	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV
	Started	524	377
Completed	445	311	40
Not completed	79	66	8
Adverse event, serious fatal	1	2	-
Physician decision	3	5	-
Subject/legal Guardian Decision	20	14	1
Adverse event, non-fatal	35	21	2
Other	2	1	-
Pregnancy	1	3	1
Anaphylaxis or Hypersensitivity Reaction	1	1	-
Protocol Violation	-	-	-
Lost to follow-up	4	3	2
Insufficient Therapeutic Response	9	11	2
Randomised but not Treated	3	5	-

Number of subjects in period 2 <sup>[1]</sup>	Tocilizumab IV Then Tocilizumab SC
	Started
Completed	160
Not completed	26
Adverse event, serious fatal	2
Physician decision	-
Subject/legal Guardian Decision	6
Adverse event, non-fatal	12
Other	-
Pregnancy	1
Anaphylaxis or Hypersensitivity Reaction	-
Protocol Violation	1
Lost to follow-up	1
Insufficient Therapeutic Response	3

Randomised but not Treated	-
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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Out of 1136 subjects who completed the 24 weeks double blind period, 234 were switched to either tocilizumab IV infusion (48 subjects) or tocilizumab SC (186 subjects) in 72 weeks open label extension period.

## Baseline characteristics

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### Reporting groups

Reporting group title	24 Weeks Double Blind Period
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Reporting group description: -

<b>Reporting group values</b>	24 Weeks Double Blind Period	Total	
Number of subjects	1262	1262	
Age categorical Units: Subjects			
Adults (18-64 years)	1041	1041	
From 65-84 years	219	219	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	52.7		
standard deviation	± 12.44	-	
Gender, Male/Female Units: participants			
Female	1041	1041	
Male	221	221	

## End points

### End points reporting groups

Reporting group title	Tocilizumab SC
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Reporting group description:

Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Reporting group title	Tocilizumab IV
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Reporting group description:

Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Reporting group title	Tocilizumab SC
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Reporting group description:

Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Reporting group title	Tocilizumab IV
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Reporting group description:

Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Reporting group title	Tocilizumab SC Then Tocilizumab IV
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Reporting group description:

Subjects who received tocilizumab 162 mg subcutaneous (SC) injection weekly and placebo to tocilizumab IV every 4 weeks for 24 weeks in double blind treatment period switched to tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Reporting group title	Tocilizumab IV Then Tocilizumab SC
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Reporting group description:

Subjects who received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC once a week in double blind treatment period switched to tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose will be continued throughout the study.

### Primary: Percentage of Subject Achieving an American College of Rheumatology Criteria (ACR20) Response at Week 24

End point title	Percentage of Subject Achieving an American College of Rheumatology Criteria (ACR20) Response at Week 24 <sup>[1]</sup>
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End point description:

ACR20 response:  $\geq 20\%$  reduction from baseline for both TJC68 and SJC66, as well as for 3 of 5 additional ACR variables: Patient's Assessment of Pain in last 24 hours using a Visual Analog Scale (VAS) (0=no pain and 100=unbearable pain); Patient's and Physician's Global Assessment of Disease Activity in last 24 hours using a VAS (0=no disease activity and 100=maximum disease activity); Health Assessment Questionnaire: 20 questions in 8 areas (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities) answered on a scale of 0=without difficulty to 3=unable to do; and

acute-phase reactant (either C-reactive protein [CRP] or Erythrocyte Sedimentation Rate [ESR]). Per Protocol Population included all randomised subjects who received study drug and had no major protocol violations. Last Observation Carried Forward was used for missing joint counts, no imputation for other components. CRP will be used primarily for calculation of response. If missing, ESR will be used.

End point type	Primary
End point timeframe:	
Baseline, 24 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: Inferential statistical analysis was not performed.

End point values	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	558	537		
Units: Percentage of subjects				
number (confidence interval 95%)	69.4 (65.5 to 73.2)	73.4 (69.6 to 77.1)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Adverse Events, Serious Adverse Events and Clinically Significant Laboratory Assessments

End point title	Percentage of Subjects With Adverse Events, Serious Adverse Events and Clinically Significant Laboratory Assessments <sup>[2]</sup>
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End point description:

The safety population includes all subjects who received at least one dose of study drug, whether re-randomised or not, and who had at least one post-dose safety assessment. Data are included from double blind and open label (OL) periods in the SC and IV arms but only from the OL period in IV-SC and SC-IV switch arms.

End point type	Primary
End point timeframe:	
Baseline to up to 3 months after last dose of study drug (approximately up to 2 years)	

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: Inferential statistical analysis was not performed.

End point values	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV	Tocilizumab IV Then Tocilizumab SC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	631	631	48	186
Units: percentage of subjects				
number (not applicable)				
Adverse Events (AEs)	91.6	87.8	81.3	86.6
Serious Adverse Events (SAEs)	13.9	12.7	12.5	11.3
Clinically Significant Laboratory Assessments	37.7	28.2	25	19.4

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Achieving an American College of Rheumatology Criteria (ACR50) Response at Week 24

End point title	Percentage of Subjects Achieving an American College of Rheumatology Criteria (ACR50) Response at Week 24
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End point description:

ACR50 response is defined as  $\geq 50\%$  reduction from baseline for both TJC68 and SJC66, as well as for 3 of 5 additional ACR variables: Patient's Assessment of Pain in last 24 hours using a Visual Analog Scale (VAS) (0=no pain and 100=unbearable pain); Patient's and Physician's Global Assessment of Disease Activity in last 24 hours using a VAS (0=no disease activity and 100=maximum disease activity); Health Assessment Questionnaire: 20 questions in 8 areas (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities) answered on a scale of 0=without difficulty to 3=unable to do; and acute-phase reactant (either CRP or ESR). Per Protocol Population included all randomised subjects who received study drug and had no major protocol violations. Last Observation Carried Forward was used for missing joint counts, no imputation for other ACR components. CRP will be used primarily for the calculation of the ACR response. If missing, the ESR will be used for that subject.

End point type	Secondary
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End point timeframe:

Baseline, 24 weeks

End point values	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	558	537		
Units: percentage of subject				
number (not applicable)	47	48.6		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Achieving an American College of Rheumatology Criteria (ACR70) Response at Week 24

End point title	Percentage of Subjects Achieving an American College of Rheumatology Criteria (ACR70) Response at Week 24
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End point description:

ACR70 response is defined as  $\geq 70\%$  reduction from baseline for both TJC68 and SJC66, as well as for 3 of 5 additional ACR variables: Patient's Assessment of Pain in last 24 hours using a Visual Analog Scale (VAS) (0=no pain and 100=unbearable pain); Patient's and Physician's Global Assessment of Disease Activity in last 24 hours using a VAS (0=no disease activity and 100=maximum disease activity); Health Assessment Questionnaire: 20 questions in 8 areas (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities) answered on a scale of 0=without difficulty to 3=unable to do; and

acute-phase reactant (either CRP or ESR). Per Protocol Population included all randomised subjects who received study drug and had no major protocol violations. LOCF was used for missing joint counts, no imputation for other ACR components. CRP will be used primarily for the calculation of the ACR response. If missing, the ESR will be used for that subject.

End point type	Secondary
End point timeframe:	
Baseline, 24 weeks	

End point values	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	558	537		
Units: percentage of subject				
number (not applicable)	24	27.9		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Disease Activity Score 28 (DAS28) Remission at Week 24

End point title	Percentage of Subjects With Disease Activity Score 28 (DAS28) Remission at Week 24
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End point description:

The DAS28 (ESR) score is a measure of the subject's disease activity. It is calculated using the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity VAS where left side of the line 0=no disease activity to right side of the line 100=extreme disease activity and ESR. DAS28-(ESR) total scores range from 0 - 10. Remission is defined as achieving a DAS28-ESR score of less than 2.6. Subjects from the Per Protocol Population (randomised subjects who received study drug and had no major protocol violations) with data available for analysis. Missing SJC and TJC will be imputed using the last post-baseline value for the subject(LOCF). No imputation for missing ESR or patient's global assessment of disease activity.

End point type	Secondary
End point timeframe:	
Week 24	

End point values	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	516	498		
Units: percentage of subject				
number (not applicable)	38.4	36.9		

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of Subjects Achieving a Decrease of  $\geq 0.3$  in the Health Assessment Questionnaire-Disability Index (HAQ-DI) From Baseline to Week 24**

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End point title	Percentage of Subjects Achieving a Decrease of $\geq 0.3$ in the Health Assessment Questionnaire-Disability Index (HAQ-DI) From Baseline to Week 24
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End point description:

The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a subject completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 4 (unable to do). HAQ-DI = sum of worst scores in each domain divided by the number of domains answered. A decrease indicates improvement. Subjects from the Per Protocol Population (all randomised subjects who received study drug and had no major protocol violations) with data available for analysis. No imputation of missing scores will be made other than for missing baseline scores, for which last score prior to defined protocol baseline time window will be carried forward.

End point type	Secondary
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End point timeframe:

Baseline, 24 Weeks

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End point values	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	500		
Units: percentage of subjects				
number (not applicable)	65.2	67.4		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percentage of Subjects Who Withdrew Because of Lack of Therapeutic Response at Week 24**

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End point title	Percentage of Subjects Who Withdrew Because of Lack of Therapeutic Response at Week 24
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End point description:

The percentage of subjects who withdrew from the study because they were not responding to treatment with the study drug. Per Protocol Population included all randomised subjects who received study drug and had no major protocol violations.

End point type	Secondary
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End point timeframe:

24 Weeks

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<b>End point values</b>	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	558	537		
Units: percentage of subject				
number (not applicable)	1.8	0.9		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With American College of Rheumatology Criteria (ACR20, ACR50, ACR70) at Week 97

End point title	Percentage of Subjects With American College of Rheumatology Criteria (ACR20, ACR50, ACR70) at Week 97
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End point description:

ACR20, ACR50 and ACR70:  $\geq 20\%$ ,  $\geq 50\%$  and  $\geq 70\%$  reduction from baseline for both TJC68 and SJC66, as well as for 3 of 5 additional ACR variables: Patient's Assessment of Pain in last 24 hours using a Visual Analog Scale (VAS) (0=no pain and 100=unbearable pain); Patient's and Physician's Global Assessment of Disease Activity in last 24 hours using a VAS (0=no disease activity and 100=maximum disease activity); Health Assessment Questionnaire: 20 questions in 8 areas (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities) answered on a scale of 0=without difficulty to 3=unable to do; and acute-phase reactant (either CRP or ESR). Re-Randomized Intent-to-Treat Population (ITT Population) included all subject who completed double blind period and were re-randomised at Week 24, received at least 1 dose of study drug. CRP was used for calculation of ACR. If missing, ESR was used. Here, number of subject analysed is subjects for whom parameter was collected.

End point type	Secondary
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End point timeframe:

Week 97

<b>End point values</b>	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV	Tocilizumab IV Then Tocilizumab SC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	451	317	40	165
Units: percentage of subject				
number (not applicable)				
ACR20	83.6	83.3	82.5	88.5
ACR50	65.4	62.5	57.5	67.3
ACR70	44.8	42	37.5	47.3

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Disease Activity Score 28 (DAS28) Remission at Week 97

End point title	Percentage of Subjects With Disease Activity Score 28 (DAS28) Remission at Week 97
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End point description:

The DAS28 (ESR) score is a measure of the subject's disease activity. It is calculated using the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity VAS where left side of the line 0=no disease activity to right side of the line 100=extreme disease activity and ESR. DAS28-(ESR) total scores range from 0 - 10. Remission is defined as achieving a DAS28-ESR score of less than 2.6. LOCF used for tender and swollen joint counts, no imputation used for ESR and Patient's Global Assessment of Disease Activity VAS. ITT Population included all subject who completed double blind period and were re-randomised at Week 24 and received at least one dose of study drug. If ESR=0 then ESR=1 is substituted into the DAS28 calculation to enable a non-missing DAS28 score. Here, number of subjects analysed is the subjects for whom parameter was collected.

End point type	Secondary
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End point timeframe:

Week 97

End point values	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV	Tocilizumab IV Then Tocilizumab SC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	446	306	40	162
Units: percentage of subject number (not applicable)	53.4	46.4	50	55.6

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Achieving a Decrease of $\geq 0.3$ in the Health Assessment Questionnaire-Disability Index (HAQ-DI) From Baseline to Week 97

End point title	Percentage of Subjects Achieving a Decrease of $\geq 0.3$ in the Health Assessment Questionnaire-Disability Index (HAQ-DI) From Baseline to Week 97
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End point description:

The HAQ-DI is a subject completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component ranging from 0 (without any difficulty) to 4 (unable to do). HAQ-DI=sum of worst scores in each domain divided by number of domains answered. A decrease indicates improvement. No imputation of missing scores was made other than for missing baseline scores, for which last score prior to baseline will be carried forward. For subjects who prematurely withdrew, data collected at withdrawal visit was used and data thereafter is missing. ITT Population included all subjects who completed double blind period and were re-randomised at Week 24 and received at least one dose of study drug. Here, number of subjects analysed is the subjects for whom parameter was collected.

End point type	Secondary
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End point timeframe:

Baseline, Week 97

<b>End point values</b>	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV	Tocilizumab IV Then Tocilizumab SC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	445	317	39	162
Units: percentage of subjects				
number (not applicable)	72.4	69.1	56.4	71

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Withdrew Because of Lack of Therapeutic Response at Week 97

End point title	Percentage of Subjects Who Withdrew Because of Lack of Therapeutic Response at Week 97
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End point description:

The percentage of subjects who withdrew from the study because they were not responding to treatment with the study drug. ITT Population included all subjects who completed double blind period and were re-randomised at Week 24 and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Week 97

<b>End point values</b>	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV	Tocilizumab IV Then Tocilizumab SC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	521	372	48	186
Units: percentage of subjects				
number (not applicable)	1.7	3	4.2	1.6

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Serum Concentration Curve of Tocilizumab After First SC Injection or IV Infusion

End point title	Area Under the Serum Concentration Curve of Tocilizumab After First SC Injection or IV Infusion
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End point description:

Pharmacokinetic-Evaluable Population included all subject who provided at least one evaluable PK sample were included in the pharmacokinetic analysis (PK) analysis. Here, number of subject analysed who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Week 0: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after first dose.

<b>End point values</b>	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: microgram*hour/milliliter (mcg*hr/mL)				
arithmetic mean (standard deviation)	1444 (± 839)	30988 (± 9114)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Serum Concentration Curve of Tocilizumab at Steady State for SC and IV Treatment

End point title	Area Under the Serum Concentration Curve of Tocilizumab at Steady State for SC and IV Treatment
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End point description:

Pharmacokinetic-Evaluable Population included all subjects who provided at least one evaluable PK sample were included in the pharmacokinetic analysis (PK) analysis. Here, number of subjects analysed who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose.

<b>End point values</b>	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: µg*hr/mL				
arithmetic mean (standard deviation)	7542 (± 3989)	41304 (± 15104)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Minimum Serum Concentration (Cmin) of Tocilizumab

End point title	Minimum Serum Concentration (Cmin) of Tocilizumab
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End point description:

Pharmacokinetic-Evaluable Population included all subjects who provided at least one evaluable PK sample were included in the PK analysis. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

End point type	Secondary
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End point timeframe:

Week 0, Week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose

<b>End point values</b>	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: microgram/milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Week 0 (after first dose) (n=17, 16)	7.48 (± 4.91)	6.65 (± 6.05)		
Week 20 (n=13, 13)	35.7 (± 16.2)	16 (± 10.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Serum Concentration (Cmax) of Tocilizumab

End point title | Maximum Serum Concentration (Cmax) of Tocilizumab

End point description:

Pharmacokinetic-Evaluable Population included all subjects who provided at least one evaluable PK sample were included in the PK analysis. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

End point type | Secondary

End point timeframe:

Week 0, Week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose

<b>End point values</b>	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: mcg/mL				
arithmetic mean (standard deviation)				
Week 0 (after first dose) (n=17, 16)	14.7 (± 8.74)	180 (± 40.1)		
Week 20 (n=13, 13)	52.7 (± 27.3)	233 (± 117)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Maximum Serum Concentration (Tmax) of Tocilizumab

End point title | Time to Maximum Serum Concentration (Tmax) of Tocilizumab

End point description:

Pharmacokinetic-Evaluable Population included all subjects who provided at least one evaluable PK

sample were included in the PK analysis. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

End point type	Secondary
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End point timeframe:

Week 0, Week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose

End point values	Tocilizumab SC	Tocilizumab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: hour (hr)				
median (full range (min-max))				
Week 0 (after first dose) (n=17, 16)	74 (24 to 121)	6 (3 to 7)		
Week 20 (n=13, 13)	70 (0 to 122)	6 (4 to 46)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Serum Interleukin-6 (IL-6) Concentration at Week 25

End point title	Change From Baseline in Serum Interleukin-6 (IL-6) Concentration at Week 25
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End point description:

The ITT-PK population includes all subjects who were eligible for the ITT population and provided at least 1 evaluable PK sample in the double blind or open label periods. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

End point type	Secondary
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End point timeframe:

Baseline, Week 25

End point values	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV	Tocilizumab IV Then Tocilizumab SC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	493	359	46	186
Units: picogram/milliliter (pg/mL)				
arithmetic mean (standard deviation)				
Baseline (n=493, 359, 46, 186)	39.04 (± 55.456)	52.48 (± 240.964)	62.18 (± 125.081)	50.07 (± 161.045)
Change at Week 25 (n=385, 280, 33, 149)	34.42 (± 110.842)	52.61 (± 507.157)	37.54 (± 93.464)	44.12 (± 136.955)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Serum Soluble Interleukin-6 Receptor (sIL-6R) Concentration at Week 97

End point title	Change From Baseline in Serum Soluble Interleukin-6 Receptor (sIL-6R) Concentration at Week 97
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End point description:

The ITT-PK population includes all subjects who were eligible for the ITT population and provided at least 1 evaluable PK sample in the double blind or open label periods. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

End point type	Secondary
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End point timeframe:

Baseline, Week 97

End point values	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV	Tocilizumab IV Then Tocilizumab SC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	504	366	46	186
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=504, 366, 46, 186)	44.53 (± 35.47)	45.72 (± 40.219)	44.71 (± 13.068)	43.28 (± 16.197)
Change at Week 25 (n=416, 296, 37, 157)	601.52 (± 222.141)	575.75 (± 244.398)	569.6 (± 213.588)	586.5 (± 226.915)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Developed Antibodies To Tocilizumab at Week 97

End point title	Percentage of Subjects Who Developed Antibodies To Tocilizumab at Week 97
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End point description:

The safety population includes all subjects who received at least one dose of study drug, whether re-randomised or not, and who had at least one post-dose safety assessment. Here, 'n' indicates number of subjects in the safety population tested by screening assay at any time point.

End point type	Secondary
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End point timeframe:

Week 97

<b>End point values</b>	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV	Tocilizumab IV Then Tocilizumab SC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	629	629	46	184
Units: percentage of subjects				
number (not applicable)	1.3	1	0	0.5

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to up to 3 months after last dose of study drug (approximately up to 2 years)

Adverse event reporting additional description:

The safety population includes all subjects who received at least one dose of study drug, whether re-randomized or not, and who had at least one post-dose safety assessment. Data are included from double blind and open label (OL) periods in the SC and IV arms but only from the OL period in IV-SC and SC-IV switch arms.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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### Reporting groups

Reporting group title	Tocilizumab SC
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Reporting group description:

Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Participants continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Reporting group title	Tocilizumab IV
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Reporting group description:

Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Reporting group title	Tocilizumab SC Then Tocilizumab IV
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Reporting group description:

Subjects who received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for 24 weeks in double blind treatment period switched to tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

Reporting group title	Tocilizumab IV Then Tocilizumab SC
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Reporting group description:

Subjects who received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly in double blind treatment period switched to tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose will be continued throughout the study.

<b>Serious adverse events</b>	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 631 (13.95%)	80 / 631 (12.68%)	6 / 48 (12.50%)
number of deaths (all causes)	4	4	0
number of deaths resulting from adverse events	2	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Breast Cancer			
subjects affected / exposed	2 / 631 (0.32%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm malignant			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma stage 0			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenoma			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibroadenoma of breast			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal tract adenoma			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lentigo maligna			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Morton's neuroma			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour benign			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schwannoma			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 631 (0.16%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			

subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Surgical and medical procedures</b>			
Abortion induced			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Pregnancy, puerperium and perinatal conditions</b>			
Abortion spontaneous			
subjects affected / exposed	2 / 631 (0.32%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Imminent abortion			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>General disorders and administration site conditions</b>			
Device dislocation			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Ischaemic ulcer			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Immune system disorders</b>			
<b>Hypersensitivity</b>			
subjects affected / exposed	3 / 631 (0.48%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Amyloidosis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Anaphylactic reaction</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Reproductive system and breast disorders</b>			
<b>Cervical dysplasia</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Ovarian cyst ruptured</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Pelvic floor muscle weakness</b>			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Pelvic pain</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Uterine polyp			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 631 (0.16%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 631 (0.32%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Pleurisy			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Lipase increased			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 631 (0.48%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Adrenal gland injury			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic ulcer haemorrhage			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropod sting			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chillblains			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Comminuted fracture			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haematoma			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary contusion			

subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial rupture			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 631 (0.00%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Angina unstable			
subjects affected / exposed	2 / 631 (0.32%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 631 (0.32%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac arrest</b>			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac valve disease</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Mitral valve incompetence</b>			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Myocardial ischaemia</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Nervous system disorders</b>			
<b>Sciatica</b>			
subjects affected / exposed	2 / 631 (0.32%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Transient ischaemic attack</b>			
subjects affected / exposed	0 / 631 (0.00%)	3 / 631 (0.48%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cerebral infarction</b>			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
<b>Encephalopathy</b>			

subjects affected / exposed	2 / 631 (0.32%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 631 (0.00%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery thrombosis			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar ischaemia			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Haemorrhagic stroke</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Headache</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Hemiparesis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Hepatic encephalopathy</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Ischaemic cerebral infarction</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
<b>Lumbar radiculopathy</b>			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Migraine</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Syncope</b>			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Retinal artery occlusion			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 631 (0.32%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Gastroesophageal reflux disease</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Haemorrhoidal haemorrhage</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Ileus</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Impaired gastric emptying</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Inguinal hernia</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Lumbar hernia</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Megacolon</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Oesophageal ulcer</b>			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	3 / 631 (0.48%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Hepatic steatosis</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Sphincter of oddi dysfunction</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Renal and urinary disorders</b>			
<b>Renal failure acute</b>			
subjects affected / exposed	2 / 631 (0.32%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Haematuria</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Renal colic</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Osteoarthritis</b>			
subjects affected / exposed	3 / 631 (0.48%)	5 / 631 (0.79%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Intervertebral disc protrusion</b>			
subjects affected / exposed	2 / 631 (0.32%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rheumatoid arthritis			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 631 (0.00%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	2 / 631 (0.32%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 631 (0.00%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Compartment syndrome			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			

subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Myalgia</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Spinal column stenosis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Spondylolisthesis</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
<b>Pneumonia</b>			
subjects affected / exposed	4 / 631 (0.63%)	6 / 631 (0.95%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	3 / 4	5 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cellulitis</b>			
subjects affected / exposed	8 / 631 (1.27%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	6 / 8	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Gastroenteritis</b>			
subjects affected / exposed	2 / 631 (0.32%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Septic Shock</b>			
subjects affected / exposed	3 / 631 (0.48%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Urinary tract infection</b>			

subjects affected / exposed	3 / 631 (0.48%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Peritonitis</b>			
subjects affected / exposed	2 / 631 (0.32%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Wound infection</b>			
subjects affected / exposed	0 / 631 (0.00%)	3 / 631 (0.48%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Arthritis bacterial</b>			
subjects affected / exposed	0 / 631 (0.00%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Arthritis infective</b>			
subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bursitis infective</b>			
subjects affected / exposed	0 / 631 (0.00%)	2 / 631 (0.32%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Pelvic abscess</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Sepsis</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
<b>Subcutaneous abscess</b>			

subjects affected / exposed	1 / 631 (0.16%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Abscess</b>			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Abscess limb</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Atypical pneumonia</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bone tuberculosis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bronchitis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bronchopneumonia</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bronchopulmonary aspergillosis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Burkholderia pseudomallei infection</b>			

subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Dacryocystitis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Device related infection</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Diverticulitis</b>			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Empyema</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Endocarditis</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Groin abscess</b>			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infectious pleural effusion</b>			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Intervertebral discitis</b>			

subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle abscess			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericollic abscess			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal abscess			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			

subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	0 / 631 (0.00%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal abscess			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed	0 / 631 (0.00%)	1 / 631 (0.16%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			

subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Urosepsis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Whipple's disease</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Metabolism and nutrition disorders</b>			
<b>Acidosis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Diabetes mellitus</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Diabetic ketoacidosis</b>			
subjects affected / exposed	1 / 631 (0.16%)	0 / 631 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Tocilizumab IV Then Tocilizumab SC		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 186 (11.29%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
Breast Cancer			

subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	2 / 186 (1.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain neoplasm malignant			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial adenoma			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fibroadenoma of breast			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal tract adenoma			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leiomyoma			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lentigo maligna			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Morton's neuroma			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parathyroid tumour benign			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Schwannoma			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small cell lung cancer			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shock			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis limb			

subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Surgical and medical procedures</b>			
Abortion induced			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pregnancy, puerperium and perinatal conditions</b>			
Abortion spontaneous			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Imminent abortion			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>General disorders and administration site conditions</b>			
Device dislocation			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic ulcer			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Immune system disorders</b>			
<b>Hypersensitivity</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Amyloidosis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Anaphylactic reaction</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Reproductive system and breast disorders</b>			
<b>Cervical dysplasia</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Ovarian cyst ruptured</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pelvic floor muscle weakness</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pelvic pain</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Uterine polyp			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	2 / 186 (1.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pleurisy			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Lipase increased			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Adrenal gland injury				
subjects affected / exposed	1 / 186 (0.54%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anastomotic ulcer haemorrhage				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthropod sting				
subjects affected / exposed	1 / 186 (0.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	1 / 186 (0.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chillblains				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Comminuted fracture				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic haematoma				

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pubis fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary contusion			

subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sternal fracture			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Synovial rupture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Angina unstable				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 186 (0.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial tachycardia				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block first degree				

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac arrest</b>			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac valve disease</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Mitral valve incompetence</b>			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Myocardial ischaemia</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Nervous system disorders</b>			
<b>Sciatica</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Transient ischaemic attack</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Cerebral infarction</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Encephalopathy</b>			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Ischaemic stroke</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Carotid artery thrombosis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Cerebellar ischaemia</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Cerebral haemorrhage</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Cerebral ischaemia</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Cerebrovascular insufficiency</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Dysarthria</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Grand mal convulsion</b>			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Haemorrhagic stroke</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Headache</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Hemiparesis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Hepatic encephalopathy</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Ischaemic cerebral infarction</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Lumbar radiculopathy</b>			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Migraine</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Syncope</b>			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient global amnesia			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Amaurosis			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Retinal artery occlusion			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ischaemic			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired gastric emptying			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar hernia			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Megacolon			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal ulcer			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal perforation			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bile duct stone			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis acute			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Hepatic steatosis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Sphincter of oddi dysfunction</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders</b>			
<b>Renal failure acute</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Haematuria</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Renal colic</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Osteoarthritis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Intervertebral disc protrusion</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Rheumatoid arthritis				
subjects affected / exposed	1 / 186 (0.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bursitis				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Compartment syndrome				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Costochondritis				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc degeneration				
subjects affected / exposed	0 / 186 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc disorder				

subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Myalgia</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Spinal column stenosis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Spondylolisthesis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
<b>Pneumonia</b>			
subjects affected / exposed	4 / 186 (2.15%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 1		
<b>Cellulitis</b>			
subjects affected / exposed	2 / 186 (1.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Gastroenteritis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Septic Shock</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Urinary tract infection</b>			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Peritonitis</b>			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Wound infection</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Arthritis bacterial</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Arthritis infective</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Bursitis infective</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pelvic abscess</b>			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Sepsis</b>			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
<b>Subcutaneous abscess</b>			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Abscess</b>			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Abscess limb</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Atypical pneumonia</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Bone tuberculosis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Bronchitis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Bronchopneumonia</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Bronchopulmonary aspergillosis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Burkholderia pseudomallei infection</b>			

subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Dacryocystitis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Device related infection</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Diverticulitis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Empyema</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Endocarditis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Groin abscess</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Infectious pleural effusion</b>			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Intervertebral discitis</b>			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lobar pneumonia			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle abscess			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericolonic abscess			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngeal abscess			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pseudomonal sepsis			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis chronic			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal abscess			
subjects affected / exposed	1 / 186 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal abscess			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tooth infection			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tracheitis			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			

subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Urosepsis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Whipple's disease</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Metabolism and nutrition disorders</b>			
<b>Acidosis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Diabetes mellitus</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Diabetic ketoacidosis</b>			
subjects affected / exposed	0 / 186 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Tocilizumab SC	Tocilizumab IV	Tocilizumab SC Then Tocilizumab IV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	488 / 631 (77.34%)	430 / 631 (68.15%)	29 / 48 (60.42%)
<b>Investigations</b>			
<b>Alanine aminotransferase increased</b>			
subjects affected / exposed	188 / 631 (29.79%)	140 / 631 (22.19%)	7 / 48 (14.58%)
occurrences (all)	247	184	10

Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	135 / 631 (21.39%) 171	96 / 631 (15.21%) 115	3 / 48 (6.25%) 5
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	33 / 631 (5.23%) 39	25 / 631 (3.96%) 28	1 / 48 (2.08%) 1
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	49 / 631 (7.77%) 56	65 / 631 (10.30%) 77	4 / 48 (8.33%) 4
Nervous system disorders Headache subjects affected / exposed occurrences (all)	46 / 631 (7.29%) 62	41 / 631 (6.50%) 55	3 / 48 (6.25%) 3
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	62 / 631 (9.83%) 85	50 / 631 (7.92%) 74	2 / 48 (4.17%) 4
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	33 / 631 (5.23%) 188	5 / 631 (0.79%) 53	1 / 48 (2.08%) 1
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)	55 / 631 (8.72%) 67  35 / 631 (5.55%) 42	39 / 631 (6.18%) 44  40 / 631 (6.34%) 54	1 / 48 (2.08%) 1  2 / 48 (4.17%) 2
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	32 / 631 (5.07%) 35	27 / 631 (4.28%) 34	1 / 48 (2.08%) 1
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	33 / 631 (5.23%) 36	34 / 631 (5.39%) 37	2 / 48 (4.17%) 2
Osteoarthritis subjects affected / exposed occurrences (all)	21 / 631 (3.33%) 26	11 / 631 (1.74%) 12	3 / 48 (6.25%) 3
Arthralgia subjects affected / exposed occurrences (all)	24 / 631 (3.80%) 26	28 / 631 (4.44%) 31	3 / 48 (6.25%) 3
Rheumatoid arthritis subjects affected / exposed occurrences (all)	29 / 631 (4.60%) 36	26 / 631 (4.12%) 37	3 / 48 (6.25%) 3
<b>Infections and infestations</b>			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	122 / 631 (19.33%) 192	130 / 631 (20.60%) 182	8 / 48 (16.67%) 12
Urinary tract infection subjects affected / exposed occurrences (all)	67 / 631 (10.62%) 100	53 / 631 (8.40%) 73	4 / 48 (8.33%) 5
Nasopharyngitis subjects affected / exposed occurrences (all)	88 / 631 (13.95%) 146	68 / 631 (10.78%) 86	7 / 48 (14.58%) 13
Bronchitis subjects affected / exposed occurrences (all)	44 / 631 (6.97%) 51	35 / 631 (5.55%) 38	2 / 48 (4.17%) 2
Gastroenteritis subjects affected / exposed occurrences (all)	41 / 631 (6.50%) 45	26 / 631 (4.12%) 28	3 / 48 (6.25%) 3
Pharyngitis subjects affected / exposed occurrences (all)	23 / 631 (3.65%) 25	39 / 631 (6.18%) 51	2 / 48 (4.17%) 2
Sinusitis subjects affected / exposed occurrences (all)	33 / 631 (5.23%) 38	19 / 631 (3.01%) 27	0 / 48 (0.00%) 0

<b>Non-serious adverse events</b>	Tocilizumab IV Then Tocilizumab SC		
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Total subjects affected by non-serious adverse events subjects affected / exposed	118 / 186 (63.44%)		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	29 / 186 (15.59%) 36		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	14 / 186 (7.53%) 17		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	7 / 186 (3.76%) 7		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	8 / 186 (4.30%) 8		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	9 / 186 (4.84%) 9		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	13 / 186 (6.99%) 19		
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	9 / 186 (4.84%) 122		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)	14 / 186 (7.53%) 16  4 / 186 (2.15%) 4		
Skin and subcutaneous tissue disorders			

Rash subjects affected / exposed occurrences (all)	2 / 186 (1.08%) 3		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	9 / 186 (4.84%) 10		
Osteoarthritis subjects affected / exposed occurrences (all)	1 / 186 (0.54%) 1		
Arthralgia subjects affected / exposed occurrences (all)	6 / 186 (3.23%) 7		
Rheumatoid arthritis subjects affected / exposed occurrences (all)	11 / 186 (5.91%) 12		
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	33 / 186 (17.74%) 41		
Urinary tract infection subjects affected / exposed occurrences (all)	15 / 186 (8.06%) 17		
Nasopharyngitis subjects affected / exposed occurrences (all)	26 / 186 (13.98%) 42		
Bronchitis subjects affected / exposed occurrences (all)	6 / 186 (3.23%) 7		
Gastroenteritis subjects affected / exposed occurrences (all)	6 / 186 (3.23%) 7		
Pharyngitis subjects affected / exposed occurrences (all)	4 / 186 (2.15%) 4		
Sinusitis			

subjects affected / exposed	6 / 186 (3.23%)		
occurrences (all)	7		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2010	1) Given the course of treatment and fatal outcome of the anaphylaxis case reported, continued treatment with TCZ was no longer acceptable for subjects who experience serious hypersensitivity reactions. Subjects who experience serious hypersensitivity reactions that led to a disruption were to be permanently discontinued from TCZ treatment and withdrawn from the study. Treatment recommendations were removed from the protocol to allow health care providers to include all therapies available, according to the standard of care appropriate for the subject's reaction. Addition of event-driven sampling to detect anti-TCZ antibodies in subjects who withdraw due to anaphylaxis or serious hypersensitivity. 2) To aid recruitment, the inclusion criteria were revised to include subjects with either elevated CRP and/or ESR. 3) Clarification that subjects who have received previous treatment with any cell-depleting therapy were excluded from participating in this trial. 4) No tocilizumab to be given at the Week 97 visit. 5) Clarification of the minimum and maximum interval required between each subcutaneous injection and that the first 2 injections must be administered by site staff, but the following injections can be administered by the subject or her/his caregiver with specific recommendation regarding the injection sites. 6) The PK/PD sub-study and Roche clinical repository sampling has been removed from the open-label period. 7) To allow a window around the baseline visit of +/- 3 days, clarify the +/-3 day visit window and the minimum period between IV infusions. 8) Extension of DMARD wash out, clarify that subjects are eligible for this study if they have had previous inadequate response to DMARDs and clarify concomitant DMARDs during the study. 9) As the study has a safety follow-up period of 8 weeks, all adverse events will be collected through the follow-up Week 8 visit.
02 December 2011	A drug-free serum sample should be obtained after an appropriate washout period for TCZ to optimize anti-TCZ antibody detection. TCZ is predicted to be cleared from serum at 6 weeks after the last 8 mg/kg IV infusion and 4 weeks after the last 162 mg SC weekly injection. In order not to interrupt subject treatment during the study, protocol version C is amended to allow for this additional sample collection from subjects who have terminated from the study early, completed the study or missed TCZ treatment during the study, when the TCZ concentration is expected to be cleared from the serum.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported