Clinical trial results:
A Multi-center, Open-Label Study of CP-690,550 in Subjects With Moderate to Severe Ulcerative Colitis

Summary

EudraCT number	2011-004581-14
Trial protocol	CZ DK HU EE GB LV BE NL ES AT DE SK PL IT HR
Global end of trial date	06 August 2020

Results information

Result version number	v1 (current)
This version publication date	19 August 2021
First version publication date	19 August 2021

Trial information

Trial identification

Sponsor protocol code	A3921139

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01470612
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States,
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, 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	16 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of long-term tofacitinib therapy in subjects with ulcerative colitis (UC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Belgium: 61
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 50
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Japan: 53
Country: Number of subjects enrolled	Korea, Republic of: 51
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Netherlands: 32
Country: Number of subjects enrolled	New Zealand: 29

Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Serbia: 34
Country: Number of subjects enrolled	Slovakia: 33
Country: Number of subjects enrolled	South Africa: 26
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Ukraine: 47
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	United States: 166
Worldwide total number of subjects	944
EEA total number of subjects	415

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)	881
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects enrolled in this Study A3921139: 1) who had completed or had early withdrawal due to treatment failure in Study A3921096 (NCT01458574) 2) or who were non-responders after completing induction studies A3921094 (NCT01465763) or A3921095 (NCT01458951). Eligible participants were assigned to either Tofacitinib 5 mg BID or 10 mg BID group.

Pre-assignment

Screening details:

Treatment failure for A3921096: Increase in Mayo score of >=3 points from baseline and rectal bleeding sub score by >=1 point and endoscopic sub score of >=1 point post minimum of 8 weeks treatment. If endoscopic sub score and baseline endoscopic sub score was 3 (maximum), then increase by >=1 point was not needed, but all other criteria must met.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tofacitinib 5 mg BID

Arm description:

Subjects who completed Study A3921096 and were in remission at Week 52 of Study A3921096, received Tofacitinib 5 milligram (mg) tablets twice daily (BID) for maximum of 80 months in this Study A3921139. Remission was defined as total Mayo score less than or equal to (<=) 2 with no individual sub score greater than (>)1 and rectal bleeding sub score of 0.

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Tofacitinib 5 mg tablets orally twice daily.

Arm title	Tofacitinib 10 mg BID

Arm description:

Subjects who had completed Study A3921096 and not in remission, or who had early withdrawal due to treatment failure from Study A3921096, or who were non responders after completing A3921094 or A3921095 received Tofacitinib 10 mg tablets twice daily for maximum of 84 months in this Study A3921139.

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Tofacitinib 10 mg tablets orally twice daily.

Number of subjects in period 1	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Started	175	769
Completed	91	104
Not completed	84	665
Adverse event, serious fatal	-	1
Consent withdrawn by subject	24	79
Did not meet entrance criteria	-	1
Adverse event, non-fatal	20	80
Pregnancy	2	10
Unspecified	14	156
Lost to follow-up	2	5
Lack of efficacy	20	326
Protocol deviation	2	7

Baseline characteristics

Reporting groups	
Reporting group title	Tofacitinib 5 mg BID
Reporting group description:	
Subjects who completed Study A3921096 and were in remission at Week 52 of Study A3921096, received Tofacitinib 5 milligram (mg) tablets twice daily (BID) for maximum of 80 months in this Study A3921139. Remission was defined as total Mayo score less than or equal to (<=) 2 with no individual sub score greater than (>)1 and rectal bleeding sub score of 0.	
Reporting group title	Tofacitinib 10 mg BID
Reporting group description:	
Subjects who had completed Study A3921096 and not in remission, or who had early withdrawal due to treatment failure from Study A3921096, or who were non responders after completing A3921094 or A3921095 received Tofacitinib 10 mg tablets twice daily for maximum of 84 months in this Study A3921139.	

Reporting group values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Total
Number of subjects	175	769	944
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	161	720	881
From 65-84 years	14	49	63
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	44.5	40.5	
standard deviation	± 14.6	± 13.5	-
Sex: Female, Male Units: subjects			
Female	79	310	389
Male	96	459	555
Race/Ethnicity, Customized Units: Subjects			
White	136	615	751
Black	0	9	9
Asian	25	97	122
Other	9	24	33
Unspecified	5	24	29

End points

End points reporting groups

Reporting group title	Tofacitinib 5 mg BID

Reporting group description:

Subjects who completed Study A3921096 and were in remission at Week 52 of Study A3921096, received Tofacitinib 5 milligram (mg) tablets twice daily (BID) for maximum of 80 months in this Study A3921139. Remission was defined as total Mayo score less than or equal to (<=) 2 with no individual sub score greater than (>)1 and rectal bleeding sub score of 0.

Reporting group title	Tofacitinib 10 mg BID

Reporting group description:

Subjects who had completed Study A3921096 and not in remission, or who had early withdrawal due to treatment failure from Study A3921096, or who were non responders after completing A3921094 or A3921095 received Tofacitinib 10 mg tablets twice daily for maximum of 84 months in this Study A3921139.

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

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

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 81 months for Tofacitininb 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group that were absent before treatment or that worsened relative to pretreatment state. AEs included both serious and non-serious AEs. Safety analysis set (SAS) included all subjects who received at least 1 dose of study medication in this study.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: subjects				
Subject with AEs	154	626		
Subject with SAEs	39	147		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Serious Infections as Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Serious Infections as Treatment Emergent Adverse Events (TEAEs)[2]

End point description:

Serious infections were treated infections that required parenteral antimicrobial therapy or hospitalization for treatment or; met other criteria that required the infection to be classified as a serious adverse event (SAE). SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group that were absent before treatment or that worsened relative to pretreatment state. SAS included all subjects who received at least 1 dose of study medication in this study.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: subjects	8	31		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Laboratory Test Abnormalities

End point title	Number of Subjects With Laboratory Test Abnormalities[3]

End point description:

Laboratory abnormalities: Hb, hematocrit, RBC: <0.8*LLN; reticulocytes (absolute [Abs], %):<0.5*LLN,>1.5*ULN;
MCV,MCH:<0.9*LLN,>1.1*ULN;platelets:<0.5*LLN,>1.75*ULN;WBC:<0.6*LLN,>1.5*ULN;lymphocytes (Abs,%), total neutrophils(Abs,%):<0.8*LLN,>1.2* ULN;Basophils(Abs,%),eosinophils(Abs,%),monocytes(Abs,%):>1.2*ULN; total bilirubin,direct and indirect bilirubin:>1.5* ULN;AST,ALT,gamma GT,LDH,ALP:>3.0* ULN;total protein,albumin:<0.8* LLN,>1.2*ULN:BUN,creatinine: >1.3*ULN;uric acid:>1.2*ULN;cholesterol,triglycerides:>1.3*ULN;cholesterol (HDL: <0.8*LLN;LDL:>1.2*ULN);sodium:<0.95*LLN,>1.05*ULN;potassium,chloride,calcium,bicarbonate:<0.9 *LLN, >1.1*ULN; glucose: <0.6*LLN; creatine kinase >2.0*ULN; urine specific gravity: <1.003; urine pH: <4.5; urine (glucose,protein,blood,nitrite,leukocyte,esterase): >=1; Urine (RBC,WBC):>=20;urine

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	761		
Units: subjects	162	670		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Vital Sign Abnormalities

End point title	Number of Subjects With Vital Sign Abnormalities[4]

End point description:

Vital sign abnormalities included >=30 millimeter of mercury [mmHg] increase in systolic blood pressure (BP), >=30 mmHg decrease in systolic BP, Systolic BP (<90 mmHg), >=20 mmHg increase in diastolic BP, >=20 mmHg decrease in diastolic BP, diastolic BP (<50 mmHg), pulse rate (<40 beats per minute [BPM]), pulse rate (>120 BPM). SAS included all subjects who received at least 1 dose of study medication in this study. Here, "Number of subjects analysed" signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable at each specified category.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	763		
Units: subjects				
Systolic BP (>=30 mmHg increase) (n=172, 748)	20	113		
Systolic BP (>=30 mmHg decrease) (n=172, 748)	19	44		
Systolic BP (<90 mmHg) (n=175, 763)	3	13		
Diastolic BP (>=20 mmHg increase) (n=172, 748)	21	137		
Diastolic BP (>=20 mmHg decrease) (n=172, 748)	37	78		
Diastolic BP (<50 mmHg) (n=175, 763)	3	16		
Pulse Rate (<40 BPM) (n=175, 763)	1	0		
Pulse Rate (>120 BPM) (n=175, 763)	0	8		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Physical

Examinations From Baseline

End point title	Number of Subjects With Clinically Significant Changes in Physical Examinations From Baseline[5]

End point description:

Physical examinations included weight, general appearance, head, ears, eyes, nose, mouth, throat, thyroid, skin (presence of rash), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs, peripheral edema), abdominal (palpation and auscultation), perianal, musculoskeletal, extremities, neurologic (mental status, gait, reflexes, motor and sensory function, coordination) and lymph nodes. Clinically significant changes were judged by the investigator. SAS included all subjects who received at least 1 dose of study medication in this study.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: subjects	84	391		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Electrocardiogram (ECG) Abnormalities[6]

End point description:

ECG abnormalities criteria: maximum PR interval (>=300 millisecond); maximum QRS complex (>=200 millisecond); and maximum QT interval (>=500 millisecond). SAS included all subjects who received at least 1 dose of study medication in this study. Here, "Number of subjects analyzed" signifies number of subjects evaluable for this endpoint and "n" signifies subjects evaluable at each specified category.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	707		
Units: subjects				
Maximum PR interval (>=300) (n=157,706)	0	0		

Maximum QRS complex (>=200)(n=158,707)	0	0		
Maximum QT interval (>=500)(n=158,707)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence Rates for Adjudicated Cardiovascular, Malignancy, Opportunistic Infections and Thromboembolic Safety Events

End point title	Incidence Rates for Adjudicated Cardiovascular, Malignancy, Opportunistic Infections and Thromboembolic Safety Events[7]

End point description:

Incidence rates (number of subjects with events per 100 subjects-years) for adjudicated cardiovascular (major adverse cardiovascular event [MACE]), malignancy (non-melanoma skin cancer [NMSC], malignancy excluding NMSC, opportunistic infections (OIs) (both herpes zoster and non herpes zoster OIs) and thromboembolic events (venous thromboembolism) safety events was analyzed.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: Incidence rate				
number (confidence interval 95%)				
MACE	0.31 (0.04 to 1.13)	0.11 (0.01 to 0.40)		
NMSC	0.96 (0.35 to 2.08)	0.68 (0.35 to 1.19)		
Malignancies excluding NMSC	1.09 (0.44 to 2.25)	1.00 (0.60 to 1.59)		
Herpes Zoster OI	0.47 (0.10 to 1.37)	0.79 (0.43 to 1.32)		
Non Herpes Zoster OI	0.16 (0.00 to 0.87)	0.17 (0.03 to 0.49)		
Venous thromboembolism	0.00 (0.00 to 0.57)	0.33 (0.12 to 0.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Remission at Months 2, 12, 24 and 36: Observed Cases

End point title	Number of Subjects in Remission at Months 2, 12, 24 and 36: Observed Cases

End point description:

Remission in subjects was defined as a total Mayo score of less than or equals to (<=) 2, with no individual sub score exceeding 1 point and a rectal bleeding sub score of 0. Mayo score was an instrument designed to measure disease activity of ulcerative colitis (UC). It consisted of 4 sub scores: stool frequency, rectal bleeding, findings of flexible sigmoidoscopy and physician global assessment (PGA), each sub score graded from 0 to 3 with higher scores indicated higher disease severity. These sub scores were summed up to give a total score range of 0 to 12, where higher score indicated more severe disease. FAS included all subjects who received at least 1 dose of study medication in this study. Here, "Number of subjects analysed" signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable at each specified timepoint. Data is presented for observed cases, no imputation technique was applied.

End point type	Secondary

End point timeframe:

Months 2, 12, 24 and 36

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	676		
Units: subjects				
Month 2 (n= 164, 676)	131	188		
Month 12 (n= 154, 447)	129	279		
Month 24 (n= 132, 371)	103	264		
Month 36 (n= 113, 299)	98	239		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Remission at Months 2, 12, 24 and 36: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point title	Number of Subjects in Remission at Months 2, 12, 24 and 36: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point description:

Remission in subjects was defined as a total Mayo score of <=2, with no individual sub score exceeding 1 point and a rectal bleeding sub score of 0. Mayo score was an instrument designed to measure disease activity of UC. It consisted of 4 sub scores: stool frequency, rectal bleeding, findings of flexible sigmoidoscopy and PGA, each sub score graded from 0 to 3 with higher scores indicated higher disease severity. These sub scores were summed up to give a total score range of 0 to 12, where higher score indicated more severe disease. FAS included all subjects who received at least 1 dose of study medication in this study. NRI method was used for missing data except for visits after a subject advanced to other studies where LOCF method was used.

End point type	Secondary

End point timeframe:

Months 2, 12, 24 and 36

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: subjects				
Month 2	131	188		
Month 12	129	279		
Month 24	103	264		
Month 36	103	259		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Clinical Remission at Months 2, 12, 24 and 36: Observed Cases

End point title	Number of Subjects in Clinical Remission at Months 2, 12, 24 and 36: Observed Cases

End point description:

Clinical remission in subjects was defined as a total mayo score of <=2 with no individual sub score exceeding 1 point. Mayo score was an instrument designed to measure disease activity of UC. It consisted of 4 sub scores: stool frequency, rectal bleeding, findings of flexible sigmoidoscopy and PGA, each graded from 0 to 3 with higher scores indicated higher disease severity. These sub scores were summed up to give a total score range of 0 to 12, where higher score indicated more severe disease. Here, "Number of subjects analysed" signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable at each specified time point. Data is presented for observed cases, no imputation technique was applied.

End point type	Secondary

End point timeframe:

Months 2, 12, 24 and 36

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	676		
Units: subjects				
Month 2 (n= 164, 676)	132	191		
Month 12 (n= 154, 447)	129	282		
Month 24 (n= 132, 371)	104	266		
Month 36 (n= 113, 299)	102	240		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Clinical Remission at Months 2, 12, 24 and 36: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point title	Number of Subjects in Clinical Remission at Months 2, 12, 24 and 36: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point description:

Clinical remission in subjects was defined as a total mayo score of <=2 with no individual sub score exceeding 1 point. Mayo score was an instrument designed to measure disease activity of UC. It consisted of 4 sub scores: stool frequency, rectal bleeding, findings of flexible sigmoidoscopy and PGA, each graded from 0 to 3 with higher scores indicated higher disease severity. These sub scores were summed up to give a total score range of 0 to 12, where higher score indicated more severe disease. FAS included all subjects who received at least 1 dose of study medication in this study. NRI method was used for missing data except for visits after a subject advanced to other studies where LOCF method was used.

End point type	Secondary

End point timeframe:

Months 2, 12, 24 and 36

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: subjects				
Month 2	132	191		
Month 12	129	282		
Month 24	104	266		
Month 36	107	260		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Partial Mayo Score (PMS) Remission at Months 1, 4, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81 and 84: Observed Cases

End point title	Number of Subjects in Partial Mayo Score (PMS) Remission at Months 1, 4, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81 and 84: Observed Cases

End point description:

PMS was an instrument designed to measure disease activity of UC without endoscopy. It consisted of 3 sub scores: stool frequency, rectal bleeding and PGA, each sub score graded from 0 to 3 with higher scores indicated higher disease severity. These sub scores were summed up to give a total score range of 0 to 9, where higher score indicated more severe disease. PMS remission was defined as a partial Mayo score <=2 with no individual sub score >1. Here, "Number of subjects analysed" signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable at each specified timepoint. Data is presented for observed cases, no imputation technique was applied. Here, 99999 indicated data could not be reported as no subjects were evaluable at that time point.

End point type	Secondary

End point timeframe:

Months 1, 4, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81 and 84

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	729		
Units: subjects				
Month 1 (n= 165, 729)	158	275		
Month 4 (n= 165, 532)	152	375		
Month 6 (n= 166, 505)	155	395		
Month 9 (n= 160, 469)	154	390		
Month 15 (n= 145, 418)	139	361		
Month 18 (n= 144, 404)	137	354		
Month 21 (n= 138, 394)	125	351		
Month 27 (n= 125, 348)	117	319		
Month 30 (n= 124, 338)	117	307		
Month 33 (n= 118, 326)	111	304		
Month 39 (n= 105, 281)	102	261		
Month 42 (n= 100, 253)	95	236		
Month 45 (n= 102, 226)	95	212		
Month 48 (n= 92, 199)	87	183		
Month 51 (n= 89, 175)	87	162		
Month 54 (n= 71, 147)	68	140		
Month 57 (n= 56, 128)	54	120		
Month 60 (n= 39, 107)	38	98		
Month 63 (n= 28, 89)	28	80		
Month 66 (n= 89, 175)	19	67		
Month 69 (n= 11, 54)	10	49		
Month 72 (n= 6, 44)	6	40		
Month 75 (n= 3, 26)	3	24		
Month 78 (n= 4, 19)	4	18		
Month 81 (n= 0, 11)	99999	10		
Month 84 (n= 0, 8)	99999	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Partial Mayo Score (PMS) Remission at Months 1, 4, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81 and 84: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point title	Number of Subjects in Partial Mayo Score (PMS) Remission at Months 1, 4, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81 and 84: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point description:

PMS was an instrument designed to measure disease activity of UC without endoscopy. It consisted of 3 sub scores: stool frequency, rectal bleeding and PGA, each sub score graded from 0 to 3 with higher scores indicated higher disease severity. These sub scores were summed up to give a total score range of 0 to 9, where higher score indicated more severe disease. PMS remission was defined as a partial Mayo score <=2 with no individual sub score >1. FAS included all subjects who received at least 1 dose of study medication in this study. Here, "n" signifies subjects evaluable at each specified time point. NRI method was used for missing data at all visits except for visits after a participant advanced to other studies and would reach the visits if the subject stayed in the study where LOCF method was used.

End point type	Secondary

End point timeframe:

Months 1, 4, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81 and 84

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: subjects				
Month 1 (n= 175, 769)	158	275		
Month 4 (n= 175, 769)	152	375		
Month 6 (n= 175, 769)	155	395		
Month 9 (n= 175, 769)	154	390		
Month 15 (n= 175, 769)	139	361		
Month 18 (n= 175, 769)	137	354		
Month 21 (n= 175, 769)	125	351		
Month 27 (n= 175, 769)	117	325		
Month 30 (n= 175, 769)	117	316		
Month 33 (n= 175, 769)	114	317		
Month 39 (n= 175, 769)	108	293		
Month 42 (n= 175, 769)	102	286		
Month 45 (n= 175, 769)	102	283		
Month 48 (n= 175, 769)	95	274		
Month 51 (n= 175, 769)	96	267		
Month 54 (n= 170, 764)	76	250		
Month 57 (n= 160, 753)	61	234		
Month 60 (n= 149, 732)	44	213		
Month 63 (n= 135, 707)	31	194		
Month 66 (n= 125, 659)	22	168		
Month 69 (n= 114, 562)	13	131		
Month 72 (n= 109, 468)	7	102		
Month 75 (n= 102, 412)	3	73		
Month 78 (n= 96, 339)	4	52		
Month 81 (n= 95, 284)	0	29		
Month 84 (n= 91, 210)	0	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Achieved Mucosal Healing at Months 2, 12, 24 and 36: Observed Cases

End point title	Number of Subjects who Achieved Mucosal Healing at Months 2, 12, 24 and 36: Observed Cases

End point description:

Mucosal healing in subjects was defined as mayo endoscopic sub score of 0 or 1. The mayo endoscopic sub score consisted of the findings of flexible sigmoidoscopy, graded from 0 to 3 with higher sub scores

indicated higher disease severity. FAS included all subjects who received at least 1 dose of study medication in this study. Here, "Number of subjects analysed" signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable at each specified time point. Data is presented for observed cases, no imputation technique was applied.

End point type	Secondary

End point timeframe:

Months 2, 12, 24 and 36

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	690		
Units: subjects				
Month 2 (n= 169, 690)	152	279		
Month 12 (n= 156, 458)	140	340		
Month 24 (n= 136, 382)	119	307		
Month 36 (n= 115, 307)	107	265		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Achieved Mucosal Healing at Months 2, 12, 24 and 36: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point title	Number of Subjects who Achieved Mucosal Healing at Months 2, 12, 24 and 36: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point description:

Mucosal healing in subjects was defined as mayo endoscopic sub score of 0 or 1. The mayo endoscopic sub score consisted of the findings of flexible sigmoidoscopy, graded from 0 to 3 with higher sub scores indicating higher disease severity. FAS included all subjects who received at least 1 dose of study medication in this study. NRI method was used for missing data at all visits and LOCF method was used for visits after a subject advanced to next study.

End point type	Secondary

End point timeframe:

Months 2, 12, 24 and 36

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: subjects				
Month 2	152	279		
Month 12	140	340		
Month 24	119	307		
Month 36	113	285		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Total Inflammatory Bowel Disease Questionnaire (IBDQ) Score >=170 at Months 2, 6, 12, 18, 24, 30, 36, 48, 60, 72 and 84: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point title	Number of Subjects With Total Inflammatory Bowel Disease Questionnaire (IBDQ) Score >=170 at Months 2, 6, 12, 18, 24, 30, 36, 48, 60, 72 and 84: Non-responder Imputation- Last Observation Carried Forward (NRI-LOCF)

End point description:

IBDQ was a psychometrically validated patient reported outcome (PRO) instrument for measuring the disease-specific quality of life in subjects with inflammatory bowel disease (IBD), including ulcerative colitis consisted of 32 items scored from 1 (worst response) to 7 (best response). For each domain, higher score indicates better quality of life (QOL). Total score was the sum of each item score, and ranged from 32 to 224 with a higher score indicated better QOL. FAS included all subjects who received at least 1 dose of study medication in this study. Here, "n" signifies subjects evaluable at each specified time point. NRI method was used for missing data at all visits except for visits after a subject advanced to other studies and would reach the visits if the subject stayed in the study where LOCF method was used.

End point type	Secondary

End point timeframe:

Months 2, 6, 12, 18, 24, 30, 36, 48, 60, 72 and 84

End point values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	769		
Units: subjects				
Month 2 (n= 175, 769)	154	419		
Month 6 (n= 175, 769)	151	395		
Month 12 (n= 175, 769)	140	365		
Month 18 (n= 175, 769)	123	354		
Month 24 (n= 175, 769)	120	315		
Month 30 (n= 175, 769)	115	299		
Month 36 (n= 175, 769)	111	294		
Month 48 (n= 175, 769)	93	265		
Month 60 (n= 149, 732)	45	215		
Month 72 (n= 109, 468)	8	99		
Month 84 (n= 91, 210)	0	14		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose of study drug (up to 81 months for Tofacitinib 5 mg BID group and up to 85 months for Tofacitinib 10 mg BID group)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Analysis performed on safety analysis set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Tofacitinib 5 mg BID

Reporting group description:

Subjects who completed Study A3921096 and were in remission at Week 52 of Study A3921096, received Tofacitinib 5 milligram (mg) tablets twice daily (BID) for maximum of 80 months in this Study A3921139. Remission was defined as total Mayo score <=2 with no individual sub score >1 and rectal bleeding sub score of 0.

Reporting group title	Tofacitinib 10 mg BID

Reporting group description:

Subjects who had completed Study A3921096 and not in remission, or who had early withdrawal due to treatment failure from Study A3921096, or who were non responders after completing A3921094 or A3921095 received Tofacitinib 10 mg tablets twice daily for maximum of 84 months in this Study A3921139.

Serious adverse events	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 175 (22.29%)	147 / 769 (19.12%)	
number of deaths (all causes)	0	6	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma metastatic			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma of colon			

subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoma benign			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	2 / 175 (1.14%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 175 (1.14%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	1 / 175 (0.57%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer metastatic			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus associated lymphoma			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic angiosarcoma			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyosarcoma			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Meningioma			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 175 (0.57%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest discomfort			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 175 (0.57%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix haemorrhage uterine			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ovarian cyst			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 175 (0.00%)	5 / 769 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary mass			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Suicide attempt			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 175 (0.57%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	2 / 175 (1.14%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ligament rupture			
subjects affected / exposed	2 / 175 (1.14%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 175 (0.57%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar haemorrhage			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal skin tags			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	4 / 175 (2.29%)	38 / 769 (4.94%)	
occurrences causally related to treatment / all	0 / 4	4 / 39	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon dysplasia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frequent bowel movements			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 175 (0.57%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			

subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acne conglobata			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis contact			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic pustular folliculitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema nodosum			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	1 / 175 (0.57%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid mass			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	1 / 175 (0.57%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoroacetabular impingement			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Anal abscess			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 175 (0.00%)	3 / 769 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial vaginosis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated appendicitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus hepatitis			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 175 (0.57%)	4 / 769 (0.52%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histoplasmosis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mycosis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 175 (0.00%)	2 / 769 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 769 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 175 (0.00%)	1 / 769 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 175 (76.57%)	550 / 769 (71.52%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	4 / 175 (2.29%)	14 / 769 (1.82%)	
occurrences (all)	4	15	
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 175 (9.71%)	28 / 769 (3.64%)	
occurrences (all)	18	31	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 175 (2.86%)	33 / 769 (4.29%)	
occurrences (all)	6	37	
Oedema peripheral			
subjects affected / exposed	4 / 175 (2.29%)	13 / 769 (1.69%)	
occurrences (all)	4	14	
Pyrexia			
subjects affected / exposed	2 / 175 (1.14%)	25 / 769 (3.25%)	
occurrences (all)	2	28	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 175 (8.00%)	38 / 769 (4.94%)	
occurrences (all)	19	41	
Dyspnoea			
subjects affected / exposed	5 / 175 (2.86%)	7 / 769 (0.91%)	
occurrences (all)	5	8	
Rhinorrhoea			

subjects affected / exposed	4 / 175 (2.29%)	4 / 769 (0.52%)	
occurrences (all)	4	4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 175 (3.43%)	16 / 769 (2.08%)	
occurrences (all)	6	16	
Depression			
subjects affected / exposed	4 / 175 (2.29%)	12 / 769 (1.56%)	
occurrences (all)	5	12	
Insomnia			
subjects affected / exposed	5 / 175 (2.86%)	18 / 769 (2.34%)	
occurrences (all)	5	19	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 175 (3.43%)	11 / 769 (1.43%)	
occurrences (all)	6	11	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 175 (2.86%)	8 / 769 (1.04%)	
occurrences (all)	5	8	
Blood cholesterol increased			
subjects affected / exposed	7 / 175 (4.00%)	18 / 769 (2.34%)	
occurrences (all)	7	20	
Blood creatine phosphokinase increased			
subjects affected / exposed	19 / 175 (10.86%)	85 / 769 (11.05%)	
occurrences (all)	22	108	
Lymphocyte count decreased			
subjects affected / exposed	3 / 175 (1.71%)	18 / 769 (2.34%)	
occurrences (all)	7	24	
White blood cell count decreased			
subjects affected / exposed	4 / 175 (2.29%)	8 / 769 (1.04%)	
occurrences (all)	5	9	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	4 / 175 (2.29%)	8 / 769 (1.04%)	
occurrences (all)	4	8	

Skin laceration			
subjects affected / exposed	5 / 175 (2.86%)	4 / 769 (0.52%)	
occurrences (all)	5	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 175 (2.29%)	14 / 769 (1.82%)	
occurrences (all)	4	15	
Headache			
subjects affected / exposed	12 / 175 (6.86%)	57 / 769 (7.41%)	
occurrences (all)	23	81	
Paraesthesia			
subjects affected / exposed	2 / 175 (1.14%)	17 / 769 (2.21%)	
occurrences (all)	2	17	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 175 (1.71%)	36 / 769 (4.68%)	
occurrences (all)	4	38	
Lymphopenia			
subjects affected / exposed	6 / 175 (3.43%)	13 / 769 (1.69%)	
occurrences (all)	9	23	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 175 (3.43%)	47 / 769 (6.11%)	
occurrences (all)	8	54	
Abdominal pain upper			
subjects affected / exposed	4 / 175 (2.29%)	24 / 769 (3.12%)	
occurrences (all)	8	33	
Colitis ulcerative			
subjects affected / exposed	44 / 175 (25.14%)	131 / 769 (17.04%)	
occurrences (all)	57	150	
Constipation			
subjects affected / exposed	7 / 175 (4.00%)	20 / 769 (2.60%)	
occurrences (all)	7	20	
Diarrhoea			
subjects affected / exposed	9 / 175 (5.14%)	34 / 769 (4.42%)	
occurrences (all)	11	38	
Dyspepsia			

subjects affected / exposed	8 / 175 (4.57%)	12 / 769 (1.56%)	
occurrences (all)	9	12	
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 175 (5.71%)	15 / 769 (1.95%)	
occurrences (all)	11	15	
Haemorrhoids			
subjects affected / exposed	3 / 175 (1.71%)	20 / 769 (2.60%)	
occurrences (all)	3	21	
Nausea			
subjects affected / exposed	1 / 175 (0.57%)	30 / 769 (3.90%)	
occurrences (all)	1	37	
Vomiting			
subjects affected / exposed	3 / 175 (1.71%)	20 / 769 (2.60%)	
occurrences (all)	3	23	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 175 (2.86%)	20 / 769 (2.60%)	
occurrences (all)	5	22	
Rash			
subjects affected / exposed	4 / 175 (2.29%)	38 / 769 (4.94%)	
occurrences (all)	4	41	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 175 (9.71%)	76 / 769 (9.88%)	
occurrences (all)	22	96	
Back pain			
subjects affected / exposed	11 / 175 (6.29%)	28 / 769 (3.64%)	
occurrences (all)	16	31	
Musculoskeletal pain			
subjects affected / exposed	2 / 175 (1.14%)	18 / 769 (2.34%)	
occurrences (all)	2	24	
Myalgia			
subjects affected / exposed	6 / 175 (3.43%)	10 / 769 (1.30%)	
occurrences (all)	6	12	
Osteoarthritis			

subjects affected / exposed	6 / 175 (3.43%)	9 / 769 (1.17%)	
occurrences (all)	6	10	
Tendonitis			
subjects affected / exposed	5 / 175 (2.86%)	4 / 769 (0.52%)	
occurrences (all)	5	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	17 / 175 (9.71%)	30 / 769 (3.90%)	
occurrences (all)	26	44	
Ear infection			
subjects affected / exposed	4 / 175 (2.29%)	6 / 769 (0.78%)	
occurrences (all)	4	6	
Gastroenteritis			
subjects affected / exposed	12 / 175 (6.86%)	51 / 769 (6.63%)	
occurrences (all)	15	60	
Herpes zoster			
subjects affected / exposed	12 / 175 (6.86%)	50 / 769 (6.50%)	
occurrences (all)	13	52	
Influenza			
subjects affected / exposed	23 / 175 (13.14%)	63 / 769 (8.19%)	
occurrences (all)	32	76	
Latent tuberculosis			
subjects affected / exposed	4 / 175 (2.29%)	13 / 769 (1.69%)	
occurrences (all)	4	13	
Oral herpes			
subjects affected / exposed	1 / 175 (0.57%)	18 / 769 (2.34%)	
occurrences (all)	3	42	
Nasopharyngitis			
subjects affected / exposed	41 / 175 (23.43%)	157 / 769 (20.42%)	
occurrences (all)	91	302	
Pharyngitis			
subjects affected / exposed	8 / 175 (4.57%)	14 / 769 (1.82%)	
occurrences (all)	8	16	
Pneumonia			
subjects affected / exposed	4 / 175 (2.29%)	9 / 769 (1.17%)	
occurrences (all)	5	9	

Sinusitis			
subjects affected / exposed	8 / 175 (4.57%)	25 / 769 (3.25%)	
occurrences (all)	13	30	
Rhinitis			
subjects affected / exposed	5 / 175 (2.86%)	7 / 769 (0.91%)	
occurrences (all)	5	8	
Upper respiratory tract infection			
subjects affected / exposed	19 / 175 (10.86%)	77 / 769 (10.01%)	
occurrences (all)	27	114	
Urinary tract infection			
subjects affected / exposed	13 / 175 (7.43%)	34 / 769 (4.42%)	
occurrences (all)	20	60	
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 175 (2.86%)	7 / 769 (0.91%)	
occurrences (all)	5	7	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 175 (0.57%)	38 / 769 (4.94%)	
occurrences (all)	1	43	
Hyperlipidaemia			
subjects affected / exposed	4 / 175 (2.29%)	10 / 769 (1.30%)	
occurrences (all)	4	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2018	This amendment specified the end of the trial will be approximately in July 2020. This 2 year extension of the study allowed for additional collection of long term safety and efficacy data in UC patients on tofacitinib.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported