Clinical trial results:
Open-label Extension Treatment with TNFR:Fc for Participating Patients in TNFR:Fc Clinical Trials

Summary

EudraCT number	2012-001145-40
Trial protocol	Outside EU/EEA
Global end of trial date	10 December 2008

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	20021618

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00357903
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Dr., Thousand Oaks, CA, United States, 91320
Public contact	Amgen Medical Information, Amgen, 001 8007726436, medinfo@amgen.com
Scientific contact	Amgen Medical Information, Amgen, 001 8007726436, medinfo@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000299-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 December 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were the following:
• Evaluate the long term safety of etanercept in various subject populations with rheumatoid arthritis (RA) or juvenile idiopathic arthritis (JIA)
• Evaluate improvement in physical function/disability and quality of life.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations. All subjects, the subject's parent/guardian, or the subject's legal representative provided written informed consent before undergoing any study-related procedures, including screening procedures. The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 1997
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 623
Country: Number of subjects enrolled	Canada: 16
Worldwide total number of subjects	639
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	29
Adolescents (12-17 years)	29
Adults (18-64 years)	474
From 65 to 84 years	106
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This multicenter, open-label study enrolled subjects who had been enrolled in previous etanercept studies.

Pre-assignment

Screening details:

All subjects from an initial etanercept study were eligible to enroll in Study 20021618.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Adult Subjects

Arm description:

Adult subjects with rheumatoid arthritis treated with a maximum etanercept dose of 50 mg administered subcutaneously once weekly.

Arm type	Experimental
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	Enbrel, TNFR:Fc
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All subjects received a maximum etanercept dose of 50 mg subcutaneously (SC) administered once weekly as two 25-mg injections on the same day or 3 to 4 days apart for a minimum of 1 year or until an administrative decision was made to discontinue the study. Adults who entered Study 20021618 with well controlled arthritis symptoms were allowed to continue with the etanercept dose administered in their initial protocol (10 mg or 25 mg twice weekly). Pediatric subjects received a 0.8-mg/kg weekly SC dose of etanercept either once weekly (maximum dose of 50 mg per injection) or a 0.4-mg/kg SC dose twice weekly 3 to 4 days apart, with the maximum dose of 50 mg per week.

Arm title	Pediatric Subjects

Arm description:

Pediatric subjects with juvenile rheumatoid arthritis who received a maximum 50 mg dose of etanercept administered subcutaneously once weekly.

Arm type	Experimental
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	Enbrel, TNFR:Fc
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All subjects received a maximum etanercept dose of 50 mg subcutaneously (SC) administered once weekly as two 25-mg injections on the same day or 3 to 4 days apart for a minimum of 1 year or until an administrative decision was made to discontinue the study. Adults who entered Study 20021618 with well controlled arthritis symptoms were allowed to continue with the etanercept dose administered in their initial protocol (10 mg or 25 mg twice weekly). Pediatric subjects received a 0.8-mg/kg weekly SC dose of etanercept either once weekly (maximum dose of 50 mg per injection) or a 0.4-mg/kg SC dose twice weekly 3 to 4 days apart, with the maximum dose of 50 mg per week.

Number of subjects in period 1	Adult Subjects	Pediatric Subjects
Started	581	58
Completed	218	15
Not completed	363	43
Physician decision	39	5
Consent withdrawn by subject	57	7
Completed month 12 only	-	1
Death	33	-
Other	49	10
Adverse event	87	4
Protocol issues	14	3
Lost to follow-up	23	4
Response status	61	9

Baseline characteristics

Reporting groups	
Reporting group title	Adult Subjects
Reporting group description:	
Adult subjects with rheumatoid arthritis treated with a maximum etanercept dose of 50 mg administered subcutaneously once weekly.	
Reporting group title	Pediatric Subjects
Reporting group description:	
Pediatric subjects with juvenile rheumatoid arthritis who received a maximum 50 mg dose of etanercept administered subcutaneously once weekly.	

Reporting group values	Adult Subjects	Pediatric Subjects	Total
Number of subjects	581	58	639
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.87	11.02	
standard deviation	± 12.03	± 3.8	-
Gender categorical Units: Subjects			
Female	465	39	504
Male	116	19	135
Race Units: Subjects			
American Indian or Alaska Native	4	1	5
Asian	10	1	11
Black or African American	18	4	22
Hispanic or Latino	25	9	34
White or Caucasian	522	43	565
Other	2	0	2

End points

End points reporting groups

Reporting group title	Adult Subjects
Reporting group description:	
Adult subjects with rheumatoid arthritis treated with a maximum etanercept dose of 50 mg administered subcutaneously once weekly.	
Reporting group title	Pediatric Subjects
Reporting group description:	
Pediatric subjects with juvenile rheumatoid arthritis who received a maximum 50 mg dose of etanercept administered subcutaneously once weekly.	

Primary: Total Exposure to Etanercept With Gaps

End point title	Total Exposure to Etanercept With Gaps[1]
End point description:	
Total participant exposure to etanercept (Enbrel) with gaps	
End point type	Primary
End point timeframe:	
Up to 10 years	

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: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581[2]	58[3]		
Units: Subject-years				
number (not applicable)	4033.07	341.98		

Notes:

[2] - All subjects who received at least one dose of etanercept

[3] - All subjects who received at least one dose of etanercept

Statistical analyses

No statistical analyses for this end point

Primary: Total Exposure Adjusted Rate of Malignancies

End point title	Total Exposure Adjusted Rate of Malignancies[4]
End point description:	
Exposure-adjusted rate of malignancies, excluding nonmelanoma skin cancers, occurring on study within 30 days of the last dose of etanercept	
End point type	Primary
End point timeframe:	
Up to 10 years	

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis was tested. The primary objective was to examine safety parameters, which

were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: Malignancies per 100 subject-years				
number (not applicable)	1.41	0		

Statistical analyses

No statistical analyses for this end point

Primary: Total Exposure Adjusted Rate of Deaths

End point title	Total Exposure Adjusted Rate of Deaths[5]

End point description:

Rate of deaths within 30 days of the last dose of etanercept, adjusted for total exposure to etanercept

End point type	Primary

End point timeframe:

Up to 10 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: Deaths per 100 subject-years				
number (not applicable)	0.57	0		

Statistical analyses

No statistical analyses for this end point

Primary: Total Exposure Adjusted Rate of Serious Infectious Events

End point title	Total Exposure Adjusted Rate of Serious Infectious Events[6]

End point description:

Exposure-adjusted rate of serious infectious events (associated with hospitalization or IV antibiotics) occurring on study within 30 days of the last dose of etanercept.

End point type	Primary

End point timeframe:

Up to 10 years

Notes:

[6] - 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: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: Events per 100 subject-years				
number (not applicable)	5.18	3.22		

Statistical analyses

No statistical analyses for this end point

Primary: Total Exposure Adjusted Rate of Lymphomas

End point title	Total Exposure Adjusted Rate of Lymphomas[7]

End point description:

Rate of lymphomas occurring on study within 30 days of the last dose of etanercept, adjusted for total exposure to etanercept.

End point type	Primary

End point timeframe:

Up to 10 years

Notes:

[7] - 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: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: Lymphomas per 100 subject-years				
number (not applicable)	0.15	0		

Statistical analyses

No statistical analyses for this end point

Primary: Malignancy

End point title	Malignancy[8]

End point description:

Occurrence of one or more malignancies on study within 30 days of the last dose of etanercept.

End point type	Primary

End point timeframe:

Up to 10 years

Notes:

[8] - 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: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: subjects	48	0		

Statistical analyses

No statistical analyses for this end point

Primary: Lymphoma

End point title	Lymphoma[9]

End point description:

Occurrence of one or more lymphomas on study within 30 days of the last dose of etanercept.

End point type	Primary

End point timeframe:

Up to 10 years

Notes:

[9] - 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: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: subjects	6	0		

Statistical analyses

No statistical analyses for this end point

Primary: Serious Infectious Event

End point title	Serious Infectious Event[10]

End point description:

Occurrence of one or more serious infectious events within the participant on study within 30 days of the last dose of study medication. A serious infectious event is a serious adverse event that is infectious.

End point type	Primary

End point timeframe:

Up to 10 years

Notes:

[10] - 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: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: subject	114	8		

Statistical analyses

No statistical analyses for this end point

Primary: Death

End point title	Death[11]

End point description:

Occurrence of death on study within 30 days of the last dose of etanercept.

End point type	Primary

End point timeframe:

Up to 10 years

Notes:

[11] - 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: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: subjects	23	0		

Statistical analyses

No statistical analyses for this end point

Primary: Total Exposure Adjusted Rate of Serious Adverse Events

End point title	Total Exposure Adjusted Rate of Serious Adverse Events[12]

End point description:

Rate of serious adverse events adjusted to total exposure to etanercept (events / exposure * 100).

End point type	Primary

End point timeframe:

Up to 10 years

Notes:

[12] - 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: No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively.

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: Events per 100 subject-years				
number (not applicable)	20.95	12.87		

Statistical analyses

No statistical analyses for this end point

Secondary: Dosing Period

End point title	Dosing Period
End point description:	
Duration of etanercept dosing	
End point type	Secondary
End point timeframe:	
Up to 10 years	

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: days				
arithmetic mean (standard deviation)	2535.4 (± 1433.77)	2153.6 (± 1379.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tender Joint Count

End point title	Tender Joint Count
End point description:	
Number of tender joints, as assessed by the investigator using criteria based on pressure and joint manipulation.	
End point type	Secondary
End point timeframe:	
Month 12	

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	509[13]	15[14]		
Units: joints				
arithmetic mean (standard deviation)	9.55 (± 10.97)	11.6 (± 10.61)		

Notes:

[13] - All subjects who received at least one dose of etanercept and had available data

[14] - All subjects who received at least one dose of etanercept and had available data

Statistical analyses

No statistical analyses for this end point

Secondary: Swollen Joint Count

End point title	Swollen Joint Count
End point description: Number of swollen joints	
End point type	Secondary
End point timeframe: 12 months	

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	510[15]	28[16]		
Units: joints				
arithmetic mean (standard deviation)	9.14 (± 8.83)	11.93 (± 11.86)		

Notes:

[15] - All subjects who received at least one dose of etanercept and had available data

[16] - All subjects who received at least one dose of etanercept and had available data

Statistical analyses

No statistical analyses for this end point

Secondary: Health Assessment Questionnaire Disability Index

End point title	Health Assessment Questionnaire Disability Index[17]
End point description: Health Assessment Questionnaire Disability Index (HAQ DI). This index is a weighted average of 24 items, each scored 0 (no difficulty) to 3 (unable to function).	
End point type	Secondary
End point timeframe: Month 12	

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: HAQ DI was only assessed in adult subjects

End point values	Adult Subjects			
Subject group type	Reporting group			
Number of subjects analysed	485[18]			
Units: units on a scale				
arithmetic mean (standard deviation)	0.96 (± 0.71)			

Notes:

[18] - All subjects who received at least one dose of etanercept and had available data

Statistical analyses

No statistical analyses for this end point

Secondary: Childhood Health Assessment Questionnaire

End point title	Childhood Health Assessment Questionnaire[19]

End point description:

Childhood Health Assessment Questionnaire (CHAQ) disability index, having a range of 0 (no difficulty) to 3 (unable to do).

End point type	Secondary

End point timeframe:

Month 12

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: CHAQ was only assessed in pediatric subjects

End point values	Pediatric Subjects			
Subject group type	Reporting group			
Number of subjects analysed	46[20]			
Units: units on a scale				
arithmetic mean (standard deviation)	1.08 (± 0.95)			

Notes:

[20] - All subjects who received at least one dose of etanercept and had available data

Statistical analyses

No statistical analyses for this end point

Secondary: C-Reactive Protein

End point title	C-Reactive Protein

End point description:

C-reactive protein at month 12

End point type	Secondary

End point timeframe:

Month 12

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	509[21]	48[22]		
Units: mg/dL				
arithmetic mean (standard deviation)	1.37 (± 1.85)	2.11 (± 3.82)		

Notes:

[21] - All subjects who received at least one dose of etanercept and had available data

[22] - All subjects who received at least one dose of etanercept and had available data

Statistical analyses

No statistical analyses for this end point

Secondary: ACR20 at Month 3 in Adults

End point title	ACR20 at Month 3 in Adults[23]

End point description:

American College of Rheumatology (ACR) 20, defined as a 20% improvement in both tender and swollen joints (78 joints) and a 20% improvement in 3 of 5 items (including physician and patient global assessments), in adults

End point type	Secondary

End point timeframe:

Baseline and Month 3

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ACR was only assessed in adult subjects

End point values	Adult Subjects			
Subject group type	Reporting group			
Number of subjects analysed	560[24]			
Units: subjects	372			

Notes:

[24] - Subjects who received at least 1 dose of etanercept and had available data at Baseline and Month 3

Statistical analyses

No statistical analyses for this end point

Secondary: JRA DOI 30 at Month 3 in Juveniles

End point title	JRA DOI 30 at Month 3 in Juveniles[25]

End point description:

Juvenile Rheumatoid Arthritis Definition of Improvement 30 (JRA DOI 30), defined as a 30% improvement from baseline in 3 of 6 items (including Childhood Health Assessment Questionnaire, disease severity, overall well-being, and erythrocyte sedimentation rate) and a worsening of >30% in at most one of the remaining items.

End point type	Secondary

End point timeframe:

Baseline and Month 3

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: JRA DOI was ony assessed in pediatric subjects

End point values	Pediatric Subjects			
Subject group type	Reporting group			
Number of subjects analysed	53[26]			
Units: subjects	46			

Notes:

[26] - Subjects who received at least 1 dose of etanercept and were evaluable for this endpoint at Month 3

Statistical analyses

No statistical analyses for this end point

Secondary: Standardized Incidence Rate for All SEER Cancers

End point title	Standardized Incidence Rate for All SEER Cancers

End point description:

Standardized incidence rate for all cancers tracked by the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) system.

End point type	Secondary

End point timeframe:

Up to 10 years

End point values	Adult Subjects	Pediatric Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	581	58		
Units: Observed count / expected count				
number (confidence interval 95%)	1.3 (0.97 to 1.71)	0 (0 to 53.87)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 11.29 years	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Pediatric Subjects
Reporting group description:	
Pediatric subjects with juvenile rheumatoid arthritis who received a maximum 50 mg dose of etanercept administered subcutaneously once weekly.	
Reporting group title	Adult Subjects
Reporting group description:	
Adult subjects with rheumatoid arthritis treated with a maximum etanercept dose of 50 mg administered subcutaneously once weekly.	

Serious adverse events	Pediatric Subjects	Adult Subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 58 (27.59%)	293 / 581 (50.43%)	
number of deaths (all causes)	0	41	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct cancer			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder cancer			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer female			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer in situ			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma stage 0			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer recurrent			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Follicle centre lymphoma diffuse small cell lymphoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gliosarcoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	2 / 58 (3.45%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer stage I			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna stage unspecified			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytic leukaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lymphocytic lymphoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma benign			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to ovary			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to small intestine			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-small cell lung cancer stage I			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian epithelial cancer			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolymphocytic leukaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	0 / 58 (0.00%)	6 / 581 (1.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Angiopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic aneurysm rupture			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Circulatory collapse			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 58 (0.00%)	6 / 581 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertension			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral vascular disorder			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			

subjects affected / exposed	1 / 58 (1.72%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac ablation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture treatment			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint arthroplasty			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg amputation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder arthroplasty			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder operation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse event			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest discomfort			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 58 (0.00%)	10 / 581 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	3 / 58 (5.17%)	25 / 581 (4.30%)	
occurrences causally related to treatment / all	0 / 4	1 / 33	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	
Fatigue			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 58 (1.72%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sudden death			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Allergy to arthropod sting			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 58 (1.72%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Joint prosthesis user			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal erythema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 58 (1.72%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse alveolar damage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 58 (0.00%)	6 / 581 (1.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 58 (0.00%)	7 / 581 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	1 / 4	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure abnormal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone density decreased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventriculogram left			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation cardiac			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate abnormal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Caustic injury			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocation of joint prosthesis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 58 (0.00%)	8 / 581 (1.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femoral neck fracture			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 58 (0.00%)	8 / 581 (1.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 58 (1.72%)	6 / 581 (1.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation postoperative			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open fracture			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Gastrointestinal arteriovenous malformation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 58 (0.00%)	7 / 581 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bradycardia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 4	
Cardiac failure			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 58 (0.00%)	13 / 581 (2.24%)	
occurrences causally related to treatment / all	0 / 0	2 / 19	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 58 (0.00%)	12 / 581 (2.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diastolic dysfunction			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 58 (0.00%)	20 / 581 (3.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 25	
deaths causally related to treatment / all	0 / 0	0 / 4	
Myocarditis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral thrombosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 58 (0.00%)	7 / 581 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 58 (1.72%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 58 (0.00%)	6 / 581 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coagulopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia obstructive			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 58 (1.72%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 58 (3.45%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diverticulum oesophageal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	2 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal rupture			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis alcoholic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation bile duct			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal cyst			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			

subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Renal failure acute			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal tubular necrosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 58 (1.72%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	1 / 58 (1.72%)	8 / 581 (1.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 58 (0.00%)	6 / 581 (1.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture delayed union			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand deformity			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Juvenile arthritis			
subjects affected / exposed	2 / 58 (3.45%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb discomfort			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low turnover osteopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle necrosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myositis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 58 (0.00%)	15 / 581 (2.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic deformity			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	6 / 58 (10.34%)	28 / 581 (4.82%)	
occurrences causally related to treatment / all	0 / 15	1 / 45	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 58 (0.00%)	9 / 581 (1.55%)	
occurrences causally related to treatment / all	0 / 0	7 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bursitis infective			
subjects affected / exposed	0 / 58 (0.00%)	4 / 581 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 58 (0.00%)	19 / 581 (3.27%)	
occurrences causally related to treatment / all	0 / 0	13 / 29	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis staphylococcal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis streptococcal			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 58 (0.00%)	7 / 581 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis B			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 58 (3.45%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia gangrenous			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 58 (0.00%)	6 / 581 (1.03%)	
occurrences causally related to treatment / all	0 / 0	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			

subjects affected / exposed	1 / 58 (1.72%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningococcal sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 58 (1.72%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	36 / 581 (6.20%)	
occurrences causally related to treatment / all	0 / 0	18 / 43	
deaths causally related to treatment / all	0 / 0	2 / 2	
Post procedural infection			
subjects affected / exposed	1 / 58 (1.72%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pneumonia			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteus infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 58 (1.72%)	6 / 581 (1.03%)	
occurrences causally related to treatment / all	1 / 1	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	1 / 58 (1.72%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 58 (1.72%)	10 / 581 (1.72%)	
occurrences causally related to treatment / all	1 / 1	6 / 10	
deaths causally related to treatment / all	0 / 0	2 / 2	
Septic shock			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Shigella infection			

subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	2 / 58 (3.45%)	14 / 581 (2.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 58 (0.00%)	5 / 581 (0.86%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			

subjects affected / exposed	1 / 58 (1.72%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic shock syndrome streptococcal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 58 (0.00%)	7 / 581 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	1 / 58 (1.72%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 58 (0.00%)	1 / 581 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 58 (0.00%)	3 / 581 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 581 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 58 (1.72%)	0 / 581 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pediatric Subjects	Adult Subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 58 (84.48%)	484 / 581 (83.30%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 58 (5.17%)	21 / 581 (3.61%)	
occurrences (all)	4	30	
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 58 (0.00%)	35 / 581 (6.02%)	
occurrences (all)	0	43	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 58 (5.17%)	36 / 581 (6.20%)	
occurrences (all)	3	44	
Headache			
subjects affected / exposed	20 / 58 (34.48%)	80 / 581 (13.77%)	
occurrences (all)	46	126	
Migraine			
subjects affected / exposed	3 / 58 (5.17%)	13 / 581 (2.24%)	
occurrences (all)	5	18	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	8 / 58 (13.79%)	65 / 581 (11.19%)	
occurrences (all)	103	275	
Fatigue			
subjects affected / exposed	1 / 58 (1.72%)	36 / 581 (6.20%)	
occurrences (all)	1	41	
Injection site pain			
subjects affected / exposed	3 / 58 (5.17%)	3 / 581 (0.52%)	
occurrences (all)	4	4	
Injection site pruritus			
subjects affected / exposed	3 / 58 (5.17%)	39 / 581 (6.71%)	
occurrences (all)	97	121	
Injection site swelling			
subjects affected / exposed	6 / 58 (10.34%)	25 / 581 (4.30%)	
occurrences (all)	29	73	
Pyrexia			
subjects affected / exposed	6 / 58 (10.34%)	9 / 581 (1.55%)	
occurrences (all)	6	10	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	7 / 58 (12.07%)	15 / 581 (2.58%)	
occurrences (all)	11	17	

Abdominal pain			
subjects affected / exposed	5 / 58 (8.62%)	25 / 581 (4.30%)	
occurrences (all)	6	31	
Diarrhoea			
subjects affected / exposed	4 / 58 (6.90%)	52 / 581 (8.95%)	
occurrences (all)	4	62	
Dyspepsia			
subjects affected / exposed	4 / 58 (6.90%)	37 / 581 (6.37%)	
occurrences (all)	4	42	
Nausea			
subjects affected / exposed	5 / 58 (8.62%)	40 / 581 (6.88%)	
occurrences (all)	9	44	
Vomiting			
subjects affected / exposed	4 / 58 (6.90%)	13 / 581 (2.24%)	
occurrences (all)	4	13	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 58 (5.17%)	3 / 581 (0.52%)	
occurrences (all)	4	5	
Nasal congestion			
subjects affected / exposed	5 / 58 (8.62%)	13 / 581 (2.24%)	
occurrences (all)	7	15	
Cough			
subjects affected / exposed	3 / 58 (5.17%)	17 / 581 (2.93%)	
occurrences (all)	3	21	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 58 (12.07%)	50 / 581 (8.61%)	
occurrences (all)	7	74	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 58 (0.00%)	38 / 581 (6.54%)	
occurrences (all)	0	44	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 58 (0.00%)	53 / 581 (9.12%)	
occurrences (all)	0	75	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 58 (6.90%)	89 / 581 (15.32%)	
occurrences (all)	4	125	
Conjunctivitis infective			
subjects affected / exposed	4 / 58 (6.90%)	19 / 581 (3.27%)	
occurrences (all)	4	24	
Cystitis			
subjects affected / exposed	0 / 58 (0.00%)	57 / 581 (9.81%)	
occurrences (all)	0	81	
Ear infection			
subjects affected / exposed	4 / 58 (6.90%)	12 / 581 (2.07%)	
occurrences (all)	5	12	
Gastroenteritis viral			
subjects affected / exposed	4 / 58 (6.90%)	17 / 581 (2.93%)	
occurrences (all)	5	18	
Influenza			
subjects affected / exposed	7 / 58 (12.07%)	60 / 581 (10.33%)	
occurrences (all)	9	69	
Pharyngitis			
subjects affected / exposed	13 / 58 (22.41%)	30 / 581 (5.16%)	
occurrences (all)	27	36	
Otitis media			
subjects affected / exposed	5 / 58 (8.62%)	17 / 581 (2.93%)	
occurrences (all)	8	19	
Pharyngitis streptococcal			
subjects affected / exposed	5 / 58 (8.62%)	5 / 581 (0.86%)	
occurrences (all)	5	8	
Pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	31 / 581 (5.34%)	
occurrences (all)	1	38	
Sinusitis			
subjects affected / exposed	8 / 58 (13.79%)	121 / 581 (20.83%)	
occurrences (all)	12	201	

Skin infection			
subjects affected / exposed	9 / 58 (15.52%)	84 / 581 (14.46%)	
occurrences (all)	15	129	
Upper respiratory tract infection			
subjects affected / exposed	36 / 58 (62.07%)	207 / 581 (35.63%)	
occurrences (all)	93	328	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 1997	• Clarified maximum pediatric dose of 25 mg twice weekly. • Decreased washout period of cyclosporine from 6 months to 2 weeks; exclusion criteria was also revised to reflect this. • Clarified that subjects from Study 016.0014 may be on combination MTX and etanercept. • Clarified subject population for which serum bilirubin was required to be ≤ 2X ULN (pediatric subjects from 016.0016 only). • Clarified use of pain medication in pediatric subjects. • Eliminated monthly assessments during tapering of NSAIDS, MTX, or corticosteroids. • Clarified maximum corticosteroid dose to be used during disease flare (40 mg prednisone equivalent/day). • Clarified NSAID usage following disease flare. • Added the following evaluations: hematology and chemistry profile, and UA/micro. • Clarified that chest X-rays would not be required for pediatric subjects in Study 016.0016. • Clarified transfusion procedures for pediatric subjects in Appendix E. • Clarified toxicity scale for reporting low lymphocytes
11 December 1997	• Clarified dose for adult and pediatric subjects. • Added autoimmune features checklist to safety evaluations. • Decreased time from receipt of investigational drugs prior to etanercept from 3 months to 1 month. • Clarified baseline for long term evaluation. • Clarified instructions for MTX administration. • Clarified dose escalation of etanercept from 10 mg to 25 mg. • Provided additional criteria for premature discontinuations. • Allowed treatment period of previous study to satisfy the 12-week requirement for change in permissible medication. • Revised reporting of injection site reactions. • Clarified requirements for baseline pregnancy test, and chest, hand, wrists, and forefoot x-rays. • Allowed for a more thorough evaluation of subjects developing signs and symptoms consistent with new connective tissue disease.
06 July 1998	• Defined study design of extension period. • Added physical/function and quality of life endpoints. • Allowed adjustment of medications after 1 year of etanercept therapy. • Clarified subjects who could waive screening procedures before entering Study 016.0018.
30 October 1998	• Defined study design and evaluations scheduled to be performed during the extension period. • Updated the definition for adverse event. • Added sub-study to evaluate concurrent administration of pneumococcal and influenza vaccine with etanercept.
19 April 1999	• Corrected error in units for hemoglobin. • Added Tanner Score to capture growth velocity for pediatric subjects. • Clarified when safety evaluations should be obtained. • Clarified collection of concomitant medications during the extension study.
10 October 2001	• Revised follow-up requirements.

12 September 2003	• Clarified the collection of safety data for patients who discontinue study drug. • Updated adverse event section in accordance with IB. • Changed the study drug dosing frequency and offered the option to administer their weekly dose on one day, instead of 2 injections weekly, 3 or 4 days apart. • Clarified the number of missed doses of etanercept, during the study extension phase that would result in discontinuation. • Clarified that Methotrexate (MTX) was the only permissible DMARD during the study. • Added the development of diagnosed cancer and known HIV seropositivity as a reason for prematurely discontinuing.
09 February 2006	• A 25 mg prefilled syringe was offered as an option. • Updated the definition of adverse event to include the definition from ICH Guideline for GCP and to include the broadened definition of an adverse event as the worsening of any occurrence or pre-existing condition from the time the informed consent is signed to the initiation of the investigational product. • Updated the Reporting Procedures for All Serious Adverse Events, Serious Adverse Events Report, and Subject Informed Consent Template. • Included the Serious Adverse Event Fax Transmittal Form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported