Clinical trial results:
A Long-Term, Open-Label Follow-Up Study of Tofacitinib (CP-690,550) for Treatment of Rheumatoid Arthritis

Summary

EudraCT number	2006-005035-19
Trial protocol	BE ES AT SE IT HU CZ GR DE SK GB BG FI DK IE
Global end of trial date	30 November 2016

Results information

Result version number	v1
This version publication date	03 December 2017
First version publication date	03 December 2017

Trial information

Trial identification

Sponsor protocol code	A3921024

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00413699
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2016
Global end of trial reached?	Yes
Global end of trial date	30 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the long-term safety and tolerability of 5mg twice daily and 10mg twice daily of tofacitinib for treatment of the signs and symptoms of rheumatoid arthritis.

Appendix 26 (dated 25 July 2016) added the option for participants in Belgium and Germany who completed 2 years in the lymphocyte sub-study to participate in the supplemental sub-study which provided tofacitinib until December 2018 or until tofacitinib was marketed in those countries, whichever came first.

Protection of trial subjects:

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. In addition, all local and regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Background therapy:

The following DMARDs were allowed in doses consistent with local standards of care: Auranofin (oral gold), aurothioglucose (injectable gold), aurothiomalate (injectable gold); Sulfasalazine, chloroquine, hydroxychloroquine, leflunomide (Arava®), and methotrexate, d-penicillamine and tetracyclines. In Ireland, methotrexate doses higher than 20 mg weekly were not permitted under any circumstances.

Evidence for comparator:

Not applicable

Actual start date of recruitment	05 February 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 60
Country: Number of subjects enrolled	Australia: 99
Country: Number of subjects enrolled	Austria: 31
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bosnia and Herzegovina: 5
Country: Number of subjects enrolled	Brazil: 237
Country: Number of subjects enrolled	Bulgaria: 110
Country: Number of subjects enrolled	Canada: 70
Country: Number of subjects enrolled	Chile: 133
Country: Number of subjects enrolled	China: 192
Country: Number of subjects enrolled	Colombia: 97
Country: Number of subjects enrolled	Costa Rica: 10

Country: Number of subjects enrolled	Croatia: 20
Country: Number of subjects enrolled	Czech Republic: 364
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Dominican Republic: 22
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 193
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	India: 115
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Korea, Republic of: 210
Country: Number of subjects enrolled	Malaysia: 41
Country: Number of subjects enrolled	Mexico: 212
Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	Philippines: 44
Country: Number of subjects enrolled	Poland: 267
Country: Number of subjects enrolled	Puerto Rico: 7
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 140
Country: Number of subjects enrolled	Slovakia: 90
Country: Number of subjects enrolled	Spain: 117
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Taiwan: 28
Country: Number of subjects enrolled	Thailand: 55
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Ukraine: 201
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 1190
Worldwide total number of subjects	4481
EEA total number of subjects	1293

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3754
From 65 to 84 years	724
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 414 sites globally.

Pre-assignment

Screening details:

Participants had previously participated in qualifying studies of tofacitinib.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tofa 5mg BID; ppts with avg total daily dose across study <15

Arm description:

Tofacitinib 5 mg BID. Participants with non-zero average total daily dose across study <15 were assigned to 5 mg BID.
avg=average; BID=twice daily; mg=milligram; ppts=participants; tofa=tofacitinib

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	CP-690550-10
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg BID

Arm title	Tofa 10mg BID; ppts with avg total daily dose across study ≥15

Arm description:

Tofacitinib 10 mg BID. Participants with non-zero average total daily dose across study ≥15 were assigned to 10 mg BID.
avg=average; BID=twice daily; mg=milligram; ppts=participants; tofa=tofacitinib

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	CP-690550-10
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg BID

Number of subjects in period 1	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15
Started	1123	3358
Completed	484	1653
Not completed	639	1705
Adverse event, serious fatal	25	30
Did not meet entrance criteria	2	2
Study terminated by Sponsor	-	1
Not specified	67	211
Missing end of study page	-	4
Medication error without adverse event	-	1
No longer willing to participate	116	368
Adverse event not related to study drug	113	248
Pregnancy	10	8
Lost to follow-up	31	101
Adverse event related to study drug	178	527
Lack of efficacy	59	115
Protocol deviation	38	89

Baseline characteristics

Reporting groups	
Reporting group title	Tofa 5mg BID; ppts with avg total daily dose across study <15
Reporting group description:	
Tofacitinib 5 mg BID. Participants with non-zero average total daily dose across study <15 were assigned to 5 mg BID. avg=average; BID=twice daily; mg=milligram; ppts=participants; tofa=tofacitinib	
Reporting group title	Tofa 10mg BID; ppts with avg total daily dose across study ≥15
Reporting group description:	
Tofacitinib 10 mg BID. Participants with non-zero average total daily dose across study ≥15 were assigned to 10 mg BID. avg=average; BID=twice daily; mg=milligram; ppts=participants; tofa=tofacitinib	

Reporting group values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	Total
Number of subjects	1123	3358	4481
Age Categorical			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
<18 years	0	0	0
18 to 64 years	916	2838	3754
>=65 years	207	520	727
Age continuous			
Units: years			
arithmetic mean	54.0	53.0	
standard deviation	± 12.1	± 11.5	-
Gender, Male/Female			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
Female	927	2744	3671
Male	196	614	810

Subject analysis sets	
Subject analysis set title	All Tofacitinib
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants treated with tofacitinib from 5 mg BID and 10 mg BID groups	
Subject analysis set title	Tofacitinib 5 milligram (mg) twice daily (BID)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with non-zero average total daily dose across study <15 were assigned to 5 mg BID	
Subject analysis set title	Tofacitinib 10 mg BID
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with non-zero average total daily dose across study ≥15 were assigned to 10 mg BID	

Subject analysis set title	Tofacitinib 10 mg BID Continuous Visit 3
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Interrupted Visit 3
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants whose treatment with tofacitinib was interrupted for 2 weeks post-randomization	
Subject analysis set title	Tofacitinib 10 mg BID Continuous Visit 4
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Interrupted Visit 4
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants whose treatment with tofacitinib was interrupted for 2 weeks post-randomization	
Subject analysis set title	Tofacitinib 10 mg BID Continuous
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Interrupted
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants whose treatment with tofacitinib was interrupted for 2 weeks post-randomization	
Subject analysis set title	Tofacitinib 10 mg Continuous
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Continuous Visit 2
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Interrupted Visit 2
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants whose treatment with tofacitinib was interrupted for 2 weeks post-randomization	
Subject analysis set title	Tofacitinib 10 mg BID Continuous Visit 3
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Interrupted Visit 4
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients whose treatment with tofacitinib was interrupted for 2 weeks post-randomization	

Reporting group values	All Tofacitinib	Tofacitinib 5 milligram (mg) twice daily (BID)	Tofacitinib 10 mg BID
Number of subjects	4481	1123	3358
Age Categorical			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			

<18 years	0	0	0
18 to 64 years	3754	916	2838
>=65 years	727	207	520
Age continuous			
Units: years			
arithmetic mean	53.3	54.0	53.0
standard deviation	± 11.6	± 12.1	± 11.5
Gender, Male/Female			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
Female	3671	927	2744
Male	810	196	614

Reporting group values	Tofacitinib 10 mg BID Continuous Visit 3	Tofacitinib 10 mg BID Interrupted Visit 3	Tofacitinib 10 mg BID Continuous Visit 4
Number of subjects	91	91	92
Age Categorical			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
<18 years			
18 to 64 years			
>=65 years			
Age continuous			
Units: years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
Female			
Male			

Reporting group values	Tofacitinib 10 mg BID Interrupted Visit 4	Tofacitinib 10 mg BID Continuous	Tofacitinib 10 mg BID Interrupted
Number of subjects	91	92	91
Age Categorical			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
<18 years			
18 to 64 years			
>=65 years			
Age continuous			
Units: years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			

Female Male			

Reporting group values	Tofacitinib 10 mg Continuous	Tofacitinib 10 mg BID Continuous Visit 2	Tofacitinib 10 mg BID Interrupted Visit 2
Number of subjects	92	92	91
Age Categorical			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
<18 years 18 to 64 years >=65 years			
Age continuous Units: years arithmetic mean standard deviation	 0 ± 0	 0 ± 0	 0 ± 0
Gender, Male/Female			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
Female Male			

Reporting group values	Tofacitinib 10 mg BID Continuous Visit 3	Tofacitinib 10 mg BID Interrupted Visit 4	
Number of subjects	92	91	
Age Categorical			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
<18 years 18 to 64 years >=65 years			
Age continuous Units: years arithmetic mean standard deviation	 0 ± 0	 0 ± 0	
Gender, Male/Female			
The subject analysis set groups for tofacitinib 10mg BID continuous and interrupted are from the vaccine sub-study. Age and gender characteristics are presented for the main study only.			
Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Tofa 5mg BID; ppts with avg total daily dose across study <15
Reporting group description:	
Tofacitinib 5 mg BID. Participants with non-zero average total daily dose across study <15 were assigned to 5 mg BID. avg=average; BID=twice daily; mg=milligram; ppts=participants; tofa=tofacitinib	
Reporting group title	Tofa 10mg BID; ppts with avg total daily dose across study ≥15
Reporting group description:	
Tofacitinib 10 mg BID. Participants with non-zero average total daily dose across study ≥15 were assigned to 10 mg BID. avg=average; BID=twice daily; mg=milligram; ppts=participants; tofa=tofacitinib	
Subject analysis set title	All Tofacitinib
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants treated with tofacitinib from 5 mg BID and 10 mg BID groups	
Subject analysis set title	Tofacitinib 5 milligram (mg) twice daily (BID)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with non-zero average total daily dose across study <15 were assigned to 5 mg BID	
Subject analysis set title	Tofacitinib 10 mg BID
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with non-zero average total daily dose across study ≥15 were assigned to 10 mg BID	
Subject analysis set title	Tofacitinib 10 mg BID Continuous Visit 3
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Interrupted Visit 3
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants whose treatment with tofacitinib was interrupted for 2 weeks post-randomization	
Subject analysis set title	Tofacitinib 10 mg BID Continuous Visit 4
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Interrupted Visit 4
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants whose treatment with tofacitinib was interrupted for 2 weeks post-randomization	
Subject analysis set title	Tofacitinib 10 mg BID Continuous
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants receiving continuous tofacitinib treatment	
Subject analysis set title	Tofacitinib 10 mg BID Interrupted
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants whose treatment with tofacitinib was interrupted for 2 weeks post-randomization	
Subject analysis set title	Tofacitinib 10 mg Continuous
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receiving continuous tofacitinib treatment

Subject analysis set title	Tofacitinib 10 mg BID Continuous Visit 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receiving continuous tofacitinib treatment

Subject analysis set title	Tofacitinib 10 mg BID Interrupted Visit 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants whose treatment with tofacitinib was interrupted for 2 weeks post-randomization

Subject analysis set title	Tofacitinib 10 mg BID Continuous Visit 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receiving continuous tofacitinib treatment

Subject analysis set title	Tofacitinib 10 mg BID Interrupted Visit 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients whose treatment with tofacitinib was interrupted for 2 weeks post-randomization

Primary: Primary endpoints were standard laboratory safety data (chemistry, hematology, etc.) and adverse event (AE) reports

End point title	Primary endpoints were standard laboratory safety data (chemistry, hematology, etc.) and adverse event (AE) reports

End point description:

Treatment-emergent non serious AEs by System Organ Class (SOC) (all causalities) and Laboratory Test Abnormalities (without regard to baseline).
The stated number of participants analyzed was the total number of participants in each group. The actual number of participants analyzed for each laboratory parameter varied, and is provided for each.
Abs=absolute; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ESR=erythrocyte sedimentation rate; GGT=gamma glutamyl transferase; hgb=hemoglobin; HDL=high density lipids; LDL=low density lipids; LLN=lower limit of normal; qual=qualitative; Tot=total; ULN=upper limit of normal; WBC=white blood cell

End point type	Primary

End point timeframe:

Includes laboratory test abnormality data for all visits and AE data up to 999 days after last dose of study drug

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	3358	4481	
Units: Number of participants				
Participants with non-serious AEs	991	2963	3954	
Blood and lymphatic system disorders	159	395	554	
Cardiac disorders	93	185	278	
Congenital, familial and genetic disorders	6	16	22	
Ear and labyrinth disorders	67	138	205	
Endocrine disorders	29	94	123	
Eye disorders	117	259	376	

Gastrointestinal disorders	393	1011	1404	
General disorders and admin site conditions	169	477	646	
Hepatobiliary disorders	60	176	236	
Immune system disorders	18	87	105	
Infections and infestations	704	2200	2904	
Injury, poisoning and procedural complications	244	721	965	
Investigations	402	995	1397	
Metabolism and nutrition disorders	184	562	746	
Musculoskeletal and connective tissue disorders	425	1314	1739	
Neoplasms benign, malignant and unspecified	80	219	299	
Nervous system disorders	222	639	861	
Pregnancy, puerperium and perinatal conditions	1	0	1	
Product issues	2	8	10	
Psychiatric disorders	97	280	377	
Renal and urinary disorders	123	265	388	
Reproductive system and breast disorders	89	206	295	
Respiratory, thoracic and mediastinal disorders	208	634	842	
Skin and subcutaneous tissue disorders	201	682	883	
Social circumstances	1	5	6	
Surgical and medical procedures	2	4	6	
Vascular disorders	207	468	675	
Participants evaluable for lab abnormalities	1118	3346	4464	
Participants with laboratory abnormalities	1095	3208	4303	
Hemoglobin <0.8x LLN (N=1117,3343,4460)	57	148	205	
Hematocrit <0.8x LLN (N=1117,3343,4460)	29	67	96	
Red blood cell count <0.8x LLN (N=1049,3343,4392)	32	142	174	
Reticulocytes (Abs) <0.5x LLN (N=570, 75,645)	44	5	49	
Reticulocytes (Abs) >1.5x ULN (N=570,75,645)	49	9	58	
Platelets <0.5x LLN (N=1116,3343,4459)	5	2	7	
Platelets >1.75x ULN (N=1116,3343,4459)	5	25	30	
Reticulocyte count (%) <0.5x LLN (N=46,34,80)	1	1	2	
Reticulocyte count (%) >1.5x ULN (N=46,34,80)	24	17	41	
WBC count <0.6x LLN (N=1117,3343,4460)	21	33	54	
WBC count >1.5x ULN (N=1117,3343,4460)	29	71	100	
Lymphocytes (Abs) <0.8x LLN (N=1117,3343,4460)	254	789	1043	
Lymphocytes (Abs) >1.2x ULN (N=1117,3343,4460)	23	94	117	

Lymphocytes (%) <0.8x LLN (N=1043,3343,4386)	401	1267	1668	
Lymphocytes (%) >1.2x ULN (N=1043,3343,4386)	23	75	98	
Tot neutrophils (Abs) <0.8x LLN (N=1117,3343,4460)	105	305	410	
Tot neutrophils (Abs) >1.2x ULN (N=1117,3343,4460)	239	617	856	
Neutrophils (%) <0.8x LLN (N=1042,3343,4385)	23	75	98	
Neutrophils (%) >1.2x ULN (N=1042,3343,4385)	29	93	122	
Basophils (Abs) >1.2x ULN (N=1117,3343,4460)	19	10	29	
Basophils (%) >1.2x ULN (N=1043,3343,4386)	76	221	297	
Eosinophils (Abs) >1.2x ULN (N=1117,3343,4460)	24	58	82	
Eosinophils (%) >1.2x ULN (N=1043,3343,4386)	36	118	154	
Monocytes (Abs) >1.2x ULN (N=1117,3343,4460)	65	107	172	
Monocytes (%) >1.2x ULN (N=1043,3343,4386)	128	405	533	
ESR >1.5x ULN (N=1113,3343,4456)	872	2411	3283	
Total bilirubin >1.5x ULN (N=1117,3345,4462)	18	38	56	
Direct bilirubin >1.5x ULN (N=1088,3344,4432)	5	14	19	
Indirect bilirubin >1.5x ULN (N=1041,3344,4385)	4	18	22	
AST >3.0x ULN (N=1117,3343,4461)	52	111	163	
ALT >3.0x ULN (N=1117,3345,4462)	87	189	276	
GGT >3.0x ULN (N=1118,3345,4463)	82	239	321	
Alkaline phosphatase >3.0x ULN (N=1118,3345,4463)	3	10	13	
Total protein <0.8x LLN (N=1118,3345,4463)	1	0	1	
Total protein >1.2x ULN (N=1118,3345,4463)	2	4	6	
Albumin <0.8x LLN (N=1118,3345,4463)	11	28	39	
Albumin >1.2x ULN (N=1118,3345,4463)	0	0	0	
Blood urea nitrogen >1.3x ULN (N=1118,3345,4463)	87	126	213	
Creatinine >1.3x ULN (N=1118,3345,4463)	52	95	147	
Cholesterol >1.3x ULN (N=1104,3345,4449)	42	130	172	
HDL Cholesterol <0.8x LLN (N=1097,3301,4398)	32	59	91	
LDL Cholesterol >1.2x ULN (N=1094,3293,4387)	69	145	214	
Triglycerides >1.3x ULN (N=1096,3300,4396)	196	373	569	
Sodium <0.95x LLN (N=1118,3345,4463)	6	19	25	
Sodium >1.05x ULN (N=1118,3345,4463)	11	18	29	

Potassium <0.9x LLN (N=1118,3345,4463)	28	62	90	
Potassium >1.1x ULN (N=1118,3345,4463)	11	25	36	
Chloride <0.9x LLN (N=1118,3345,4463)	3	5	8	
Chloride >1.1x ULN (N=1118,3345,4463)	0	1	1	
Calcium <0.9x LLN (N=1041,3345,4386)	2	8	10	
Calcium >1.1x ULN (N=1041,3345,4386)	6	9	15	
Bicarbonate (venous) <0.9x LLN (N=1117,3345,4462)	106	277	383	
Bicarbonate (venous) >1.1x ULN (N=1117,3345,4462)	1	5	6	
Glucose <0.6x LLN (N=1118,3345,4463)	3	4	7	
Glucose >1.5x ULN (N=1118,3345,4463)	125	345	470	
Creatine Kinase >2.0x ULN (N=1041,3345,4386)	203	908	1111	
C-reactive protein >1.25x ULN (N=697,242,939)	365	106	471	
Urine specific gravity <1.003 (N=1098,3319,4417)	2	7	9	
Urine specific gravity >1.030 (N=1098,3319,4417)	203	303	506	
Urine pH <4.5 (N=1098,3319,4417)	0	0	0	
Urine pH >8 (N=1098,3319,4417)	20	17	37	
Urine glucose (qual) ≥1 (N=1095,3319,4414)	60	148	208	
Urine ketones (qual) ≥1 (N=686,103,789)	2	1	3	
Urine protein (qual) ≥1 (N=1097,3319,4416)	65	222	287	
Urine blood/hgb (qual) ≥1 (N=1098,3319,4417)	444	1260	1704	
Urine leukocyte esterase ≥1 (N=687,132,819)	158	23	181	
Urine red blood cells ≥20 (N=678,1498,2176)	198	491	689	
Urine WBC ≥20 (N=689,1603,2292)	219	507	726	
Urine epithelial cells ≥6 (N=422,38,460)	205	20	225	
Urine casts >1 (N=420,38,458)	0	0	0	
Urine granular casts >1 (N=0,2,2)	0	0	0	
Urine hyaline casts >1 (N=14,60,74)	0	0	0	
Urine bacteria >20 (N=384,35,419)	0	0	0	

Statistical analyses

Statistical analysis title	Descriptive statistics only performed
Comparison groups	Tofa 5mg BID; ppts with avg total daily dose across study <15 v Tofa 10mg BID; ppts with avg total daily dose across study ≥15

Number of subjects included in analysis	4481
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	= 0
Method	Not applicable
Parameter estimate	Not applicable

Notes:

[1] - Arbitrary analysis specification entered as only descriptive statistics performed for this endpoint

Primary: The long-term safety and tolerability of CP-690,550 5 milligrams (mg) twice daily (BID) and 10 mg BID for the treatment of rheumatoid arthritis

End point title	The long-term safety and tolerability of CP-690,550 5 milligrams (mg) twice daily (BID) and 10 mg BID for the treatment of rheumatoid arthritis

End point description:

Treatment-emergent AEs by SOC (all causalities) - all patients, by time. Data presented for Post Month 96 includes data up to and including Month 114.

End point type	Primary

End point timeframe:

Every visit until last observation

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	3358	4481	
Units: Number of participants				
number (not applicable)				
Evaluable for AEs at Months 0 to 6	1123	3358	4481	
Percent with AEs at Months 0 to 6	59.4	61.8	61.2	
Percent discontinued due to AEs at Months 0 to 6	4.2	4.0	4.0	
Evaluable for AEs at Months 6 to 12	1033	3121	4154	
Percent with AEs at Months 6 to 12	45.1	47.7	47.1	
Percent discontinued due to AEs at Months 6 to 12	2.1	3.7	3.3	
Evaluable for AEs at Months 12 to 18	969	2865	3834	
Percent with AEs at Months 12 to 18	41.2	46.8	45.4	
Percent discontinued due to AEs at Months 12 to 18	3.2	3.4	3.3	
Evaluable at Months 18 to 24	896	2660	3556	
Percent with AEs at Months 18 to 24	38.1	43.2	41.9	
Percent discontinued due to AEs at Months 18 to 24	2.8	2.9	2.9	
Evaluable for AEs at Months 24 to 30	820	2461	3281	
Percent with AEs at Months 24 to 30	40.7	44.5	43.5	
Percent discontinued due to AEs at Months 24 to 30	3.2	2.8	2.9	
Evaluable for AEs at Months 30 to 36	774	2288	3062	
Percent with AEs at Months 30 to 36	39.0	40.7	40.3	

Percent discontinued due to AEs at Months 30 to 36	2.6	2.5	2.5	
Evaluable for AEs at Months 36 to 42	729	2162	2891	
Percent with AEs at Months 36 to 42	38.1	37.5	37.6	
Percent discontinued due to AEs at Months 36 to 42	2.5	2.5	2.5	
Evaluable for AEs at Months 42 to 48	652	1843	2495	
Percent with AEs at Months 42 to 48	37.9	34.3	35.3	
Percent discontinued due to AEs at Months 42 to 48	2.8	2.9	2.9	
Evaluable for AEs at Months 48 to 54	558	1471	2029	
Percent with AEs at Months 48 to 54	36.0	36.4	36.3	
Percent discontinued due to AEs at Months 48 to 54	2.0	2.5	2.4	
Evaluable for AEs at Months 54 to 60	466	1172	1638	
Percent with AEs at Months 54 to 60	37.1	35.4	35.9	
Percent discontinued due to AEs at Months 54 to 60	3.6	2.7	3.0	
Evaluable for AEs at Months 60 to 66	414	918	1332	
Percent with AEs at Months 60 to 66	33.8	31.4	32.1	
Percent discontinued due to AEs at Months 60 to 66	2.4	1.9	2.0	
Evaluable for AEs at Months 66 to 72	379	670	1049	
Percent with AEs at Months 66 to 72	33.5	21.6	25.9	
Percent discontinued due to AEs at Months 66 to 72	3.2	0.7	1.6	
Evaluable for AEs at Months 72 to 78	336	262	598	
Percent with AEs at Months 72 to 78	33.6	22.5	28.8	
Percent discontinued due to AEs at Months 72 to 78	0.9	0.4	0.7	
Evaluable for AEs at Months 78 to 84	302	86	388	
Percent with AEs at Months 78 to 84	36.8	26.7	34.5	
Percent discontinued due to AEs at Months 78 to 84	3.3	1.2	2.8	
Evaluable for AEs at Months 84 to 90	273	42	315	
Percent with AEs at Months 84 to 90	30.8	35.7	31.4	
Percent discontinued due to AEs at Months 84 to 90	1.8	0	1.6	
Evaluable for AEs at Months 90 to 96	234	34	268	
Percent with AEs at Months 90 to 96	21.8	29.4	22.8	
Percent discontinued due to AEs at Months 90 to 96	0.9	0	0.7	
Evaluable for AEs post Month 96	130	15	145	
Percent with AEs post Month 96	20.8	46.7	23.4	
Percent discontinued due to AEs post Month 96	1.5	0	1.4	

Statistical analyses

Statistical analysis title	Descriptive statistics only performed
Comparison groups	Tofa 5mg BID; ppts with avg total daily dose across study <15 v Tofa 10mg BID; ppts with avg total daily dose across study ≥15

Number of subjects included in analysis	4481
Analysis specification	Post-hoc
Analysis type	other[2]
P-value	= 0
Method	Not applicable
Parameter estimate	Not applicable

Notes:

[2] - Arbitrary analysis specification entered as descriptive statistics only performed for this endpoint

Secondary: Percent of patients with American College of Rheumatology (ACR) 20, 50, and 70 responses

End point title	Percent of patients with American College of Rheumatology (ACR) 20, 50, and 70 responses

End point description:

The stated number of participants analyzed was the total number of participants in each group. The actual number of participants analyzed on each occasion varied, and is provided for each visit presented.

End point type	Secondary

End point timeframe:

Every visit until last observation

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	3358	4481	
Units: Percent of participants				
number (not applicable)				
ACR20 at Month 1 (N=1114,3307,4421)	70.65	73.60	72.86	
ACR20 at Month 2 (N=1080,3254,4334)	74.81	76.06	75.75	
ACR20 at Month 3 (N=1069, 3228,4297)	75.68	78.00	77.43	
ACR20 at Month 6 (N=1040,3132,4172)	75.58	77.36	76.92	
ACR20 at Month 9 (N=1003,3022,4025)	76.57	77.53	77.29	
ACR20 at Month 12 (N=972,2891,3863)	77.88	78.24	78.15	
ACR20 at Month 15 (N=938,2775,3713)	76.76	78.67	78.18	
ACR20 at Month 18 (N=910,2665,3575)	77.91	78.46	78.32	
ACR20 at Month 21 (N=860,2565,3425)	77.91	79.42	79.04	
ACR20 at Month 24 (N=824, 2464, 3288)	79.61	78.37	78.68	
ACR20 at Month 27 (N=796,2361,3157)	79.15	79.16	79.16	
ACR20 at Month 30 (N=770,2288,3058)	80.00	79.90	79.92	
ACR20 at Month 33 (N=749,2219,2968)	80.51	79.81	79.99	
ACR20 at Month 36 (N=730, 2157, 2887)	81.78	79.37	79.98	
ACR20 at Month 39 (N=690,2073,2763)	78.55	81.23	80.56	
ACR20 at Month 42 (N=657,1907,2564)	78.69	80.49	80.03	
ACR20 at Month 45 (N=616,1658,2274)	82.14	79.55	80.26	
ACR20 at Month 48 (N=581,1486,2067)	78.31	80.69	80.02	
ACR20 at Month 51 (N=490,1355,1845)	83.47	80.30	81.14	

ACR20 at Month 54 (N=471,1208,1679)	79.19	78.97	79.04	
ACR20 at Month 57 (N=441,1021,1462)	80.73	82.37	81.87	
ACR20 at Month 60 (N=411,920,1331)	81.75	82.39	82.19	
ACR20 at Month 63 (N=396,692,1010)	80.30	82.97	82.11	
ACR20 at Month 66 (N=382,705,1087)	79.84	81.42	80.86	
ACR20 at Month 69 (N=358,486,844)	82.68	83.54	83.18	
ACR20 at Month 72 (N=339, 287, 626)	82.01	82.58	82.27	
ACR20 at Month 75 (N=309,171,480)	82.20	78.95	81.04	
ACR20 at Month 78 (N=295,91,386)	81.69	80.22	81.35	
ACR20 at Month 81 (N=286,54,340)	82.52	79.63	82.06	
ACR20 at Month 84 (N=271,44,315)	82.66	81.82	82.54	
ACR20 at Month 87 (N=264,41,305)	84.47	70.73	82.62	
ACR20 at Month 90 (N=241,39,280)	82.57	74.36	81.43	
ACR20 at Month 93 (N=196,28,224)	82.14	78.57	81.70	
ACR20 at Month 96 (N=144,16,160)	78.47	81.25	78.75	
ACR20 at Month 99 (N=65,11,76)	83.08	90.91	84.21	
ACR20 at Month 102 (N=22,4,26)	77.27	50.00	73.08	
ACR20 at Month 105 (N=15,3,18)	73.33	66.67	72.22	
ACR20 at Month 108 (N=8,1,9)	62.50	100.00	66.67	
ACR20 at Month 111 (N=3,1,4)	100.00	100.00	100.00	
ACR20 at Month 114 (N=1,0,1)	100.00	0	100.00	
ACR50 at Month 1 (N=1114,3307,4421)	47.67	49.56	49.08	
ACR50 at Month 2 (N=1080,3254,4334)	50.19	53.29	52.51	
ACR50 at Month 3 (N=1069,3228,4297)	51.45	54.52	53.76	
ACR50 at Month 6 (N=1040,3132,4172)	52.79	55.75	55.01	
ACR50 at Month 9 (N=1003,3022,4025)	53.24	55.96	55.28	
ACR50 at Month 12 (N=972,2891,3863)	52.98	56.73	55.79	
ACR50 at Month 15 (N=938,2775,3713)	55.76	56.61	56.40	
ACR50 at Month 18 (N=910,2665,3575)	55.16	57.30	56.76	
ACR50 at Month 21 (N=860,2565,3425)	54.77	59.10	58.01	
ACR50 at Month 24 (N=824,2464,3288)	57.77	57.67	57.69	
ACR50 at Month 27 (N=796,2361,3157)	56.91	58.58	58.16	
ACR50 at Month 30 (N=770,2288,3058)	58.83	58.65	58.70	
ACR50 at Month 33 (N=749,2219,2968)	57.68	59.31	58.89	
ACR50 at Month 36 (N=730,2157,2887)	58.49	58.51	58.50	
ACR50 at Month 39 (N=690,2073,2763)	59.28	59.29	59.28	
ACR50 at Month 42 (N=657,1907,2564)	58.60	59.99	59.63	
ACR50 at Month 45 (N=616,1658,2274)	59.42	60.07	59.89	
ACR50 at Month 48 (N=581,1486,2067)	58.00	57.60	57.72	
ACR50 at Month 51 (N=490,1355,1845)	62.45	59.19	60.05	
ACR50 at Month 54 (N=471,1355,1845)	58.60	59.44	59.20	
ACR50 at Month 57 (N=441,1021,1462)	61.45	61.12	61.22	
ACR50 at Month 60 (N=411,920,1331)	62.53	60.65	61.23	
ACR50 at Month 63 (N=396,834,1230)	64.39	61.99	62.76	
ACR50 at Month 66 (N=382,705,1087)	60.73	60.85	60.81	
ACR50 at Month 69 (N=358,486,844)	58.10	61.11	59.83	
ACR50 at Month 72 (N=339,287,626)	62.54	59.93	61.34	
ACR50 at Month 75 (N=309,171,480)	61.49	56.14	59.58	
ACR50 at Month 78 (N=295,91,386)	60.00	58.24	59.59	
ACR50 at Month 81 (N=286,54,340)	63.99	51.85	62.06	
ACR50 at Month 84 (N=271,44,315)	63.10	54.55	61.90	
ACR50 at Month 87 (N=264,41,305)	67.05	43.90	63.93	

ACR50 at Month 90 (N=241,39,280)	61.00	46.15	58.93	
ACR50 at Month 93 (N=196,28,224)	61.22	57.14	60.71	
ACR50 at Month 96 (N=144,16,160)	61.11	56.25	60.63	
ACR50 at Month 99 (N=65,11,76)	53.85	54.55	53.95	
ACR50 at Month 102 (N=22,4,26)	54.55	25.00	50.00	
ACR50 at Month 105 (N=15,3,18)	66.67	33.33	61.11	
ACR50 at Month 108 (N=8,1,9)	50.00	0.00	44.44	
ACR50 at Month 111 (N=3,1,4)	100.00	0.00	75.00	
ACR50 at Month 114 (N=1,0,1)	100.00	0.00	100.00	
ACR70 at Month 1 (N=1114,3307,4421)	26.66	28.82	28.27	
ACR70 at Month 2 (N=1080,3254,4334)	27.78	31.53	30.60	
ACR70 at Month 3 (N=1069,3228,4297)	29.37	33.09	32.16	
ACR70 at Month 6 (N=1040,3132,4172)	31.06	33.75	33.08	
ACR70 at Month 9 (N=1003,3022,4025)	31.80	34.91	34.14	
ACR70 at Month 12 (N=972,2891,3863)	31.38	35.84	34.71	
ACR70 at Month 15 (N=937,2775,3713)	32.94	36.54	35.63	
ACR70 at Month 18 (N=910,2665,3575)	35.82	36.40	36.25	
ACR70 at Month 21 (N=860,2565,3425)	33.49	37.66	36.61	
ACR70 at Month 24 (N=824,2464,3288)	35.44	38.15	37.47	
ACR70 at Month 27 (N=796,2361,3157)	36.06	38.33	37.76	
ACR70 at Month 30 (N=770,2288,3058)	37.27	38.99	38.55	
ACR70 at Month 33 (N=749,2219,2968)	33.64	38.26	37.10	
ACR70 at Month 36 (N=730,2157,2887)	36.71	37.41	37.24	
ACR70 at Month 39 (N=690,2073,2763)	38.41	38.88	38.76	
ACR70 at Month 42 (N=657,1907,2564)	35.77	38.91	38.10	
ACR70 at Month 45 (N=616,1658,2274)	36.69	38.18	37.77	
ACR70 at Month 48 (N=581,1486,2067)	35.97	37.01	36.72	
ACR70 at Month 51 (N=490,1355,1845)	39.59	37.34	37.94	
ACR70 at Month 54 (N=471,1208,1679)	36.73	39.32	38.59	
ACR70 at Month 57 (N=441,1021,1462)	38.78	39.47	39.26	
ACR70 at Month 60 (N=411,920,1331)	37.96	38.91	38.62	
ACR70 at Month 63 (N=396,834,1230)	38.64	39.33	39.11	
ACR70 at Month 66 (N=.146,283,429)	38.22	40.14	39.47	
ACR70 at Month 69 (N=358,486,844)	38.55	41.56	40.28	
ACR70 at Month 72 (N=339,287,626)	40.12	36.59	38.50	
ACR70 at Month 75 (N=309,171,480)	40.13	36.84	38.96	
ACR70 at Month 78 (N=295,91,386)	42.37	32.97	40.16	
ACR70 at Month 81 (N=286,54,340)	41.26	35.19	40.29	
ACR70 at Month 84 (N=271,44,315)	42.07	31.82	40.63	
ACR70 at Month 87 (N=264,41,305)	42.80	21.95	40.00	
ACR70 at Month 90 (N=241,39,280)	38.17	25.64	36.43	
ACR70 at Month 93 (N=196,28,224)	41.84	39.29	41.52	
ACR70 at Month 96 (N=144,16,160)	43.75	31.25	42.50	
ACR70 at Month 99 (N=65,11,76)	40.00	18.18	36.84	
ACR70 at Month 102 (N=22,4,26)	40.91	25.00	38.46	
ACR70 at Month 105 (N=15,3,18)	46.67	33.33	44.44	
ACR70 at Month 108 (N=8,1,9)	25.00	0.00	22.22	
ACR70 at Month 111 (N=3,1,4)	100.00	0.00	75.00	
ACR70 at Month 114 (N=1,0,1)	100.00	0.00	100.00	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score (DAS)28 (C-reactive protein [CRP]) and DAS28 (erythrocyte sedimentation rate [ESR])

End point title	Disease Activity Score (DAS)28 (C-reactive protein [CRP]) and DAS28 (erythrocyte sedimentation rate [ESR])

End point description:

Descriptive statistics for DAS28-3 (CRP) and DAS28-4 (ESR). The stated number of participants analyzed was the total number of participants in each group. The actual number of participants analyzed on each occasion varied, and is provided for each visit presented.

End point type	Secondary

End point timeframe:

Every visit until last observation

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	3358	4481	
Units: Score				
arithmetic mean (standard deviation)				
DAS28-4 (ESR) Baseline (N=1002,3296,4298)	6.27 (± 1.02)	6.39 (± 1.04)	6.36 (± 1.04)	
DAS28-4 (ESR) Month 1 (N=1036,3254,4290)	3.81 (± 1.32)	3.78 (± 1.36)	3.79 (± 1.35)	
DAS28-4 (ESR) Month 2 (N=1026,3222,4248)	3.72 (± 1.27)	3.66 (± 1.32)	3.68 (± 1.31)	
DAS28-4 (ESR) Month 3 (N=1033,3203,4236)	3.75 (± 1.32)	3.61 (± 1.30)	3.65 (± 1.31)	
DAS28-4 (ESR) Month 6 (N=1015,3110,4125)	3.67 (± 1.33)	3.61 (± 1.30)	3.62 (± 1.31)	
DAS28-4 (ESR) Month 9 (N=992,3003,3995)	3.60 (± 1.31)	3.58 (± 1.32)	3.59 (± 1.31)	
DAS28-4 (ESR) Month 12 (N=967,2862,3829)	3.61 (± 1.26)	3.56 (± 1.30)	3.57 (± 1.29)	
DAS28-4 (ESR) Month 15 (N=922,2759,3681)	3.54 (± 1.26)	3.53 (± 1.30)	3.53 (± 1.29)	
DAS28-4 (ESR) Month 18 (N=899,2655,3554)	3.57 (± 1.26)	3.50 (± 1.28)	3.52 (± 1.28)	
DAS28-4 (ESR) Month 21 (N=850,2547,3397)	3.58 (± 1.25)	3.45 (± 1.27)	3.48 (± 1.26)	
DAS28-4 (ESR) Month 24 (N=818,2441,3259)	3.54 (± 1.21)	3.46 (± 1.26)	3.48 (± 1.25)	

DAS28-4 (ESR) Month 27 (N=787,2343,3130)	3.52 (± 1.20)	3.44 (± 1.25)	3.46 (± 1.24)	
DAS28-4 (ESR) Month 30 (N=764,2257,3021)	3.54 (± 1.23)	3.43 (± 1.25)	3.46 (± 1.24)	
DAS28-4 (ESR) Month 33 (N=746,2199,2945)	3.51 (± 1.22)	3.42 (± 1.27)	3.45 (± 1.26)	
DAS28-4 (ESR) Month 36 (N=720,2141,2861)	3.51 (± 1.23)	3.42 (± 1.27)	3.44 (± 1.26)	
DAS28-4 (ESR) Month 39 (N=679,2056,2735)	3.56 (± 1.27)	3.39 (± 1.24)	3.43 (± 1.25)	
DAS28-4 (ESR) Month 42 (N=642,1890,2532)	3.53 (± 1.26)	3.40 (± 1.26)	3.43 (± 1.26)	
DAS28-4 (ESR) Month 45 (N=609,1641,2250)	3.45 (± 1.20)	3.37 (± 1.21)	3.39 (± 1.20)	
DAS28-4 (ESR) Month 48 (N=570,1471,2041)	3.46 (± 1.16)	3.36 (± 1.21)	3.39 (± 1.20)	
DAS28-4 (ESR) Month 51 (N=481,1344,1825)	3.43 (± 1.20)	3.39 (± 1.24)	3.40 (± 1.23)	
DAS28-4 (ESR) Month 54 (N=467,1194,1661)	3.54 (± 1.23)	3.38 (± 1.25)	3.42 (± 1.25)	
DAS28-4 (ESR) Month 57 (N=438,1006,1444)	3.48 (± 1.19)	3.36 (± 1.21)	3.40 (± 1.20)	
DAS28-4 (ESR) Month 60 (N=408,908,1316)	3.51 (± 1.27)	3.34 (± 1.20)	3.39 (± 1.22)	
DAS28-4 (ESR) Month 63 (N=388,825,1213)	3.51 (± 1.15)	3.30 (± 1.16)	3.37 (± 1.16)	
DAS28-4 (ESR) Month 66 (N=379,700,1079)	3.58 (± 1.12)	3.34 (± 1.17)	3.42 (± 1.15)	
DAS28-4 (ESR) Month 69 (N=355,483,838)	3.51 (± 1.18)	3.35 (± 1.20)	3.41 (± 1.19)	
DAS28-4 (ESR) Month 72 (N=338,284,622)	3.45 (± 1.20)	3.42 (± 1.19)	3.44 (± 1.20)	
DAS28-4 (ESR) Month 75 (N=299,169,468)	3.43 (± 1.11)	3.41 (± 1.14)	3.43 (± 1.12)	
DAS28-4 (ESR) Month 78 (N=291,91,382)	3.44 (± 1.14)	3.32 (± 1.20)	3.41 (± 1.16)	
DAS28-4 (ESR) Month 81 (N=284,54,338)	3.40 (± 1.11)	3.56 (± 1.24)	3.42 (± 1.13)	
DAS28-4 (ESR) Month 84 (N=271,44,315)	3.32 (± 1.13)	3.42 (± 1.37)	3.34 (± 1.16)	
DAS28-4 (ESR) Month 87 (N=263,41,304)	3.33 (± 1.13)	3.19 (± 1.15)	3.31 (± 1.13)	
DAS28-4 (ESR) Month 90 (N=237,39,276)	3.34 (± 1.14)	3.28 (± 1.10)	3.33 (± 1.13)	
DAS28-4 (ESR) Month 93 (N=191,28,219)	3.33 (± 1.14)	3.23 (± 1.12)	3.32 (± 1.13)	
DAS28-4 (ESR) Month 96 (N=142,16,158)	3.30 (± 1.12)	3.48 (± 1.06)	3.32 (± 1.11)	
DAS28-4 (ESR) Month 99 (N=65,11,76)	3.26 (± 1.07)	3.04 (± 1.24)	3.23 (± 1.09)	
DAS28-4 (ESR) Month 102 (N=22,4,26)	3.34 (± 1.47)	3.10 (± 1.76)	3.30 (± 1.48)	
DAS28-4 (ESR) Month 105 (N=14,3,17)	3.64 (± 1.52)	2.65 (± 0.97)	3.46 (± 1.46)	
DAS28-4 (ESR) Month 108 (N=8,1,9)	3.36 (± 1.76)	4.65 (± 0)	3.51 (± 1.70)	
DAS28-4 (ESR) Month 111 (N=3,1,4)	2.03 (± 0.69)	3.59 (± 0)	2.42 (± 0.96)	
DAS28-4 (ESR) Month 114 (N=1,0,1)	1.28 (± 0)	0 (± 0)	1.28 (± 0)	
DAS28-3 (CRP) Baseline (N=1112,3340,4452)	5.31 (± 0.95)	5.34 (± 0.98)	5.33 (± 0.97)	
DAS28-3 (CRP) Month 1 (N=1096,3234,4330)	3.10 (± 1.19)	2.96 (± 1.22)	2.99 (± 1.21)	
DAS28-3 (CRP) Month 2 (N=1070,3180,4250)	3.01 (± 1.15)	2.87 (± 1.17)	2.90 (± 1.17)	

DAS28-3 (CRP) Month 3 (N=1057,3190,4247)	2.98 (± 1.15)	2.81 (± 1.15)	2.85 (± 1.15)	
DAS28-3 (CRP) Month 6 (N=1026,3106,4132)	2.89 (± 1.16)	2.79 (± 1.15)	2.81 (± 1.16)	
DAS28-3 (CRP) Month 9 (N=993,3008,4001)	2.82 (± 1.12)	2.74 (± 1.16)	2.76 (± 1.15)	
DAS28-3 (CRP) Month 12 (N=962,2874,3836)	2.81 (± 1.11)	2.72 (± 1.13)	2.74 (± 1.13)	
DAS28-3 (CRP) Month 15 (N=923,2761,3684)	2.73 (± 1.10)	2.69 (± 1.13)	2.70 (± 1.12)	
DAS28-3 (CRP) Month 18 (N=899,2654,3553)	2.72 (± 1.11)	2.66 (± 1.11)	2.68 (± 1.11)	
DAS28-3 (CRP) Month 21 (N=856,2556,3412)	2.75 (± 1.12)	2.62 (± 1.09)	2.65 (± 1.09)	
DAS28-3 (CRP) Month 24 (N=813,2456,3269)	2.96 (± 1.07)	2.63 (± 1.11)	2.64 (± 1.10)	
DAS28-3 (CRP) Month 27 (N=793,2345,3138)	2.66 (± 1.06)	2.60 (± 1.09)	2.62 (± 1.08)	
DAS28-3 (CRP) Month 30 (N=766,2271,3037)	2.65 (± 1.07)	2.59 (± 1.09)	2.60 (± 1.08)	
DAS28-3 (CRP) Month 33 (N=745,2209,2954)	2.64 (± 1.06)	2.58 (± 1.10)	2.60 (± 1.09)	
DAS28-3 (CRP) Month 36 (N=724,2142,2866)	2.64 (± 1.07)	2.59 (± 1.08)	2.60 (± 1.08)	
DAS28-3 (CRP) Month 39 (N=686,2057,2743)	2.65 (± 1.10)	2.57 (± 1.07)	2.59 (± 1.08)	
DAS28-3 (CRP) Month 42 (N=653,1893,2546)	2.63 (± 1.09)	2.57 (± 1.09)	2.59 (± 1.09)	
DAS28-3 (CRP) Month 45 (N=611,1644,2255)	2.57 (± 1.04)	2.53 (± 1.03)	2.54 (± 1.03)	
DAS28-3 (CRP) Month 48 (N=579,1469,2048)	2.59 (± 1.03)	2.54 (± 1.05)	2.56 (± 1.04)	
DAS28-3 (CRP) Month 51 (N=487,1348,1835)	2.59 (± 0.99)	2.57 (± 1.07)	2.57 (± 1.05)	
DAS28-3 (CRP) Month 54 (N=468,1198,1666)	2.68 (± 1.07)	2.56 (± 1.05)	2.59 (± 1.06)	
DAS28-3 (CRP) Month 57 (N=439,1011,1450)	2.63 (± 1.03)	2.54 (± 1.04)	2.56 (± 1.03)	
DAS28-3 (CRP) Month 60 (N=407,913,1320)	2.66 (± 1.09)	2.53 (± 1.03)	2.57 (± 1.05)	
DAS28-3 (CRP) Month 63 (N=390,824,1214)	2.67 (± 1.01)	2.51 (± 0.98)	2.56 (± 0.99)	
DAS28-3 (CRP) Month 66 (N=376,702,1078)	2.70 (± 1.02)	2.53 (± 1.01)	2.59 (± 1.02)	
DAS28-3 (CRP) Month 69 (N=355,483,838)	2.67 (± 1.06)	2.55 (± 1.00)	2.60 (± 1.03)	
DAS28-3 (CRP) Month 72 (N=337,285,622)	2.65 (± 1.04)	2.64 (± 1.03)	2.64 (± 1.04)	
DAS28-3 (CRP) Month 75 (N=304,170,474)	2.63 (± 1.05)	2.59 (± 1.02)	2.61 (± 1.04)	
DAS28-3 (CRP) Month 78 (N=292,91,383)	2.59 (± 1.02)	2.68 (± 1.01)	2.61 (± 1.02)	
DAS28-3 (CRP) Month 81 (N=285,54,339)	2.54 (± 0.96)	2.82 (± 1.13)	2.59 (± 0.99)	
DAS28-3 (CRP) Month 84 (N=269,44,313)	2.49 (± 0.94)	2.84 (± 1.20)	2.54 (± 0.99)	
DAS28-3 (CRP) Month 87 (N=264,41,305)	2.52 (± 0.97)	2.56 (± 0.91)	2.52 (± 0.96)	
DAS28-3 (CRP) Month 90 (N=240,39,279)	2.55 (± 1.00)	2.58 (± 0.95)	2.55 (± 0.99)	
DAS28-3 (CRP) Month 93 (N=196,28,224)	2.59 (± 1.00)	2.59 (± 0.85)	2.59 (± 0.98)	

DAS28-3 (CRP) Month 96 (N=144,16,160)	2.59 (± 0.93)	2.68 (± 0.80)	2.60 (± 0.92)	
DAS28-3 (CRP) Month 99 (N=64,11,75)	2.58 (± 0.89)	2.49 (± 1.12)	2.57 (± 0.92)	
DAS28-3 (CRP) Month 102 (N=13,3,16)	2.66 (± 0.78)	2.29 (± 1.01)	2.59 (± 0.81)	
DAS28-3 (CRP) Month 105 (N=12,2,14)	3.31 (± 1.23)	1.76 (± 0.34)	3.09 (± 1.26)	
DAS28-3 (CRP) Month 108 (N=7,1,8)	3.46 (± 1.59)	3.70 (± 0)	3.49 (± 1.47)	
DAS28-3 (CRP) Month 111 (N=3,1,4)	1.82 (± 0.50)	2.49 (± 0)	1.98 (± 0.53)	
DAS28-3 (CRP) Month 114 (N=1,0,1)	2.67 (± 0)	0 (± 0)	2.67 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number (%) of participants with DAS28-4 (ESR) and DAS28-3 (CRP) <2.6 and ≤3.2

End point title	Number (%) of participants with DAS28-4 (ESR) and DAS28-3 (CRP) <2.6 and ≤3.2

End point description:

Percent participants with DAS28-4 (ESR) <2.6 and ≤3.2 and percent participants with DAS28-3 (CRP) <2.6 and ≤3.2. The stated number of participants analyzed was the total number of participants in each group. The actual number of participants analyzed on each occasion varied, and is provided for each visit presented.

End point type	Secondary

End point timeframe:

Every visit until last observation

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	3358	4481	
Units: Percent of participants				
number (not applicable)				
DAS28-4 (ESR) <2.6 Baseline (N=1002,3296,4298)	0.2	0.3	0.3	
DAS28-4 (ESR) <2.6 Month 1 (N=1036,3254,4290)	19.9	20.4	20.3	
DAS28-4 (ESR) <2.6 Month 2 (N=1026,3222,4248)	20.5	22.5	22.0	
DAS28-4 (ESR) <2.6 Month 3 (N=1033,3203,4236)	20.0	22.9	22.2	
DAS28-4 (ESR) <2.6 Month 6 (N=1015,3110,4125)	22.9	23.4	23.3	
DAS28-4 (ESR) <2.6 Month 9 (N=992,3003,3995)	24.4	25.1	24.9	
DAS28-4 (ESR) <2.6 Month 12 (N=967,2862,3829)	22.3	24.4	23.9	
DAS28-4 (ESR) <2.6 Month 15 (N=922,2759,3681)	23.8	25.7	25.2	

DAS28-4 (ESR) <2.6 Month 18 (N=899,2655,3554)	25.3	26.9	26.4	
DAS28-4 (ESR) <2.6 Month 21 (N=850,2547,3397)	22.2	27.1	25.9	
DAS28-4 (ESR) <2.6 Month 24 (N=818,2441,3259)	22.7	26.8	25.8	
DAS28-4 (ESR) <2.6 Month 27 (N=787,2343,3130)	22.6	27.9	26.5	
DAS28-4 (ESR) <2.6 Month 30 (N=764,2257,3021)	24.6	27.7	26.9	
DAS28-4 (ESR) <2.6 Month 33 (N=746,2199,2945)	23.7	28.3	27.1	
DAS28-4 (ESR) <2.6 Month 36 (N=720,2141,2861)	25.6	28.9	28.1	
DAS28-4 (ESR) <2.6 Month 39 (N=679,2056,2735)	23.9	28.4	27.3	
DAS28-4 (ESR) <2.6 Month 42 (N=642,1890,2532)	24.3	27.9	27.0	
DAS28-4 (ESR) <2.6 Month 45 (N=609,1641,2250)	24.1	27.5	26.6	
DAS28-4 (ESR) <2.6 Month 48 (N=570,1471,2041)	23.5	28.0	26.8	
DAS28-4 (ESR) <2.6 Month 51 (N=481,1344,1825)	28.3	27.3	27.6	
DAS28-4 (ESR) <2.6 Month 54 (N=467,1194,1661)	21.4	28.3	26.4	
DAS28-4 (ESR) <2.6 Month 57 (N=438,1006,1444)	23.1	28.0	26.5	
DAS28-4 (ESR) <2.6 Month 60 (N=408,908,1316)	24.0	28.6	27.2	
DAS28-4 (ESR) <2.6 Month 63 (N=388,825,1213)	22.4	29.5	27.2	
DAS28-4 (ESR) <2.6 Month 66 (N=379,700,1079)	19.5	26.9	24.3	
DAS28-4 (ESR) <2.6 Month 69 (N=355,483,838)	23.9	26.3	25.3	
DAS28-4 (ESR) <2.6 Month 72 (N=338,284,622)	25.7	25.0	25.4	
DAS28-4 (ESR) <2.6 Month 75 (N=299,169,468)	23.7	26.0	24.6	
DAS28-4 (ESR) <2.6 Month 78 (N=291,91,382)	24.7	33.0	26.7	
DAS28-4 (ESR) <2.6 Month 81 (N=284,54,338)	24.6	22.2	24.3	
DAS28-4 (ESR) <2.6 Month 84 (N=271,44,315)	27.3	27.3	27.3	
DAS28-4 (ESR) <2.6 Month 87 (N=263,41,304)	31.2	31.7	31.3	
DAS28-4 (ESR) <2.6 Month 90 (N=237,39,276)	28.7	25.6	28.3	
DAS28-4 (ESR) <2.6 Month 93 (N=191,28,219)	28.3	28.6	28.3	
DAS28-4 (ESR) <2.6 Month 96 (N=142,16,158)	25.4	18.8	24.7	
DAS28-4 (ESR) <2.6 Month 99 (N=65,11,76)	27.7	36.4	28.9	
DAS28-4 (ESR) <2.6 Month 102 (N=22,4,26)	31.8	50.0	34.6	
DAS28-4 (ESR) <2.6 Month 105 (N=14,3,17)	28.6	33.3	29.4	
DAS28-4 (ESR) <2.6 Month 108 (N=8,1,9)	25.0	0	22.2	

DAS28-4 (ESR) </=3.2 Baseline (N=1002,3296,4298)	0.4	0.7	0.6	
DAS28-4 (ESR) </=3.2 Month 1 (N=1036,3254,4290)	34.2	37.6	36.8	
DAS28-4 (ESR) </=3.2 Month 2 (N=1026,3222,4248)	36.7	40.5	39.6	
DAS28-4 (ESR) </=3.2 Month 3 (N=1033,3203,4236)	36.6	41.6	40.4	
DAS28-4 (ESR) </=3.2 Month 6 (N=1015,3110,4125)	39.8	42.5	41.9	
DAS28-4 (ESR) </=3.2 Month 9 (N=992,3003,3995)	41.3	43.8	43.2	
DAS28-4 (ESR) </=3.2 Month 12 (N=967,2862,3829)	42.1	42.5	42.4	
DAS28-4 (ESR) </=3.2 Month 18 (N=899,2655,3554)	42.7	45.0	44.4	
DAS28-4 (ESR) </=3.2 Month 21 (N=850,2547,3397)	41.9	47.2	45.9	
DAS28-4 (ESR) </=3.2 Month 24 (N=818,2441,3259)	42.5	46.5	45.5	
DAS28-4 (ESR) </=3.2 Month 27 (N=787,2343,3130)	44.9	46.9	46.4	
DAS28-4 (ESR) </=3.2 Month 30 (N=764,2257,3021)	42.8	47.4	46.2	
DAS28-4 (ESR) </=3.2 Month 33 (N=746,2199,2945)	42.8	47.5	46.3	
DAS28-4 (ESR) </=3.2 Month 36 (N=720,2141,2861)	44.6	48.4	47.5	
DAS28-4 (ESR) </=3.2 Month 39 (N=679,2056,2735)	42.6	48.3	46.9	
DAS28-4 (ESR) </=3.2 Month 42 (N=642,1890,2532)	45.8	49.2	48.3	
DAS28-4 (ESR) </=3.2 Month 45 (N=609,1641,2250)	45.3	48.4	47.6	
DAS28-4 (ESR) </=3.2 Month 48 (N=570,1471,2041)	46.1	49.4	48.5	
DAS28-4 (ESR) </=3.2 Month 51 (N=481,1344,1825)	44.9	49.0	47.9	
DAS28-4 (ESR) </=3.2 Month 54 (N=467,1194,1661)	43.7	49.4	47.8	
DAS28-4 (ESR) </=3.2 Month 57 (N=438,1006,1444)	45.2	50.3	48.8	
DAS28-4 (ESR) </=3.2 Month 60 (N=408,908,1316)	46.3	49.9	48.8	
DAS28-4 (ESR) </=3.2 Month 63 (N=388,825,1213)	41.0	49.9	47.1	
DAS28-4 (ESR) </=3.2 Month 66 (N=379,700,1079)	38.8	49.7	45.9	
DAS28-4 (ESR) </=3.2 Month 69 (N=355,483,838)	45.6	50.3	48.3	
DAS28-4 (ESR) </=3.2 Month 72 (N=338,284,622)	44.7	48.2	46.3	
DAS28-4 (ESR) </=3.2 Month 75 (N=299,169,458)	43.1	48.5	45.1	
DAS28-4 (ESR) </=3.2 Month 78 (N=291,91,382)	44.7	45.1	44.8	
DAS28-4 (ESR) </=3.2 Month 81 (N=284,54,338)	49.3	48.1	49.1	
DAS28-4 (ESR) </=3.2 Month 84 (N=271,44,315)	47.2	45.5	47.0	
DAS28-4 (ESR) </=3.2 Month 87 (N=263,41,304)	47.9	46.3	47.7	

DAS28-4 (ESR) </=3.2 Month 90 (N=237,39,276)	46.0	46.2	46.0	
DAS28-4 (ESR) </=3.2 Month 93 (N=191,28,219)	48.2	50.0	48.4	
DAS28-4 (ESR) </=3.2 Month 96 (N=142,16,158)	47.2	43.8	46.8	
DAS28-4 (ESR) </=3.2 Month 99 (N=142,16,158)	43.1	54.5	44.7	
DAS28-4 (ESR) </=3.2 Month 102 (N=22,4,26)	45.5	50.0	46.2	
DAS28-4 (ESR) </=3.2 Month 105 (N=14,3,17)	42.9	66.7	47.1	
DAS28-4 (ESR) </=3.2 Month 108 (N=8,1,9)	50.0	0	44.4	
DAS28-3 (CRP) <2.6 Baseline 1 (N=1112,3340,4452)	0.5	0.9	0.8	
DAS28-3 (CRP) <2.6 Month 1 (N=1096,3234,4330)	38.0	43.0	41.7	
DAS28-3 (CRP) <2.6 Month 2 (N=1070,3180,4250)	39.7	47.1	45.2	
DAS28-3 (CRP) <2.6 Month 3 (N=1057,3190,4247)	42.3	47.5	46.2	
DAS28-3 (CRP) <2.6 Month 6 (N=1026,3106,4132)	45.2	49.0	48.1	
DAS28-3 (CRP) <2.6 Month 9 (N=993,3008,4001)	47.1	50.7	49.8	
DAS28-3 (CRP) <2.6 Month 12 (N=962,2874,3836)	47.8	51.8	50.8	
DAS28-3 (CRP) <2.6 Month 15 (N=923,2761,3684)	50.6	52.3	51.9	
DAS28-3 (CRP) <2.6 Month 18 (N=899,2654,3553)	51.3	54.1	53.4	
DAS28-3 (CRP) <2.6 Month 21 (N=856,2556,3412)	51.1	55.5	54.4	
DAS28-3 (CRP) <2.6 Month 24 (N=813,2456,3269)	51.9	55.3	54.4	
DAS28-3 (CRP) <2.6 Month 27 (N=793,2345,3138)	53.2	55.8	55.2	
DAS28-3 (CRP) <2.6 Month 30 (N=766,2271,3037)	53.3	56.8	55.9	
DAS28-3 (CRP) <2.6 Month 33 (N=745,2209,2954)	54.1	56.0	55.6	
DAS28-3 (CRP) <2.6 Month 36 (N=724,2142,2866)	52.9	55.6	54.9	
DAS28-3 (CRP) <2.6 Month 39 (N=686,2057,2743)	54.2	56.9	56.2	
DAS28-3 (CRP) <2.6 Month 42 (N=653,1893,2546)	54.2	56.8	56.2	
DAS28-3 (CRP) <2.6 Month 45 (N=611,1644,2255)	56.3	58.6	58.0	
DAS28-3 (CRP) <2.6 Month 48 (N=579,1469,2048)	55.4	59.3	58.2	
DAS28-3 (CRP) <2.6 Month 51 (N=487,1348,1835)	56.1	57.3	56.9	
DAS28-3 (CRP) <2.6 Month 54 (N=468,1198,1666)	52.6	57.8	56.3	
DAS28-3 (CRP) <2.6 Month 57 (N=439,1011,1450)	55.6	57.7	57.0	
DAS28-3 (CRP) <2.6 Month 60 (N=407,913,1320)	55.0	57.9	57.0	
DAS28-3 (CRP) <2.6 Month 63 (N=390,824,1214)	51.0	58.1	55.8	

DAS28-3 (CRP) <2.6 Month 66 (N=376,702,1078)	51.9	59.3	56.7	
DAS28-3 (CRP) <2.6 Month 69 (N=355,483,838)	53.5	57.8	56.0	
DAS28-3 (CRP) <2.6 Month 72 (N=337,285,622)	52.2	55.4	53.7	
DAS28-3 (CRP) <2.6 Month 75 (N=304,170,474)	53.9	53.5	53.8	
DAS28-3 (CRP) <2.6 Month 78 (N=292,91,383)	58.2	51.6	56.7	
DAS28-3 (CRP) <2.6 Month 81 (N=285,54,339)	58.6	51.9	57.5	
DAS28-3 (CRP) <2.6 Month 84 (N=269,44,313)	61.7	43.2	59.1	
DAS28-3 (CRP) <2.6 Month 87 (N=264,41,305)	60.2	48.8	58.7	
DAS28-3 (CRP) <2.6 Month 90 (N=240,39,279)	60.8	46.2	58.8	
DAS28-3 (CRP) <2.6 Month 93 (N=196,28,224)	56.1	53.6	55.8	
DAS28-3 (CRP) <2.6 Month 96 (N=144,16,160)	56.3	37.5	54.4	
DAS28-3 (CRP) <2.6 Month 99 (N=64,11,75)	50.0	63.6	52.0	
DAS28-3 (CRP) <2.6 Month 102 (N=13,3,16)	46.2	66.7	50.0	
DAS28-3 (CRP) <2.6 Month 105 (N=12,2,14)	33.3	100	42.9	
DAS28-3 (CRP) <2.6 Month 108 (N=7,1,8)	42.9	0	37.5	
DAS28-3 (CRP) <2.6 Month 111 (N=3,1,4)	100	100	100	
DAS28-3 (CRP) </=3.2 Month 1 (N=1096,3234,4330)	55.3	61.9	60.2	
DAS28-3 (CRP) </=3.2 Month 2 (N=1070,3180,4250)	60.7	64.5	63.6	
DAS28-3 (CRP) </=3.2 Month 3 (N=1057,3190,4247)	60.6	66.3	64.9	
DAS28-3 (CRP) </=3.2 Month 6 (N=1026,3106,4132)	64.4	67.1	66.4	
DAS28-3 (CRP) </=3.2 Month 9 (N=993,3008,4001)	66.4	68.3	67.8	
DAS28-3 (CRP) </=3.2 Month 12 (N=962,2874,3836)	66.1	70.0	69.0	
DAS28-3 (CRP) </=3.2 Month 15 (N=923,2761,3684)	70.0	70.0	70.0	
DAS28-3 (CRP) </=3.2 Month 18 (N=899,2654,3553)	69.2	71.7	71.1	
DAS28-3 (CRP) </=3.2 Month 21 (N=856,2556,3412)	69.5	72.5	71.8	
DAS28-3 (CRP) </=3.2 Month 24 (N=813,2456,3269)	71.7	72.5	72.3	
DAS28-3 (CRP) </=3.2 Month 27 (N=793,2345,3138)	72.6	73.0	72.9	
DAS28-3 (CRP) </=3.2 Month 30 (N=766,2271,3037)	73.0	73.8	73.6	
DAS28-3 (CRP) </=3.2 Month 33 (N=745,2209,2954)	72.2	74.5	73.9	
DAS28-3 (CRP) </=3.2 Month 36 (N=724,2142,2866)	73.8	73.4	73.5	
DAS28-3 (CRP) </=3.2 Month 39 (N=686,2057,2743)	73.2	74.6	74.2	

DAS28-3 (CRP) </=3.2 Month 42 (N=653,1893,2546)	73.8	74.7	74.5	
DAS28-3 (CRP) </=3.2 Month 45 (N=611,1644,2255)	74.6	75.2	75.1	
DAS28-3 (CRP) </=3.2 Month 48 (N=579,1469,2048)	74.6	75.0	74.9	
DAS28-3 (CRP) </=3.2 Month 51 (N=487,1348,1835)	74.3	75.1	74.9	
DAS28-3 (CRP) </=3.2 Month 54 (N=468,1198,1666)	71.4	76.4	75.0	
DAS28-3 (CRP) </=3.2 Month 57 (N=439,1011,1450)	73.6	75.2	74.7	
DAS28-3 (CRP) </=3.2 Month 60 (N=407,913,1320)	72.5	77.0	75.6	
DAS28-3 (CRP) </=3.2 Month 63 (N=390,824,1214)	72.8	76.5	75.3	
DAS28-3 (CRP) </=3.2 Month 66 (N=376,702,1078)	71.5	78.1	75.8	
DAS28-3 (CRP) </=3.2 Month 69 (N=355,483,838)	69.9	77.0	74.0	
DAS28-3 (CRP) </=3.2 Month 72 (N=337,285,622)	74.8	73.3	74.1	
DAS28-3 (CRP) </=3.2 Month 75 (N=304,170,474)	77.0	72.9	75.5	
DAS28-3 (CRP) </=3.2 Month 78 (N=292,91,383)	74.3	70.3	73.4	
DAS28-3 (CRP) </=3.2 Month 81 (N=285,54,339)	75.8	68.5	74.6	
DAS28-3 (CRP) </=3.2 Month 84 (N=269,44,313)	79.2	68.2	77.6	
DAS28-4 (CRP) </=3.2 Month 87 (N=264,41,305)	81.1	70.7	79.7	
DAS28-3 (CRP) </=3.2 Month 90 (N=240,39,279)	77.1	74.4	76.7	
DAS28-3 (CRP) </=3.2 Month 93 (N=196,28,224)	75.0	67.9	74.1	
DAS28-3 (CRP) </=3.2 Month 96 (N=144,16,160)	77.1	87.5	78.1	
DAS28-3 (CRP) </=3.2 Month 99 (N=64,11,75)	76.6	81.8	77.3	
DAS28-3 (CRP) </=3.2 Month 102 (N=13,3,16)	84.6	66.7	81.3	
DAS28-3 (CRP) </=3.2 Month 105 (N=12,2,14)	50.0	100	57.1	
DAS28-3 (CRP) </=3.2 Month 108 (N=7,1,8)	42.9	0	37.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Health Assessment Questionnaire – Disability Index (HAQ-DI) Score

End point title	Health Assessment Questionnaire – Disability Index (HAQ-DI) Score

End point description:

Change from baseline by visit. The stated number of participants analyzed was the total number of participants in each group. The actual number of participants analyzed on each occasion varied, and is provided for each visit presented.

End point type	Secondary
End point timeframe:	
Every visit until last observation	

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	1123	4481	
Units: Score				
arithmetic mean (standard deviation)				
Month 1 (N=1098,3264,4362)	-0.57 (± 0.62)	-0.61 (± 0.63)	-0.60 (± 0.63)	
Month 2 (N=1067,3213,4280)	-0.58 (± 0.62)	-0.65 (± 0.65)	-0.63 (± 0.65)	
Month 3 (N=1057,3196,4253)	-0.58 (± 0.63)	-0.66 (± 0.65)	-0.64 (± 0.65)	
Month 6 (N=1029,3105,4134)	-0.58 (± 0.65)	-0.65 (± 0.66)	-0.64 (± 0.66)	
Month 9 (N=990,2992,3982)	-0.58 (± 0.64)	-0.66 (± 0.66)	-0.64 (± 0.66)	
Month 12 (N=960,2866,3826)	-0.58 (± 0.65)	-0.66 (± 0.67)	-0.64 (± 0.67)	
Month 15 (N=926,2756,3682)	-0.61 (± 0.65)	-0.68 (± 0.68)	-0.66 (± 0.67)	
Month 18 (N=898,2646,3544)	-0.60 (± 0.65)	-0.68 (± 0.67)	-0.66 (± 0.67)	
Month 21 (N=849,2542,3391)	-0.60 (± 0.67)	-0.69 (± 0.68)	-0.67 (± 0.68)	
Month 24 (N=815,2443,3258)	-0.60 (± 0.65)	-0.69 (± 0.68)	-0.67 (± 0.67)	
Month 27 (N=789,2341,3130)	-0.62 (± 0.65)	-0.69 (± 0.68)	-0.67 (± 0.67)	
Month 30 (N=757,2258,3015)	-0.58 (± 0.66)	-0.68 (± 0.69)	-0.66 (± 0.68)	
Month 33 (N=741,2194,2935)	-0.60 (± 0.66)	-0.67 (± 0.69)	-0.66 (± 0.68)	
Month 36 (N=720,2136,2856)	-0.63 (± 0.66)	-0.67 (± 0.68)	-0.66 (± 0.67)	
Month 39 (N=683,2053,2736)	-0.59 (± 0.67)	-0.68 (± 0.69)	-0.66 (± 0.69)	
Month 42 (N=649,1884,2533)	-0.59 (± 0.67)	-0.66 (± 0.68)	-0.65 (± 0.68)	
Month 45 (N=609,1636,2245)	-0.59 (± 0.69)	-0.64 (± 0.69)	-0.63 (± 0.69)	
Month 48 (N=575,1468,2043)	-0.58 (± 0.69)	-0.64 (± 0.68)	-0.62 (± 0.68)	
Month 51 (N=482,1332,1814)	-0.59 (± 0.67)	-0.63 (± 0.66)	-0.62 (± 0.67)	
Month 54 (N=463,1191,1654)	-0.57 (± 0.68)	-0.65 (± 0.67)	-0.63 (± 0.67)	
Month 57 (N=434,1011,1445)	-0.57 (± 0.69)	-0.66 (± 0.68)	-0.63 (± 0.68)	
Month 60 (N=405,916,1321)	-0.59 (± 0.68)	-0.66 (± 0.69)	-0.64 (± 0.69)	
Month 63 (N=392,828,1220)	-0.57 (± 0.68)	-0.68 (± 0.70)	-0.64 (± 0.69)	
Month 66 (N=375,702,1077)	-0.54 (± 0.70)	-0.67 (± 0.69)	-0.63 (± 0.70)	
Month 69 (N=353,484,837)	-0.55 (± 0.70)	-0.66 (± 0.71)	-0.61 (± 0.71)	
Month 72 (N=335,286,621)	-0.57 (± 0.71)	-0.62 (± 0.73)	-0.59 (± 0.72)	
Month 75 (N=303,171,474)	-0.57 (± 0.72)	-0.58 (± 0.73)	-0.57 (± 0.72)	
Month 78 (N=289,91,380)	-0.54 (± 0.73)	-0.61 (± 0.78)	-0.56 (± 0.74)	
Month 81 (N=282,54,336)	-0.55 (± 0.73)	-0.64 (± 0.68)	-0.56 (± 0.72)	
Month 84 (N=269,44,313)	-0.53 (± 0.73)	-0.56 (± 0.68)	-0.53 (± 0.72)	
Month 87 (N=262,41,303)	-0.53 (± 0.70)	-0.53 (± 0.60)	-0.53 (± 0.69)	
Month 90 (240,39,279)	-0.52 (± 0.72)	-0.54 (± 0.61)	-0.52 (± 0.70)	
Month 93 (194,28,222)	-0.52 (± 0.75)	-0.50 (± 0.60)	-0.52 (± 0.73)	
Month 96 (N=143,16,159)	-0.54 (± 0.77)	-0.48 (± 0.58)	-0.53 (± 0.75)	
Month 99 (N=64,11,75)	-0.53 (± 0.80)	-0.44 (± 0.51)	-0.52 (± 0.76)	
Month 102 (N=22,3,25)	-0.61 (± 0.82)	-0.29 (± 0.85)	-0.58 (± 0.81)	
Month 105 (N=15,3,18)	-0.65 (± 0.91)	-0.50 (± 0.99)	-0.63 (± 0.90)	

Month 108 (N=8,1,9)	-0.89 (± 0.97)	0.13 (± 0)	-0.78 (± 0.97)	
Month 111 (N=3,1,4)	-1.29 (± 1.34)	0.25 (± 0)	-0.91 (± 1.34)	
Month 114 (N=1,0,1)	-0.13 (± 0)	0 (± 0)	-0.13 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Short-Form-36 Health Survey (SF-36) score

End point title	Short-Form-36 Health Survey (SF-36) score

End point description:

Change from Baseline for Physical Component and Mental Component Scores by visit. The stated number of participants analyzed was the total number of participants in each group. The actual number of participants analyzed on each occasion varied, and is provided for each visit presented.

End point type	Secondary

End point timeframe:

Every visit until last observation

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	3358	4481	
Units: Score				
arithmetic mean (standard deviation)				
Physical Component Month 3 (N=983,2693,3676)	7.90 (± 8.70)	8.85 (± 8.92)	8.60 (± 8.87)	
Physical Component Month 6 (N=961,2629,3590)	8.10 (± 8.94)	9.02 (± 9.11)	8.77 (± 9.07)	
Physical Component Month 9 (N=534,2499,3033)	8.60 (± 9.07)	8.80 (± 9.20)	8.77 (± 9.18)	
Physical Component Month 12 (N=903,2449,3352)	8.44 (± 8.53)	8.78 (± 9.26)	8.69 (± 9.07)	
Physical Component Month 15 (N=733,2324,3057)	8.43 (± 8.88)	8.98 (± 9.05)	8.85 (± 9.01)	
Physical Component Month 18 (N=855,2188,3043)	8.14 (± 8.89)	8.99 (± 9.18)	8.75 (± 9.11)	
Physical Component Month 21 (N=767,2005,2772)	8.00 (± 8.70)	8.85 (± 8.96)	8.62 (± 8.90)	
Physical Component Month 24(N=797,2102,2899)	8.28 (± 8.73)	9.00 (± 9.30)	8.80 (± 9.15)	
Physical Component Month 27(N=739,1663,2402)	8.41 (± 8.84)	8.64 (± 9.16)	8.57 (± 9.06)	
Physical Component Month 30 (N=708,1566,2274)	7.78 (± 8.81)	8.56 (± 9.06)	8.32 (± 8.99)	
Physical Component Month 33 (N=682,1444,2126)	8.17 (± 8.87)	8.39 (± 9.31)	8.32 (± 9.17)	
Physical Component Month 36 (N=676,1530,2206)	8.31 (± 8.97)	8.43 (± 9.22)	8.40 (± 9.14)	

Physical Component Month 39 (N=609,1176,1785)	8.05 (± 9.26)	8.13 (± 9.14)	8.10 (± 9.18)	
Physical Component Month 42 (N=573,923,1496)	7.81 (± 9.32)	8.07 (± 9.13)	7.97 (± 9.21)	
Physical Component Month 45 (N=540,652,1192)	8.40 (± 9.87)	8.33 (± 9.40)	8.36 (± 9.61)	
Physical Component Month 48 (N=537,1044,1581)	8.12 (± 9.56)	8.27 (± 9.23)	8.22 (± 9.34)	
Physical Component Month 51 (N=417,304,721)	7.88 (± 9.69)	8.55 (± 9.70)	8.16 (± 9.69)	
Physical Component Month 54 (N=396,175,571)	7.72 (± 9.41)	8.82 (± 9.47)	8.06 (± 9.43)	
Physical Component Month 57 (N=372,105,477)	7.57 (± 9.72)	8.12 (± 9.69)	7.69 (± 9.71)	
Physical Component Month 60 (N=371,259,630)	7.94 (± 9.74)	9.29 (± 9.43)	8.49 (± 9.63)	
Physical Component Month 63 (N=345,68,413)	7.73 (± 9.76)	7.90 (± 8.98)	7.76 (± 9.63)	
Physical Component Month 66 (N=327,56,383)	7.92 (± 9.41)	7.58 (± 7.88)	7.87 (± 9.20)	
Physical Component Month 69 (N=267,40,307)	7.68 (± 9.32)	9.12 (± 7.06)	7.87 (± 9.06)	
Physical Component Month 72 (N=316,54,370)	7.90 (± 9.93)	8.70 (± 10.24)	8.02 (± 9.97)	
Physical Component Month 75 (N=84,12,96)	9.03 (± 10.96)	5.75 (± 9.05)	8.62 (± 10.75)	
Physical Component Month 78 (N=55,7,62)	10.22 (± 11.10)	7.39 (± 7.09)	9.90 (± 10.72)	
Physical Component Month 81 (N=49,4,53)	10.51 (± 10.17)	7.90 (± 13.05)	10.31 (± 10.28)	
Physical Component Month 84 (N=93,11,104)	8.93 (± 11.56)	7.14 (± 8.01)	8.74 (± 11.22)	
Physical Component Month 87 (N=26,2,28)	11.92 (± 10.49)	15.23 (± 3.64)	12.16 (± 10.15)	
Physical Component Month 90 (N=12,1,13)	13.50 (± 10.98)	16.50 (± 0)	13.73 (± 10.55)	
Physical Component Month 93 (N=1,0,1)	26.71 (± 0)	0 (± 0)	26.71 (± 0)	
Physical Component Month 96 (N=5,0,5)	4.61 (± 9.75)	0 (± 0)	4.61 (± 9.75)	
Physical Component Month 99 (N=1,0,1)	-8.26 (± 0)	0 (± 0)	-8.26 (± 0)	
Mental Component Month 3 (N=983,2693,3676)	4.37 (± 10.88)	4.91 (± 11.18)	4.77 (± 11.10)	
Mental Component Month 6 (N=961,2629,3590)	3.94 (± 10.85)	4.81 (± 11.12)	4.58 (± 11.06)	
Mental Component Month 9 (N=534,2499,3033)	4.65 (± 10.78)	5.04 (± 11.17)	4.97 (± 11.10)	
Mental Component Month 12 (N=903,2449,3352)	3.77 (± 11.03)	4.81 (± 11.43)	4.53 (± 11.33)	
Mental Component Month 15 (N=733,2324,3057)	4.14 (± 11.21)	4.79 (± 11.52)	4.63 (± 11.45)	
Mental Component Month 18 (N=855,2188,3043)	4.12 (± 11.11)	4.87 (± 11.41)	4.66 (± 11.33)	
Mental Component Month 21 (N=767,2005,2772)	4.21 (± 11.08)	4.87 (± 11.22)	4.68 (± 11.18)	
Mental Component Month 24 (N=797,2102,2899)	4.12 (± 11.06)	5.08 (± 11.32)	4.82 (± 11.26)	
Mental Component Month 27 (N=739,1663,2402)	3.67 (± 10.53)	4.91 (± 11.28)	4.53 (± 11.07)	
Mental Component Month 30 (N=708,1566,2274)	3.58 (± 11.14)	4.68 (± 11.71)	4.34 (± 11.54)	

Mental Component Month 33 (N=682,1444,2126)	3.91 (± 10.65)	4.82 (± 11.74)	4.53 (± 11.40)	
Mental Component Month 36 (N=676,1530,2206)	3.83 (± 10.94)	4.81 (± 11.60)	4.51 (± 11.40)	
Mental Component Month 39 (N=609,1176,1785)	3.60 (± 11.02)	4.59 (± 11.75)	4.25 (± 11.51)	
Mental Component Month 42 (N=573,923,1496)	3.23 (± 11.40)	4.55 (± 11.63)	4.04 (± 11.56)	
Mental Component Month 45 (N=540,652,1192)	3.16 (± 11.63)	4.40 (± 11.64)	3.83 (± 11.56)	
Mental Component Month 48 (N=537,1044,1581)	3.48 (± 11.71)	4.73 (± 11.83)	4.31 (± 11.80)	
Mental Component Month 51 (N=417,304,721)	3.61 (± 12.12)	4.83 (± 11.82)	4.13 (± 12.00)	
Mental Component Month 54 (N=396,175,571)	3.44 (± 11.77)	6.49 (± 12.67)	4.38 (± 12.12)	
Mental Component Month 57 (N=372,105,477)	3.24 (± 12.24)	5.10 (± 11.74)	3.65 (± 12.15)	
Mental Component Month 60 (N=371,259,630)	3.05 (± 12.06)	5.18 (± 12.22)	3.93 (± 12.16)	
Mental Component Month 63 (N=345,68,413)	3.04 (± 11.61)	4.22 (± 10.32)	3.23 (± 11.40)	
Mental Component Month 66 (N=327,56,383)	2.96 (± 11.32)	3.47 (± 8.33)	3.04 (± 10.93)	
Mental Component Month 69 (N=267,40,307)	3.90 (± 12.35)	4.90 (± 9.84)	4.03 (± 12.04)	
Mental Component Month 72 (N=316,54,370)	3.78 (± 11.48)	5.32 (± 12.80)	4.00 (± 11.68)	
Mental Component Month 75 (N=84,12,96)	5.04 (± 12.22)	1.52 (± 11.38)	4.60 (± 12.12)	
Mental Component Month 78 (N=55,7,62)	4.12 (± 13.37)	1.05 (± 13.28)	3.77 (± 13.29)	
Mental Component Month 81 (N=49,4,53)	6.09 (± 10.40)	2.60 (± 14.75)	5.83 (± 10.64)	
Mental Component Month 84 (N=93,11,104)	5.73 (± 13.07)	-2.36 (± 11.63)	4.87 (± 13.11)	
Mental Component Month 87 (N=26,2,28)	7.52 (± 13.03)	16.93 (± 2.66)	8.19 (± 12.79)	
Mental Component Month 90 (N=12,1,13)	4.61 (± 11.75)	18.75 (± 0)	5.65 (± 11.86)	
Mental Component Month 93 (N=1,0,1)	14.03 (± 0)	0 (± 0)	14.03 (± 0)	
Mental Component Month 96 (N=5,0,5)	7.58 (± 9.73)	0 (± 0)	7.58 (± 9.73)	
Mental Component Month 99 (N=1,0,1)	22.28 (± 0)	0 (± 0)	22.28 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: FACIT Fatigue Scale, EuroQol EQ 5D, Work Limitations Questionnaire, and RA Healthcare Resource Utilization Questionnaire (RA-HCRU)

End point title	FACIT Fatigue Scale, EuroQol EQ 5D, Work Limitations Questionnaire, and RA Healthcare Resource Utilization Questionnaire (RA-HCRU)

End point description:

Change from Baseline Scores for FACIT Fatigue Scale, EuroQol EQ 5D, Work Limitations (WL) Physical Demands, and RA Healthcare Resource Utilization Work Performance in Past 3 Months on Days Bothered by RA. The stated number of participants analyzed was the total number of participants in each group.

The actual number of participants analyzed on each occasion varied, and is provided for each visit presented.

End point type	Secondary
End point timeframe:	
Every visit until last observation	

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	3358	4481	
Units: Score				
arithmetic mean (standard deviation)				
FACIT Month 6 (N=370,2544,2914)	6.29 (± 8.98)	7.33 (± 10.57)	7.19 (± 10.39)	
FACIT Month 12 (N=582,2396,2978)	5.98 (± 9.74)	7.33 (± 10.56)	7.06 (± 10.41)	
FACIT Month 18 (N=729,2168,2897)	6.14 (± 10.06)	7.40 (± 10.65)	7.09 (± 10.51)	
FACIT Month 24 (N=704,2053,2757)	5.90 (± 9.76)	7.42 (± 10.56)	7.03 (± 10.38)	
FACIT Month 30 (N=618,1525,2143)	5.36 (± 10.08)	7.00 (± 10.91)	6.52 (± 10.70)	
FACIT Month 36 (N=589,1497,2086)	5.95 (± 9.87)	6.87 (± 10.94)	6.61 (± 10.66)	
FACIT Month 42 (N=491,898,1389)	5.35 (± 10.36)	6.83 (± 10.86)	6.31 (± 10.71)	
FACIT Month 48 (N=464,1025,1489)	6.01 (± 10.33)	6.88 (± 10.95)	6.61 (± 10.77)	
FACIT Month 54 (N=330,169,499)	6.16 (± 10.49)	8.51 (± 11.58)	6.96 (± 10.92)	
FACIT Month 60 (N=318,256,574)	5.96 (± 10.69)	8.88 (± 11.65)	7.27 (± 11.21)	
FACIT Month 66 (N=277,55,332)	5.64 (± 10.93)	6.67 (± 10.58)	5.81 (± 10.86)	
FACIT Month 72 (N=272,51,323)	5.73 (± 11.10)	8.63 (± 10.71)	6.18 (± 11.07)	
FACIT Month 78 (N=32,7,39)	12.06 (± 11.15)	0.71 (± 14.84)	10.03 (± 12.48)	
FACIT Month 84 (N=74,11,85)	9.13 (± 12.88)	2.91 (± 12.36)	8.32 (± 12.91)	
FACIT Month 90 (N=6,1,7)	18.67 (± 9.14)	10.00 (± 0)	17.43 (± 8.96)	
FACIT Month 96 (N=3,0,3)	6.00 (± 2.65)	0 (± 0)	6.00 (± 2.65)	
EuroQol Month 6 (N=323,2021,2344)	0.20 (± 0.31)	0.22 (± 0.32)	0.22 (± 0.32)	
EuroQol Month 12 (N=538,1897,2435)	0.22 (± 0.30)	0.22 (± 0.33)	0.22 (± 0.32)	
EuroQol Month 18 (N=684,1748,2432)	0.20 (± 0.32)	0.23 (± 0.33)	0.22 (± 0.33)	
EuroQol Month 24 (N=664,1619,2283)	0.20 (± 0.31)	0.23 (± 0.33)	0.22 (± 0.32)	
EuroQol Month 30 (N=616,1456,2072)	0.19 (± 0.31)	0.22 (± 0.33)	0.21 (± 0.32)	
EuroQol Month 36 (N=582,1397,1979)	0.21 (± 0.30)	0.23 (± 0.33)	0.22 (± 0.32)	
EuroQol Month 42 (N=483,874,1357)	0.18 (± 0.31)	0.24 (± 0.33)	0.22 (± 0.32)	
EuroQol Month 48 (N=464,1010,1474)	0.19 (± 0.31)	0.23 (± 0.33)	0.22 (± 0.32)	
EuroQol Month 54 (N=330,167,497)	0.22 (± 0.32)	0.32 (± 0.36)	0.22 (± 0.32)	
EuroQol Month 60 (N=317,255,572)	0.20 (± 0.33)	0.27 (± 0.35)	0.23 (± 0.34)	
EuroQol Month 66 (N=276,53,329)	0.21 (± 0.33)	0.24 (± 0.34)	0.21 (± 0.33)	
EuroQol Month 72 (N=273,50,323)	0.22 (± 0.32)	0.28 (± 0.35)	0.23 (± 0.32)	
EuroQol Month 78 (N=32,7,39)	0.36 (± 0.37)	0.10 (± 0.51)	0.31 (± 0.40)	
EuroQol Month 84 (N=75,11,86)	0.27 (± 0.35)	0.21 (± 0.43)	0.27 (± 0.36)	
EuroQol Month 90 (N=6,1,7)	0.47 (± 0.32)	0.84 (± 0)	0.52 (± 0.32)	
EuroQol Month 96 (N=3,0,3)	0.09 (± 0.04)	0 (± 0)	0.09 (± 0.04)	
WL: Physical Demands Month 6 (N=109,900,1009)	-5.34 (± 39.81)	-3.67 (± 38.17)	-3.85 (± 38.33)	

WL: Physical Demands Month 12 (N=96,808,904)	-5.31 (± 37.81)	-4.02 (± 39.25)	-4.16 (± 39.08)	
WL: Physical Demands Month 18 (N=83,706,789)	-7.97 (± 35.46)	-2.29 (± 37.48)	-2.89 (± 37.29)	
WL: Physical Demands Month 24 (N=63,544,607)	-2.62 (± 36.05)	-4.46 (± 37.54)	-4.27 (± 37.36)	
WL: Physical Demands Month 30 (N=51,444,495)	-10.12 (± 37.17)	-3.75 (± 37.67)	-4.41 (± 37.63)	
WL: Physical Demands Month 36 (N=35,350,385)	-7.31 (± 34.69)	-3.95 (± 39.58)	-4.25 (± 39.14)	
WL: Physical Demands Month 42 (N=24,245,270)	-13.51 (± 33.91)	-4.81 (± 38.98)	-5.58 (± 38.58)	
WL: Physical Demands Month 48 (N=19,126,145)	-25.86 (± 34.47)	0.73 (± 38.68)	-2.76 (± 39.09)	
WL: Physical Demands Month 54 (N=2,20,22)	-39.17 (± 62.46)	-13.27 (± 45.69)	-15.63 (± 46.18)	
WL: Physical Demands Month 60 (N=0,3,3)	0 (± 0)	-27.78 (± 34.94)	-27.78 (± 34.94)	
WL: Physical Demands Month 66 (N=0,1,1)	0 (± 0)	8.33 (± 0)	8.33 (± 0)	
RA-HCRU Month 6 (N=189,1419,1608)	-2.01 (± 6.20)	-2.08 (± 4.15)	-2.07 (± 4.44)	
RA-HCRU Month 12 (N=180,1329,1509)	-2.41 (± 6.43)	-2.26 (± 3.76)	-2.28 (± 4.17)	
RA-HCRU Month 18 (N=161,1162,1323)	-1.88 (± 2.93)	-2.24 (± 3.90)	-2.19 (± 3.80)	
RA-HCRU Month 24 (N=162,1101,1263)	-2.03 (± 3.18)	-2.22 (± 3.26)	-2.19 (± 3.25)	
RA-HCRU Month 30 (N=126,785,911)	-1.67 (± 3.02)	-2.16 (± 4.17)	-2.10 (± 4.04)	
RA-HCRU Month 36 (N=106,759,865)	-2.38 (± 2.91)	-2.32 (± 4.14)	-2.33 (± 4.01)	
RA-HCRU Month 42 (N=68,455,523)	-1.68 (± 2.84)	-2.18 (± 4.70)	-2.11 (± 4.51)	
RA-HCRU Month 48 (N=66,527,593)	-1.88 (± 3.24)	-2.15 (± 4.67)	-2.12 (± 4.53)	
RA-HCRU Month 54 (N=3,39,42)	-2.00 (± 1.00)	-2.59 (± 3.42)	-2.55 (± 3.30)	
RA-HCRU Month 60 (N=4,94,98)	-2.00 (± 3.56)	-2.88 (± 2.85)	-2.85 (± 2.87)	
RA-HCRU Month 66 (N=0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	
RA-HCRU Month 72 (N=0,4,4)	0 (± 0)	-1.25 (± 6.70)	-1.25 (± 6.70)	
RA-HCRU Month 78 (0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	
RA-HCRU Month 84 (0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	
RA-HCRU Month 90 (0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	
RA-HCRU Month 96 (0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Preservation of joint structure in participants who had baseline radiographs obtained in their qualifying index study

End point title	Preservation of joint structure in participants who had baseline radiographs obtained in their qualifying index study

End point description:

Modified Total Sharp Score per visit. Baseline score was the last available assessment from the index study. The stated number of participants analyzed was the total number of participants in each group. The actual number of participants analyzed on each occasion varied, and is provided for each visit presented. TSS=Total Sharp Score

End point type	Secondary

End point timeframe:

Every 6 months until last observation

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1123	3358	4481	
Units: Score				
arithmetic mean (standard deviation)				
Modified TSS Baseline (N=95,1061,1156)	20.55 (± 33.37)	24.13 (± 43.57)	23.84 (± 42.83)	
Modified TSS Month 6 (N=82,937,1019)	22.58 (± 35.10)	25.12 (± 44.42)	24.91 (± 43.74)	
Modified TSS Month 12 (N=85,918,1003)	21.26 (± 33.75)	24.73 (± 44.08)	24.44 (± 43.30)	
Modified TSS Month 24 (N=77,801,878)	22.07 (± 35.85)	24.85 (± 43.21)	24.61 (± 42.61)	
Modified TSS Month 36 (N=35,379,414)	25.88 (± 37.74)	28.22 (± 44.95)	28.02 (± 44.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Percent achieving a satisfactory humoral response to the pneumococcal vaccine as defined by ≥ 2-fold increase in antibody concentrations

End point title	Vaccine sub-study. Percent achieving a satisfactory humoral response to the pneumococcal vaccine as defined by ≥ 2-fold increase in antibody concentrations

End point description:

Number (%) of participants achieving a satisfactory humoral response to the pneumococcal vaccine as defined by ≥2-fold increase in antibody concentration from vaccine sub-study visit 2 (vaccination baseline) in ≥6 of 12 anti-pneumococcal antigens (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) The number of participants was the number with a determinate antibody titer to the given vaccine antigen within the population. 95% CI is based on Clopper-Pearson exact method for response rate. Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Continuous Visit 3	Tofacitinib 10 mg BID Interrupted Visit 3	Tofacitinib 10 mg BID Continuous Visit 4	Tofacitinib 10 mg BID Interrupted Visit 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	91	91	92	91
Units: Percent of participants				
number (confidence interval 95%)	18.7 (11.3 to	38.5 (28.4 to	75.0 (64.9 to	84.6 (75.5 to

28.2)	49.2)	83.4)	91.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Percent achieving a satisfactory humoral response to the seasonal influenza vaccine as defined by ≥ 4-fold increase in antibody titers

End point title	Vaccine sub-study. Percent achieving a satisfactory humoral response to the seasonal influenza vaccine as defined by ≥ 4-fold increase in antibody titers

End point description:

Number of participants achieving a satisfactory humoral response to the seasonal influenza vaccine as defined by ≥4-fold increase in antibody titers from visit 2 (vaccination baseline) in ≥2 of 3 influenza antigens (HAI B, HAI H1N1, and HAI H3N2) The number of participants was the number with a determinate antibody titer to the given vaccine antigen within the population. 95% CI is based on Clopper-Pearson exact method for response rate.
Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Continuous Visit 3	Tofacitinib 10 mg BID Interrupted Visit 3	Tofacitinib 10 mg BID Continuous Visit 4	Tofacitinib 10 mg BID Interrupted Visit 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	91	91	92	91
Units: Percent of participants				
number (confidence interval 95%)	31.9 (22.5 to 42.5)	53.8 (43.1 to 64.4)	66.3 (55.7 to 75.8)	63.7 (53.0 to 73.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Percentage of participants achieving protective antibody titers to the seasonal influenza vaccine as measured by a hemagglutination inhibition (HI) assay titer of ≥ 1:40 in ≥ 2 of 3 influenza antigens at vaccine sub-study visit 3 and 4

End point title	Vaccine sub-study. Percentage of participants achieving protective antibody titers to the seasonal influenza vaccine as measured by a hemagglutination inhibition (HI) assay titer of ≥ 1:40 in ≥ 2 of 3 influenza antigens at vaccine sub-study visit 3 and 4

End point description:

Number (%) of participants achieving protective antibody titers to the seasonal influenza vaccine as

measured by an HAI assay titer of ≥1:40 in ≥2 of 3 influenza antigens measured at vaccine sub-study visits 3 and 4. The number of participants was the number with a determinate antibody titer to the given vaccine antigen within the population. 95% CI is based on Clopper-Pearson exact method for response rate.
Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Continuous Visit 3	Tofacitinib 10 mg BID Interrupted Visit 3	Tofacitinib 10 mg BID Continuous Visit 4	Tofacitinib 10 mg BID Interrupted Visit 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	91	91	92	91
Units: Percent of participants				
number (confidence interval 95%)	56.0 (45.2 to 66.4)	69.2 (58.7 to 78.5)	75.0 (64.9 to 83.4)	82.4 (73.0 to 89.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Percentage of participants who respond to each of the 12 pneumococcal antigens as defined by ≥ 2-fold increase in antibody concentrations from vaccine sub-study visit 2 (vaccination baseline) measured at vaccine sub-study visit 4

End point title	Vaccine sub-study. Percentage of participants who respond to each of the 12 pneumococcal antigens as defined by ≥ 2-fold increase in antibody concentrations from vaccine sub-study visit 2 (vaccination baseline) measured at vaccine sub-study visit 4

End point description:

Number (%) of participants achieving a satisfactory humoral response to the pneumococcal vaccine as defined by ≥2-fold increase in antibody concentration from vaccine sub-study visit 2 (vaccination baseline) in ≥6 of 12 anti-pneumococcal antigens (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) The number of participants was the number with a determinate antibody titer to the given vaccine antigen within the population. 95% CI is based on Clopper-Pearson exact method for response rate.
Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Continuous	Tofacitinib 10 mg BID Interrupted		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	91		
Units: Percent of participants				
number (confidence interval 95%)				
Serotype 1	75 (64.9 to 83.4)	82.4 (73.0 to 89.6)		
Serotype 3	53.3 (42.6 to 63.7)	71.4 (61.0 to 80.4)		
Serotype 4	76.1 (66.1 to 84.4)	76.9 (66.9 to 85.1)		
Serotype 5	42.4 (32.1 to 53.1)	49.5 (38.8 to 60.1)		
Serotype 6B	48.9 (38.3 to 59.6)	56 (45.2 to 66.4)		
Serotype 7F	71.7 (61.4 to 80.6)	78 (68.1 to 86.0)		
Serotype 9V	64.1 (53.5 to 73.9)	78 (68.1 to 86.0)		
Serotype 14	71.7 (61.4 to 80.6)	75.8 (65.7 to 84.2)		
Serotype 18C	73.9 (63.7 to 82.5)	83.5 (74.3 to 90.5)		
Serotype 19A	54.3 (43.6 to 64.8)	56.0 (45.2 to 66.4)		
Serotype 19F	60.9 (50.1 to 70.9)	71.4 (61.0 to 80.4)		
Serotype 23F	53.3 (42.6 to 63.7)	70.3 (59.8 to 79.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Percentage of participants who respond to each of the 3 influenza antigens as defined by ≥ 4-fold increase in antibody titers from vaccine sub-study visit 2 (vaccination baseline) measured at vaccine sub-study visit 4

End point title	Vaccine sub-study. Percentage of participants who respond to each of the 3 influenza antigens as defined by ≥ 4-fold increase in antibody titers from vaccine sub-study visit 2 (vaccination baseline) measured at vaccine sub-study visit 4

End point description:

Number (%) of participants achieving a satisfactory humoral response to the seasonal influenza vaccine defined as ≥4-fold increase in antibody titers from visit 2 (vaccination baseline) in ≥2 of 3 influenza antigens (HAI B, HAI H1N1, and HAI H3N2). The number of participants was the number with a determinate antibody titer to the given vaccine antigen within the population. 95% CI is based on Clopper-Pearson exact method for response rate.
Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Continuous Visit 4	Tofacitinib 10 mg BID Interrupted Visit 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	91		
Units: Percent of participants				
number (confidence interval 95%)				
Antigen B	45.7 (35.2 to 56.4)	51.6 (40.9 to 62.3)		
Antigen H1N1	71.7 (61.4 to 80.6)	63.7 (53.0 to 73.6)		
Antigen H3N2	66.3 (55.7 to 75.8)	74.7 (64.5 to 83.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Fold increase of anti-pneumococcal antibody levels to each of the 12 pneumococcal antigens above vaccination baseline values (vaccine sub-study visit 2) at vaccine sub-study visit 4

End point title	Vaccine sub-study. Fold increase of anti-pneumococcal antibody levels to each of the 12 pneumococcal antigens above vaccination baseline values (vaccine sub-study visit 2) at vaccine sub-study visit 4

End point description:

Geometric Mean Fold Increase From Baseline of Pneumococcal Antigens Measured at Visit 4. n was the number of participants with valid and determinate assay results for the specified serotype at the given visit. The stated number of participants analyzed was the total number of participants. The actual number of participants analyzed for some serotypes varied, and is provided where it differed from the total number of participants. Confidence Intervals (CIs) were back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations.
Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Interrupted	Tofacitinib 10 mg Continuous		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	92		
Units: Antibody Level				
geometric mean (confidence interval 95%)				
Serotype 1 (N=89,86)	9.26 (6.89 to 12.44)	5.87 (4.57 to 7.55)		

Serotype 3 (N=91,89)	4.20 (3.31 to 5.32)	2.34 (1.97 to 2.79)		
Serotype 4 (N=91,89)	6.29 (4.65 to 8.51)	5.32 (4.22 to 6.71)		
Serotype 5	2.53 (2.12 to 3.02)	2.02 (1.75 to 2.34)		
Serotype 6B	3.06 (2.53 to 3.69)	2.32 (1.98 to 2.73)		
Serotype 7F (N=92,89)	6.41 (4.97 to 8.28)	4.69 (3.73 to 5.90)		
Serotype 9V (N=92,90)	4.39 (3.62 to 5.34)	3.17 (2.70 to 3.72)		
Serotype 14	7.34 (5.50 to 9.79)	5.23 (4.00 to 6.86)		
Serotype 18C	7.41 (5.77 to 9.53)	3.97 (3.28 to 4.79)		
Serotype 19A	2.93 (2.46 to 3.50)	2.33 (1.99 to 2.72)		
Serotype 19F (N=90,90)	4.60 (3.64 to 5.80)	2.97 (2.44 to 3.62)		
Serotype 23F (N=92,90)	4.54 (3.58 to 5.75)	2.74 (2.27 to 3.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Fold increase of anti-influenza antibody levels to each of the 3 influenza antigens above vaccination baseline values (vaccine sub-study visit 2) at vaccine sub-study visit 4

End point title	Vaccine sub-study. Fold increase of anti-influenza antibody levels to each of the 3 influenza antigens above vaccination baseline values (vaccine sub-study visit 2) at vaccine sub-study visit 4

End point description:

Geometric Mean Fold Increase From Baseline of Influenza Antigens Measured at Visit 4. n was the number of participants with valid and determinate assay results for the specified HAI strain at the given visit. Confidence Intervals (CIs) were back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Continuous	Tofacitinib 10 mg BID Interrupted		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	91		
Units: Antibody titer				
geometric mean (confidence interval 95%)				
Antigen B	3.33 (2.57 to 4.32)	4.17 (3.25 to 5.34)		

Antigen H1N1	7.94 (5.96 to 10.58)	6.71 (4.94 to 9.12)		
Antigen H3N2	7.80 (5.58 to 10.91)	8.51 (6.45 to 11.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Concentrations of anti-pneumococcal antibodies at vaccine sub-study visit 3 and 4

End point title	Vaccine sub-study. Concentrations of anti-pneumococcal antibodies at vaccine sub-study visit 3 and 4

End point description:

Mean pneumococcal concentrations (ug/mL) at vaccine baseline (visit 2) and post-vaccination visits (visits 3 and 4) by serotype. The stated number of participants analyzed was the total number of participants in each group. The actual number of participants analyzed for each serotype varied, and is provided for each individually. ug/mL=micrograms per milliliter
Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Interrupted Visit 3	Tofacitinib 10 mg BID Continuous Visit 4	Tofacitinib 10 mg BID Interrupted Visit 4	Tofacitinib 10 mg BID Continuous Visit 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	91	92	91	92
Units: Concentration (ug/mL)				
geometric mean (confidence interval 95%)				
Serotype 9V (N=92,90,91,91,92,91)	2.26 (1.78 to 2.87)	4.16 (3.29 to 5.27)	4.80 (3.75 to 6.16)	1.31 (1.08 to 1.60)
Serotype 14 (N=92,91,91,91,92,91)	5.03 (3.77 to 6.71)	12.09 (8.76 to 16.69)	15.01 (10.80 to 20.88)	2.31 (1.79 to 2.98)
Serotype 18C (N=92,91,91,91,92,91)	2.41 (1.82 to 3.18)	4.27 (3.34 to 5.47)	6.61 (5.01 to 8.74)	1.08 (0.86 to 1.36)
Serotype 19F (N=90,90,90,91,92,91)	2.17 (1.61 to 2.91)	3.52 (2.60 to 4.76)	5.47 (3.98 to 7.52)	1.17 (0.92 to 1.50)
Serotype 23F (92,90,90,91,92,91)	2.24 (1.75 to 2.88)	3.44 (2.66 to 4.44)	5.27 (3.96 to 7.02)	1.25 (1.01 to 1.56)

End point values	Tofacitinib 10 mg BID Interrupted Visit 2	Tofacitinib 10 mg BID Continuous Visit 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	92		
Units: Concentration (ug/mL)				

geometric mean (confidence interval 95%)				
Serotype 9V (N=92,90,91,91,92,91)	1.12 (0.89 to 1.42)	2.00 (1.64 to 2.44)		
Serotype 14 (N=92,91,91,91,92,91)	2.05 (1.59 to 2.63)	4.02 (3.04 to 5.32)		
Serotype 18C (N=92,91,91,91,92,91)	0.89 (0.70 to 1.14)	1.81 (1.43 to 2.29)		
Serotype 19F (N=90,90,90,91,92,91)	1.18 (0.89 to 1.58)	1.61 (1.25 to 2.08)		
Serotype 23F (92,90,90,91,92,91)	1.16 (0.93 to 1.44)	1.80 (1.44 to 2.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine sub-study. Titers of anti-influenza antibodies at vaccine sub-study visit 3 and 4

End point title	Vaccine sub-study. Titers of anti-influenza antibodies at vaccine sub-study visit 3 and 4

End point description:

Mean influenza antibody titers at visits 3 and 4.
Evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

From vaccine sub-study visit 2 (baseline) to sub-study visit 4

End point values	Tofacitinib 10 mg BID Continuous Visit 3	Tofacitinib 10 mg BID Interrupted Visit 3	Tofacitinib 10 mg BID Continuous Visit 4	Tofacitinib 10 mg BID Interrupted Visit 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	91	91	92	91
Units: Antibody Titer				
geometric mean (confidence interval 95%)				
HAI B	23.29 (17.92 to 30.27)	37.45 (28.17 to 49.78)	38.06 (28.71 to 50.47)	45.19 (35.01 to 58.34)
HAI H1N1	52.75 (37.97 to 73.28)	105.2 (70.76 to 156.5)	120.2 (89.83 to 160.8)	136.0 (97.67 to 189.4)
HAI H3N2	55.07 (38.19 to 79.43)	83.10 (57.38 to 120.4)	141.8 (102.9 to 195.4)	147.2 (107.8 to 201.0)

End point values	Tofacitinib 10 mg BID Continuous Visit 2	Tofacitinib 10 mg BID Interrupted Visit 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	91		

Units: Antibody Titer				
geometric mean (confidence interval 95%)				
HAI B	11.43 (9.38 to 13.91)	10.85 (8.90 to 13.22)		
HAI H1N1	15.14 (11.67 to 19.64)	20.26 (14.86 to 27.62)		
HAI H3N2	18.18 (13.53 to 24.44)	17.30 (12.98 to 23.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under American College of Rheumatology (ACR) n curve

End point title	Area under American College of Rheumatology (ACR) n curve

End point description:

No data was analyzed for this endpoint because it was removed from the protocol in a previous amendment.

End point type	Secondary

End point timeframe:

Every visit until last observation

End point values	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Not applicable				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[3] - No data analyzed for this endpoint as it was removed in a previous protocol amendment.

[4] - No data analyzed for this endpoint as it was removed in a previous protocol amendment.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
114 months	
Adverse event reporting additional description:	
Events listed by Preferred Term. Includes data up to 999 days after last dose of study medication	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Tofa 5mg BID; ppts with avg total daily dose across study <15
Reporting group description:	
Participants with non-zero average total daily dose across study <15 were assigned to 5 mg BID. avg=average; BID=twice daily; mg=milligram; ppts=participants; tofa=tofacitinib	
Reporting group title	Tofa 10mg BID; ppts with avg total daily dose across study ≥15
Reporting group description:	
Participants with non-zero average total daily dose across study ≥15 were assigned to 10 mg BID. avg=average; BID=twice daily; mg=milligram; ppts=participants; tofa=tofacitinib	
Reporting group title	All Tofacitinib
Reporting group description:	
All participants treated with tofacitinib from 5 mg BID and 10 mg BID groups	

Serious adverse events	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib
Total subjects affected by serious adverse events			
subjects affected / exposed	346 / 1123 (30.81%)	997 / 3358 (29.69%)	1343 / 4481 (29.97%)
number of deaths (all causes)	39	46	85
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
5q minus syndrome			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute promyelocytic leukaemia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Adenocarcinoma of appendix			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of the cervix			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal adenoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell small lymphocytic lymphoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	3 / 1123 (0.27%)	12 / 3358 (0.36%)	15 / 4481 (0.33%)
occurrences causally related to treatment / all	1 / 3	6 / 12	7 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign tracheal neoplasm			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	4 / 1123 (0.36%)	12 / 3358 (0.36%)	16 / 4481 (0.36%)
occurrences causally related to treatment / all	1 / 4	6 / 12	7 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Bronchial carcinoma			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	2 / 3	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma stage 0			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholesteatoma			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choroid plexus papilloma			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Colon cancer metastatic			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			

subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer stage I			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extranodal marginal zone B-cell lymphoma (MALT type)			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibroadenoma of breast			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibroma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder cancer			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Gastric cancer			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma multiforme			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Hepatic cancer			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hodgkin’s disease			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	2 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kaposi’s sarcoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyosarcoma			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposarcoma			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	3 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	2 / 2	2 / 2
Lung cancer metastatic			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	2 / 3	2 / 3
Lung neoplasm			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	2 / 1123 (0.18%)	3 / 3358 (0.09%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 2	1 / 3	1 / 5
Lymphoma			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	3 / 1123 (0.27%)	8 / 3358 (0.24%)	11 / 4481 (0.25%)
occurrences causally related to treatment / all	2 / 3	7 / 8	9 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mantle cell lymphoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Marginal zone lymphoma stage II			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medullary thyroid cancer			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Metastases to liver			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Metastases to lung			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Metastases to lymph nodes			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Metastasis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucoepidermoid carcinoma			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodular melanoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin’s lymphoma			
subjects affected / exposed	2 / 1123 (0.18%)	2 / 3358 (0.06%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 2	1 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Oesophageal carcinoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian adenoma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer metastatic			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian germ cell teratoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 1123 (0.00%)	7 / 3358 (0.21%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 0	2 / 7	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Renal cell carcinoma			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sebaceous carcinoma			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Small intestine carcinoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spindle cell sarcoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	2 / 1123 (0.18%)	10 / 3358 (0.30%)	12 / 4481 (0.27%)
occurrences causally related to treatment / all	1 / 2	6 / 10	7 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	2 / 1123 (0.18%)	2 / 3358 (0.06%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	2 / 2	1 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Squamous cell carcinoma of skin			

subjects affected / exposed	3 / 1123 (0.27%)	4 / 3358 (0.12%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	3 / 3	0 / 5	3 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the vulva			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial sarcoma			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
T-cell lymphoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid adenoma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid neoplasm			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour necrosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteral neoplasm			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	7 / 1123 (0.62%)	14 / 3358 (0.42%)	21 / 4481 (0.47%)
occurrences causally related to treatment / all	0 / 7	1 / 14	1 / 21
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval cancer stage 0			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	2 / 1123 (0.18%)	3 / 3358 (0.09%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			

subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Circulatory collapse			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Deep vein thrombosis			
subjects affected / exposed	6 / 1123 (0.53%)	9 / 3358 (0.27%)	15 / 4481 (0.33%)
occurrences causally related to treatment / all	3 / 7	3 / 10	6 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	3 / 1123 (0.27%)	7 / 3358 (0.21%)	10 / 4481 (0.22%)
occurrences causally related to treatment / all	0 / 4	2 / 8	2 / 12
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hypertensive crisis			
subjects affected / exposed	3 / 1123 (0.27%)	8 / 3358 (0.24%)	11 / 4481 (0.25%)
occurrences causally related to treatment / all	3 / 5	4 / 10	7 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Thromboangiitis obliterans			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	0 / 1123 (0.00%)	5 / 3358 (0.15%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Arthrodesis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal death			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unintended pregnancy			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Abscess sterile			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	5 / 1123 (0.45%)	12 / 3358 (0.36%)	17 / 4481 (0.38%)
occurrences causally related to treatment / all	0 / 5	0 / 12	0 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	3 / 1123 (0.27%)	1 / 3358 (0.03%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	3 / 3	1 / 1	4 / 4
Drug ineffective			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gait disturbance			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 1123 (0.18%)	2 / 3358 (0.06%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	1 / 2	1 / 2	2 / 4
deaths causally related to treatment / all	1 / 2	2 / 2	3 / 4
Non-cardiac chest pain			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 1123 (0.45%)	5 / 3358 (0.15%)	10 / 4481 (0.22%)
occurrences causally related to treatment / all	3 / 5	2 / 5	5 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergy to arthropod sting			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic shock			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Physical abuse			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast enlargement			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast hyperplasia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast mass			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical dysplasia			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endometrial dysplasia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fallopian tube cyst			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menometrorrhagia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 1123 (0.09%)	8 / 3358 (0.24%)	9 / 4481 (0.20%)
occurrences causally related to treatment / all	0 / 1	1 / 8	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatomegaly			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectocele			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	3 / 1123 (0.27%)	1 / 3358 (0.03%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterovaginal prolapse			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal prolapse			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute interstitial pneumonitis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	1 / 1	3 / 3	4 / 4
deaths causally related to treatment / all	0 / 0	2 / 2	2 / 2
Acute respiratory failure			

subjects affected / exposed	2 / 1123 (0.18%)	2 / 3358 (0.06%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	1 / 2	0 / 2	1 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Adenoidal hypertrophy			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolitis allergic			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 1123 (0.45%)	6 / 3358 (0.18%)	11 / 4481 (0.25%)
occurrences causally related to treatment / all	0 / 5	2 / 6	2 / 11
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Cough			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	2 / 1123 (0.18%)	4 / 3358 (0.12%)	6 / 4481 (0.13%)
occurrences causally related to treatment / all	1 / 2	1 / 4	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 1123 (0.27%)	16 / 3358 (0.48%)	19 / 4481 (0.42%)
occurrences causally related to treatment / all	0 / 4	4 / 16	4 / 20
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pulmonary fibrosis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiration abnormal			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory acidosis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Respiratory distress			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	5 / 1123 (0.45%)	3 / 3358 (0.09%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	2 / 5	1 / 3	3 / 8
deaths causally related to treatment / all	1 / 3	0 / 1	1 / 4
Rhinitis allergic			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcoholism			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Confusional state			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug abuse			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic stress disorder			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder due to a general medical condition			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restlessness			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device electrical impedance issue			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device loosening			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	2 / 1123 (0.18%)	2 / 3358 (0.06%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary colic			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cholangitis chronic			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 1123 (0.09%)	4 / 3358 (0.12%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	10 / 1123 (0.89%)	13 / 3358 (0.39%)	23 / 4481 (0.51%)
occurrences causally related to treatment / all	1 / 10	1 / 14	2 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder disorder			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder non-functioning			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic congestion			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hepatic steatosis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sphincter of Oddi dysfunction			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Airway peak pressure increased			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-lymphocyte count increased			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac murmur			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram abnormal			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematocrit decreased			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	2 / 4	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Human papilloma virus test positive			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metamyelocyte count increased			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelocyte count increased			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Red blood cell sedimentation rate increased			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight increased			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acetabulum fracture			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic ulcer			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			

subjects affected / exposed	2 / 1123 (0.18%)	7 / 3358 (0.21%)	9 / 4481 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burns second degree			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dislocation of vertebra			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exposure via father			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			

subjects affected / exposed	7 / 1123 (0.62%)	9 / 3358 (0.27%)	16 / 4481 (0.36%)
occurrences causally related to treatment / all	0 / 7	0 / 9	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	4 / 1123 (0.36%)	3 / 3358 (0.09%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	2 / 1123 (0.18%)	12 / 3358 (0.36%)	14 / 4481 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 12	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal exposure during pregnancy			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 1123 (0.09%)	4 / 3358 (0.12%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured ischium			

subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	6 / 1123 (0.53%)	2 / 3358 (0.06%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	2 / 1123 (0.18%)	11 / 3358 (0.33%)	13 / 4481 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 12	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incorrect dose administered			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 1123 (0.09%)	4 / 3358 (0.12%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation postoperative			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Lumbar vertebral fracture			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maternal exposure timing unspecified			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle injury			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirenal haematoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural oedema			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative hernia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	4 / 1123 (0.36%)	3 / 3358 (0.09%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 1123 (0.00%)	5 / 3358 (0.15%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 1123 (0.00%)	5 / 3358 (0.15%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Scapula fracture			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue injury			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	2 / 1123 (0.18%)	10 / 3358 (0.30%)	12 / 4481 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 10	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 1123 (0.00%)	7 / 3358 (0.21%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic liver injury			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Twiddler’s syndrome			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 1123 (0.09%)	4 / 3358 (0.12%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Developmental hip dysplasia			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocele			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tourette’s disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	4 / 1123 (0.36%)	4 / 3358 (0.12%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	0 / 4	1 / 4	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Angina pectoris			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	3 / 1123 (0.27%)	5 / 3358 (0.15%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	1 / 3	1 / 5	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			

subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	6 / 1123 (0.53%)	14 / 3358 (0.42%)	20 / 4481 (0.45%)
occurrences causally related to treatment / all	0 / 6	4 / 15	4 / 21
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block right			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Cardiac failure			
subjects affected / exposed	3 / 1123 (0.27%)	5 / 3358 (0.15%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	0 / 4	1 / 5	1 / 9
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Cardiac failure congestive			
subjects affected / exposed	4 / 1123 (0.36%)	3 / 3358 (0.09%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	3 / 1123 (0.27%)	1 / 3358 (0.03%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 3
Cardiogenic shock			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Cardiopulmonary failure			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiovascular insufficiency			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	4 / 1123 (0.36%)	11 / 3358 (0.33%)	15 / 4481 (0.33%)
occurrences causally related to treatment / all	1 / 4	0 / 11	1 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery thrombosis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Long QT syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve stenosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	8 / 1123 (0.71%)	13 / 3358 (0.39%)	21 / 4481 (0.47%)
occurrences causally related to treatment / all	1 / 8	3 / 13	4 / 21
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 3
Myocardial ischaemia			

subjects affected / exposed	4 / 1123 (0.36%)	3 / 3358 (0.09%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	1 / 4	1 / 3	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Brain stem infarction			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Carotid artery aneurysm			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system lesion			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar ataxia			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral arteriosclerosis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 1123 (0.09%)	4 / 3358 (0.12%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Cerebral infarction			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cerebrovascular accident			

subjects affected / exposed	2 / 1123 (0.18%)	6 / 3358 (0.18%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	0 / 2	1 / 6	1 / 8
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cervical cord compression			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical myelopathy			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical radiculopathy			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial nerve disorder			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Headache			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianopia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intensive care unit acquired weakness			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraventricular haemorrhage			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			

subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral radiculopathy			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoplegia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelopathy			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			

subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuritis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pachymeningitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson’s disease			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post herpetic neuralgia			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Quadriparesis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular syndrome			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured cerebral aneurysm			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sciatica			
subjects affected / exposed	1 / 1123 (0.09%)	9 / 3358 (0.27%)	10 / 4481 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 9	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory loss			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serotonin syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small fibre neuropathy			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal claudication			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal subdural haematoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylitic myelopathy			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 1123 (0.09%)	5 / 3358 (0.15%)	6 / 4481 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension headache			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 1123 (0.18%)	11 / 3358 (0.33%)	13 / 4481 (0.29%)
occurrences causally related to treatment / all	0 / 2	3 / 12	3 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis cerebral			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 1123 (0.36%)	10 / 3358 (0.30%)	14 / 4481 (0.31%)
occurrences causally related to treatment / all	1 / 4	4 / 10	5 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	1 / 1	2 / 3	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastocytosis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paratracheal lymphadenopathy			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	2 / 1123 (0.18%)	8 / 3358 (0.24%)	10 / 4481 (0.22%)
occurrences causally related to treatment / all	0 / 3	1 / 8	1 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratitis interstitial			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising retinitis			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic disc drusen			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery occlusion			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal incarcerated hernia			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 1123 (0.09%)	5 / 3358 (0.15%)	6 / 4481 (0.13%)
occurrences causally related to treatment / all	0 / 1	3 / 5	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			

subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn’s disease			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 1123 (0.18%)	8 / 3358 (0.24%)	10 / 4481 (0.22%)
occurrences causally related to treatment / all	1 / 2	2 / 8	3 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	3 / 1123 (0.27%)	5 / 3358 (0.15%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	1 / 3	3 / 5	4 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal polyp			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocele			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula of small intestine			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric polyps			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			

subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	3 / 1123 (0.27%)	4 / 3358 (0.12%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			

subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Haematochezia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic erosive gastritis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Intestinal obstruction			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal stenosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 1123 (0.09%)	4 / 3358 (0.12%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	1 / 1	1 / 5	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	4 / 1123 (0.36%)	4 / 3358 (0.12%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	1 / 4	1 / 4	2 / 8
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth impacted			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Actinic keratosis			

subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus ulcer			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panniculitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scar pain			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 1123 (0.53%)	6 / 3358 (0.18%)	12 / 4481 (0.27%)
occurrences causally related to treatment / all	1 / 6	0 / 6	1 / 12
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Anuria			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mixed incontinence			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	2 / 1123 (0.18%)	5 / 3358 (0.15%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive uropathy			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelocaliectasis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	3 / 1123 (0.27%)	1 / 3358 (0.03%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 3	1 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Renal impairment			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteral necrosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral meatus stenosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			

subjects affected / exposed	3 / 1123 (0.27%)	7 / 3358 (0.21%)	10 / 4481 (0.22%)
occurrences causally related to treatment / all	0 / 3	1 / 7	1 / 10
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Hyperparathyroidism primary			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Acquired claw toe			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 1123 (0.09%)	8 / 3358 (0.24%)	9 / 4481 (0.20%)
occurrences causally related to treatment / all	0 / 1	1 / 8	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 1123 (0.09%)	4 / 3358 (0.12%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atlantoaxial instability			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			

subjects affected / exposed	4 / 1123 (0.36%)	13 / 3358 (0.39%)	17 / 4481 (0.38%)
occurrences causally related to treatment / all	0 / 6	0 / 14	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dupuytren’s contracture			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extraskeletal ossification			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Finger deformity			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			

subjects affected / exposed	5 / 1123 (0.45%)	12 / 3358 (0.36%)	17 / 4481 (0.38%)
occurrences causally related to treatment / all	0 / 6	0 / 12	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand deformity			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	3 / 1123 (0.27%)	11 / 3358 (0.33%)	14 / 4481 (0.31%)
occurrences causally related to treatment / all	0 / 4	0 / 11	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint contracture			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint destruction			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint swelling			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kyphosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	5 / 1123 (0.45%)	4 / 3358 (0.12%)	9 / 4481 (0.20%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscal degeneration			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metatarsalgia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			

subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	21 / 1123 (1.87%)	63 / 3358 (1.88%)	84 / 4481 (1.87%)
occurrences causally related to treatment / all	0 / 25	2 / 67	2 / 92
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	2 / 1123 (0.18%)	5 / 3358 (0.15%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 2	1 / 5	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatic disorder			

subjects affected / exposed	2 / 1123 (0.18%)	1 / 3358 (0.03%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	11 / 1123 (0.98%)	23 / 3358 (0.68%)	34 / 4481 (0.76%)
occurrences causally related to treatment / all	0 / 12	2 / 24	2 / 36
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid nodule			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	7 / 3358 (0.21%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	1 / 1123 (0.09%)	8 / 3358 (0.24%)	9 / 4481 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 9	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylitis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			

subjects affected / exposed	2 / 1123 (0.18%)	8 / 3358 (0.24%)	10 / 4481 (0.22%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial disorder			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon calcification			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenosynovitis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			

subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	1 / 1	2 / 3	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess neck			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	6 / 1123 (0.53%)	11 / 3358 (0.33%)	17 / 4481 (0.38%)
occurrences causally related to treatment / all	2 / 6	2 / 11	4 / 17
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Appendicitis perforated			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 1123 (0.09%)	4 / 3358 (0.12%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 2	3 / 4	3 / 6
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Arthritis infective			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	2 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bartholin’s abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone tuberculosis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	3 / 1123 (0.27%)	5 / 3358 (0.15%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	2 / 3	3 / 5	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Bursitis infective			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 1123 (0.18%)	14 / 3358 (0.42%)	16 / 4481 (0.36%)
occurrences causally related to treatment / all	0 / 2	7 / 14	7 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis gangrenous			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic tonsillitis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Clostridium difficile infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			

subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus chorioretinitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus hepatitis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	2 / 3	2 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Diabetic gangrene			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated tuberculosis			
subjects affected / exposed	3 / 1123 (0.27%)	4 / 3358 (0.12%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	3 / 3	4 / 4	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	5 / 1123 (0.45%)	12 / 3358 (0.36%)	17 / 4481 (0.38%)
occurrences causally related to treatment / all	4 / 5	8 / 12	12 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Epstein-Barr virus infection			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	2 / 1123 (0.18%)	2 / 3358 (0.06%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	1 / 2	2 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural abscess			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye infection fungal			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	2 / 1123 (0.18%)	13 / 3358 (0.39%)	15 / 4481 (0.33%)
occurrences causally related to treatment / all	0 / 2	4 / 13	4 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			
subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
HIV infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis A			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			

subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes dermatitis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	2 / 1123 (0.18%)	16 / 3358 (0.48%)	18 / 4481 (0.40%)
occurrences causally related to treatment / all	2 / 2	16 / 16	18 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster cutaneous disseminated			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster disseminated			
subjects affected / exposed	0 / 1123 (0.00%)	5 / 3358 (0.15%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 0	5 / 5	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster oticus			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected seroma			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective spondylitis			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	3 / 1123 (0.27%)	0 / 3358 (0.00%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint tuberculosis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lyme disease			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node tuberculosis			

subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis cryptococcal			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningococcal bacteraemia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningoencephalitis bacterial			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			

subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes simplex			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	5 / 5	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal tuberculosis			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pertussis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	21 / 1123 (1.87%)	70 / 3358 (2.08%)	91 / 4481 (2.03%)
occurrences causally related to treatment / all	10 / 21	53 / 71	63 / 92
deaths causally related to treatment / all	2 / 4	3 / 4	5 / 8
Pneumonia bacterial			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Pneumonia cryptococcal			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia cytomegaloviral			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia necrotising			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Pneumonia pneumococcal			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 1123 (0.00%)	5 / 3358 (0.15%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 0	4 / 5	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Primary syphilis			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoas abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 1123 (0.09%)	7 / 3358 (0.21%)	8 / 4481 (0.18%)
occurrences causally related to treatment / all	1 / 1	7 / 7	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulpitis dental			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	3 / 1123 (0.27%)	2 / 3358 (0.06%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	3 / 3	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 1123 (0.09%)	5 / 3358 (0.15%)	6 / 4481 (0.13%)
occurrences causally related to treatment / all	0 / 1	2 / 5	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyoderma streptococcal			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyometra			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 1123 (0.00%)	5 / 3358 (0.15%)	5 / 4481 (0.11%)
occurrences causally related to treatment / all	0 / 0	4 / 5	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinitis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophoritis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary syphilis			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	5 / 1123 (0.45%)	8 / 3358 (0.24%)	13 / 4481 (0.29%)
occurrences causally related to treatment / all	1 / 5	5 / 8	6 / 13
deaths causally related to treatment / all	1 / 3	2 / 2	3 / 5
Sepsis syndrome			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	3 / 1123 (0.27%)	4 / 3358 (0.12%)	7 / 4481 (0.16%)
occurrences causally related to treatment / all	3 / 3	2 / 4	5 / 7
deaths causally related to treatment / all	1 / 1	1 / 2	2 / 3
Sinusitis			
subjects affected / exposed	0 / 1123 (0.00%)	4 / 3358 (0.12%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis aspergillus			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis fungal			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Staphylococcal sepsis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 1123 (0.09%)	2 / 3358 (0.06%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 1	2 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic shock syndrome			

subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Tuberculosis			
subjects affected / exposed	1 / 1123 (0.09%)	1 / 3358 (0.03%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis of central nervous system			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubo-ovarian abscess			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 1123 (0.00%)	2 / 3358 (0.06%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	8 / 1123 (0.71%)	14 / 3358 (0.42%)	22 / 4481 (0.49%)
occurrences causally related to treatment / all	6 / 10	9 / 14	15 / 24
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Urinary tract infection bacterial			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	2 / 1123 (0.18%)	0 / 3358 (0.00%)	2 / 4481 (0.04%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection bacterial			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 1123 (0.27%)	6 / 3358 (0.18%)	9 / 4481 (0.20%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			

subjects affected / exposed	1 / 1123 (0.09%)	3 / 3358 (0.09%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia unawareness			
subjects affected / exposed	0 / 1123 (0.00%)	1 / 3358 (0.03%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	3 / 1123 (0.27%)	1 / 3358 (0.03%)	4 / 4481 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic syndrome			
subjects affected / exposed	1 / 1123 (0.09%)	0 / 3358 (0.00%)	1 / 4481 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	0 / 1123 (0.00%)	3 / 3358 (0.09%)	3 / 4481 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tofa 5mg BID; ppts with avg total daily dose across study <15	Tofa 10mg BID; ppts with avg total daily dose across study ≥15	All Tofacitinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	807 / 1123 (71.86%)	2422 / 3358 (72.13%)	3229 / 4481 (72.06%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	63 / 1123 (5.61%)	122 / 3358 (3.63%)	185 / 4481 (4.13%)
occurrences (all)	79	155	234
Blood creatine phosphokinase increased			
subjects affected / exposed	91 / 1123 (8.10%)	247 / 3358 (7.36%)	338 / 4481 (7.54%)
occurrences (all)	127	316	443
Blood creatinine increased			
subjects affected / exposed	60 / 1123 (5.34%)	116 / 3358 (3.45%)	176 / 4481 (3.93%)
occurrences (all)	66	123	189
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	64 / 1123 (5.70%)	209 / 3358 (6.22%)	273 / 4481 (6.09%)
occurrences (all)	74	247	321
Vascular disorders			
Hypertension			
subjects affected / exposed	139 / 1123 (12.38%)	311 / 3358 (9.26%)	450 / 4481 (10.04%)
occurrences (all)	160	352	512
Nervous system disorders			
Headache			
subjects affected / exposed	67 / 1123 (5.97%)	201 / 3358 (5.99%)	268 / 4481 (5.98%)
occurrences (all)	79	239	318
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	64 / 1123 (5.70%)	176 / 3358 (5.24%)	240 / 4481 (5.36%)
occurrences (all)	75	202	277
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	72 / 1123 (6.41%)	213 / 3358 (6.34%)	285 / 4481 (6.36%)
occurrences (all)	86	252	338
Nausea			
subjects affected / exposed	56 / 1123 (4.99%)	175 / 3358 (5.21%)	231 / 4481 (5.16%)
occurrences (all)	60	196	256
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	65 / 1123 (5.79%)	202 / 3358 (6.02%)	267 / 4481 (5.96%)
occurrences (all)	75	229	304
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	87 / 1123 (7.75%)	265 / 3358 (7.89%)	352 / 4481 (7.86%)
occurrences (all)	119	341	460
Back pain			
subjects affected / exposed	106 / 1123 (9.44%)	291 / 3358 (8.67%)	397 / 4481 (8.86%)
occurrences (all)	141	330	471
Rheumatoid arthritis			
subjects affected / exposed	103 / 1123 (9.17%)	293 / 3358 (8.73%)	396 / 4481 (8.84%)
occurrences (all)	141	386	527
Infections and infestations			
Bronchitis			
subjects affected / exposed	141 / 1123 (12.56%)	430 / 3358 (12.81%)	571 / 4481 (12.74%)
occurrences (all)	226	625	851
Herpes zoster			
subjects affected / exposed	117 / 1123 (10.42%)	373 / 3358 (11.11%)	490 / 4481 (10.94%)
occurrences (all)	123	402	525
Influenza			
subjects affected / exposed	78 / 1123 (6.95%)	199 / 3358 (5.93%)	277 / 4481 (6.18%)
occurrences (all)	96	249	345
Nasopharyngitis			
subjects affected / exposed	138 / 1123 (12.29%)	517 / 3358 (15.40%)	655 / 4481 (14.62%)
occurrences (all)	220	812	1032
Pharyngitis			
subjects affected / exposed	58 / 1123 (5.16%)	148 / 3358 (4.41%)	206 / 4481 (4.60%)
occurrences (all)	61	180	241

Sinusitis			
subjects affected / exposed	70 / 1123 (6.23%)	239 / 3358 (7.12%)	309 / 4481 (6.90%)
occurrences (all)	117	358	475
Upper respiratory tract infection			
subjects affected / exposed	228 / 1123 (20.30%)	613 / 3358 (18.25%)	841 / 4481 (18.77%)
occurrences (all)	439	1083	1522
Urinary tract infection			
subjects affected / exposed	161 / 1123 (14.34%)	447 / 3358 (13.31%)	608 / 4481 (13.57%)
occurrences (all)	283	739	1022
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	62 / 1123 (5.52%)	153 / 3358 (4.56%)	215 / 4481 (4.80%)
occurrences (all)	67	170	237

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2007	The amendment was based on recommendations from the USA Food and Drug Administration about safety monitoring parameters for this protocol including some recommendations on specific cut-off values for certain parameters e.g., requiring some to be stricter than suggested by the Sponsor. For example, the (confirmed) hemoglobin level requiring discontinuation was raised from 7.5 to 8.0 g/dL. In addition, monitoring guidelines were added for subjects with serum creatinine levels >10% from baseline at the time of discontinuation.
25 July 2007	Updated exclusion criteria with the following modification for exclusion criteria number 11, 15 and 16, respectively: Included history of recurrent or disseminated herpes zoster or as otherwise judged by the Investigator; if an intra-articular injection was performed in the course of a qualifying study <4 weeks before the baseline visit of this study, the injected joint was to be considered to have its pre-injection status from the index study for the full length of this protocol; bariatric procedures, such as gastric banding, that simply divide the stomach into separate chambers were not exclusionary. Updated with rescue therapy for subjects who were not on stable, background opioid therapy. Measurement of the ESR was added to several visits, in order to facilitate determination of the DAS 28-4 (ESR) response. In addition, ACR responses were determined at every 3 months throughout the study instead of only during the first year of participation. Updated with intake of dietary supplements allowed during the study. Updated with prohibition of vaccination with live components during the study and for 8 weeks after last dose of study drug.
21 January 2009	The primary justification for this amendment was to provide for dosing of subjects at 10 mg BID and provide for long-term follow-up testing (e.g., radiographs of hands and feet, lipid profiles) consistent with tofacitinib Phase 3 protocols.
18 February 2009	Updated assessment of cardiovascular (CV) risk as every 6 months through Month 24 and then yearly after Month 24 throughout the document. Updated dose of tofacitinib as 5 mg BID and 10 mg BID in secondary objectives. Specified ESR and CRP for laboratory testing and SF-36 Health Survey in Section 6.1.3. Added DAS 2/8 assessment in Section 6.2.3 and height in Section 6.2.5.
30 June 2009	The purpose of this amendment was to align with Phase 3 protocols, to decrease the withdrawal period required for adalimumab (Humira®), and extend the supply of tofacitinib to at least 2 years after first global marketing approval.
26 February 2010	Removed the option for subjects to enroll in non-drug extension Study A3921029 after 26 February 2010. Removed text in inclusion criteria regarding subjects who discontinued their qualifying index study due to lack of efficacy. The criteria required 24 weeks of participation in the index study in order to be eligible to enroll in Study A3921024. This text was removed to accommodate differing timeframe requirements in the index study protocols. Updated monitoring and discontinuation guidelines surrounding serum creatinine elevations to allow for adjustments in concomitant medications and study drug dosing.
24 December 2010	Schedule of Activities: plasma samples for the analysis of tofacitinib concentrations were to be collected to explore relationships with long-term efficacy and safety outcomes. Included exploratory objective of establishing the PK of tofacitinib. Moved HAQ-DI to the second secondary objective. Clarified monitoring guideline for serum creatinine. Removed wording to allow intra-articular hyaluronate sodium injections prior to the Month 6 visit if appropriate and clarified frequency. Added guideline on use of opioid agent hydrocodone.

30 August 2012	Added an exclusion criterion for lymphocytopenia, monitoring and discontinuation criteria with regard to lymphocyte counts <500/mm3. Removed active tuberculosis (TB) infection to clarify that any subject with active TB infection was not allowed to receive the study drug. Added description of the relationship between treated and serious infections and lymphocyte counts <500/mm3 in the RA tofacitinib program. Added to the list of contraceptive methods that were considered highly effective. Added the requirement for written dosing instructions. Added language for drug storage temperature monitoring. Added language: "Topical administration, eg, cutaneous, ophthalmic, or intravaginal, of medications that are prohibited if administered systemically, are allowed in the study". Modified CV risk factor assessment requirements after screening. Decreased frequency for radiographs of hands and feet after Month 12. Added language allowing for additional safety endpoint adjudication. Clarified requirement for the average weekly alcohol consumption to be updated at visits every 6 months through Month 24 and then annually thereafter for all subjects.
11 March 2013	Additional hepatitis B tests added. Medical history and vaccination of zoster added. Washout period for CYP3A inhibitors and/or CYP3A inducers added. Clarified the allowed non-steroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors/oral corticosteroids during the study.
05 February 2014	Added a follow-up visit (at least 28 days after the last dose of study drug). Removed the tests of apoliprotein A and B. Decreased the frequency of ECG testing during the study. Removed work limitation questionnaire. Reduced the frequency of questionnaires (SF-36 Health Survey, FACIT Fatigue, EuroQol EQ-5D, RA-HCRU) to be performed annually. Specified the collections of radiographs of hands/feet procedures up to Month 36 only and at EOT visit. Added lymphocyte substudy. Extended the study duration to November 2019 or up to the marketing approval of tofacitinib in certain countries. Allowed subjects to reduce the study dose to 5 mg BID from 10 mg BID at the discretion of the Investigators. Allowed subjects who were enrolled to receive either 5 or 10 mg BID dose at the discretion of the Investigators. Added the discussions of potential reproductive risk and contraceptive use. Added and removed some prohibited concomitant drugs and clarified that study drug was to be interrupted if a CYP3A inhibitor was administered concomitantly. Applied the existing discontinuation criterion of opportunistic infection to all subjects.
15 January 2015	Added TB screening annually for subjects in the high-risk countries. Removed height measurements during the study and weight measurements at some timepoints during the study. Removed temperature, rheumatoid factor, anti-cyclic citrullinated peptide, ECG, urinalysis, and radiographs of hands and feet. Removed SF-36, FACIT Fatigue, EQ-5D, RA Healthcare questionnaires. Reduced the study duration to April 2016 for subjects who were not participating in the lymphocyte substudy and clarified the study durations for subjects who were participating in the lymphocyte substudy. Added more definitions/clarifications of medication errors. Clarified wording to continue a subject with latent TB infection during the study. Added Cohort 3 to enroll subjects from Study A3921237 in the lymphocyte substudy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

All information is based on protocol Amendment 25 with a database release date of 02 March 2017. One serious adverse event in the Tofacitinib 5mg BID group could not be coded ("septic shock and pneumonia") and has not been included.

Notes: