Clinical trial results:
A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Of Oral Cp-690,550 As An Induction Therapy In Subjects With Moderate To Severe Ulcerative Colitis

Summary

EudraCT number	2011-004578-27
Trial protocol	GB CZ DK HU EE LV DE BE ES NL AT SK PL IT HR
Global end of trial date	22 May 2015

Results information

Result version number	v1 (current)
This version publication date	18 May 2016
First version publication date	18 May 2016

Trial information

Trial identification

Sponsor protocol code	A3921094

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01465763
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 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	30 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of tofacitinib in inducing remission in subjects with moderately to severely active ulcerative colitis (UC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and incompliance 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:

Subjects were permitted to continue stable doses of the following during the study: oral 5-aminosalicylic acid or sulfasalazine, oral corticosteroids up to 25 mg/day prednisone equivalent, and/or chronic antibiotics for UC treatment.

Evidence for comparator: -

Actual start date of recruitment	18 April 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: 12
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Belgium: 50
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Japan: 65
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	New Zealand: 19

Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Serbia: 34
Country: Number of subjects enrolled	Slovakia: 9
Country: Number of subjects enrolled	South Africa: 15
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Ukraine: 39
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	United States: 120
Worldwide total number of subjects	614
EEA total number of subjects	260

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)	566
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were randomized to tofacitinib 10 milligram (mg) or placebo twice a day (BID) (4:1 ratio) after protocol amendment 3, which removed tofacitinib 15 mg BID. Due to low subject numbers, tofacitinib 15 mg BID was excluded from efficacy analyses, but was included in subject disposition, baseline characteristics and adverse events analyses.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Tofacitinib 10 mg BID

Arm description:

Subjects received tofacitinib 10 mg, tablets, orally, BID for 9 weeks of double blind treatment period.

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, BID for 9 weeks of double blind treatment period.

Arm title	Tofacitinib 15 mg BID

Arm description:

Subjects received tofacitinib 15 mg, tablets, orally, BID for 9 weeks of double blind treatment period.

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 15 mg, BID for 9 weeks of double blind treatment period.

Arm title	Placebo BID

Arm description:

Subjects received tofacitinib-matched placebo tablets, orally, BID for 9 weeks of double blind treatment period.

Arm type	Placebo

Investigational medicinal product name	Tofacitinib-matched placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tofacitinib-matched placebo BID for 9 weeks of double blind treatment period.

Number of subjects in period 1	Tofacitinib 10 mg BID	Tofacitinib 15 mg BID	Placebo BID
Started	476	16	122
Completed	445	15	118
Not completed	31	1	4
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	4	-	1
Adverse event, non-fatal	9	-	1
Insufficient Clinical Response	11	-	1
Unspecified	2	-	-
Protocol deviation	4	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Tofacitinib 10 mg BID
Reporting group description:	
Subjects received tofacitinib 10 mg, tablets, orally, BID for 9 weeks of double blind treatment period.	
Reporting group title	Tofacitinib 15 mg BID
Reporting group description:	
Subjects received tofacitinib 15 mg, tablets, orally, BID for 9 weeks of double blind treatment period.	
Reporting group title	Placebo BID
Reporting group description:	
Subjects received tofacitinib-matched placebo tablets, orally, BID for 9 weeks of double blind treatment period.	

Reporting group values	Tofacitinib 10 mg BID	Tofacitinib 15 mg BID	Placebo BID
Number of subjects	476	16	122
Age categorical Units: Subjects			
18 to 44 Years	295	11	72
45 to 64 Years	145	4	39
Greater Than or Equal to (>=) 65 Years	36	1	11
Gender, Male/Female Units: Subjects			
Female	199	7	45
Male	277	9	77

Reporting group values	Total		
Number of subjects	614		
Age categorical Units: Subjects			
18 to 44 Years	378		
45 to 64 Years	188		
Greater Than or Equal to (>=) 65 Years	48		
Gender, Male/Female Units: Subjects			
Female	251		
Male	363		

End points

End points reporting groups

Reporting group title	Tofacitinib 10 mg BID
Reporting group description:	
Subjects received tofacitinib 10 mg, tablets, orally, BID for 9 weeks of double blind treatment period.	
Reporting group title	Tofacitinib 15 mg BID
Reporting group description:	
Subjects received tofacitinib 15 mg, tablets, orally, BID for 9 weeks of double blind treatment period.	
Reporting group title	Placebo BID
Reporting group description:	
Subjects received tofacitinib-matched placebo tablets, orally, BID for 9 weeks of double blind treatment period.	

Primary: Percentage of Subjects With Remission at Week 8

End point title	Percentage of Subjects With Remission at Week 8[1]
End point description:	
Remission in subjects was defined by a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0. Mayo score is an instrument designed to measure disease activity of ulcerative colitis (UC). It consisted of 4 subscores: stool frequency, rectal bleeding, findings of centrally read flexible proctosigmoidoscopy and physician global assessment (PGA), each graded from 0 to 3 with higher scores indicating more severe disease. These scores were summed up to give a total score range of 0 to 12; where higher scores indicating more severe disease. Full analysis set (FAS) included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID.	
End point type	Primary
End point timeframe:	
Week 8	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be reported for this endpoint.	

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: percentage of subjects				
number (not applicable)	18.5	8.2		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8
Statistical analysis description:	
P-value based on Cochran-Mantel-Haenszel (CMH) chi-square test stratified by prior treatment with anti-tumor necrosis factor (TNF), steroid use at baseline and geographic region. Difference and its 95% CI based on normal approximation for the difference in binomial proportions. Missing data were imputed using non-responder imputation (NRI).	
Comparison groups	Tofacitinib 10 mg BID v Placebo BID

Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	CMH Chi-square test
Parameter estimate	Percent Difference
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	16.3

Secondary: Percentage of Subjects Achieving Mucosal Healing at Week 8

End point title	Percentage of Subjects Achieving Mucosal Healing at Week 8[2]

End point description:

Mucosal healing in subjects was defined by Mayo endoscopic subscore of 0 or 1. The Mayo endoscopic subscore consisted of the findings of centrally read flexible proctosigmoidoscopy, graded from 0 to 3 with higher scores indicating more severe disease. FAS included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID.

End point type	Secondary

End point timeframe:

Week 8

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: percentage of subjects				
number (not applicable)	31.3	15.6		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8

Statistical analysis description:

P-value based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Difference and its 95% CI based on normal approximation for the difference in binomial proportions. Missing data were imputed using NRI.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID

Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	CMH Chi-square test
Parameter estimate	Percent Difference
Point estimate	15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.1
upper limit	23.4

Secondary: Percentage of Subjects Achieving Clinical Response at Week 8

End point title	Percentage of Subjects Achieving Clinical Response at Week

End point description:

Clinical response in subjects was defined by a decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. Mayo score is an instrument designed to measure disease activity of UC. It consisted of 4 subscores: stool frequency, rectal bleeding, findings of centrally read flexible proctosigmoidoscopy and PGA, each graded from 0 to 3 with higher scores indicating more severe disease. These scores were summed up to give a total score range of 0 to 12; where higher scores indicating more severe disease. FAS included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID.

End point type	Secondary

End point timeframe:

Week 8

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: percentage of subjects				
number (not applicable)	59.9	32.8		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8

Statistical analysis description:

P-value based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Difference and its 95% CI based on normal approximation for the difference in binomial proportions. Missing data were imputed using NRI.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID

Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	CMH Chi-square test
Parameter estimate	Percent Difference
Point estimate	27.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.7
upper limit	36.5

Secondary: Percentage of Subjects With Endoscopic Remission at Week 8

End point title	Percentage of Subjects With Endoscopic Remission at Week 8[4]

End point description:

Endoscopic remission in subjects was defined by Mayo endoscopic subscore of 0. The Mayo endoscopic subscore consisted of the findings of centrally read flexible proctosigmoidoscopy, graded from 0 to 3 with higher scores indicating more severe disease. FAS included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID.

End point type	Secondary

End point timeframe:

Week 8

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: percentage of subjects				
number (not applicable)	6.7	1.6		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8

Statistical analysis description:

P-value based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Difference and its 95% CI based on normal approximation for the difference in binomial proportions. Missing data were imputed using NRI.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID

Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0345
Method	CMH Chi-square test
Parameter estimate	Percent Difference
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	8.3

Secondary: Percentage of Subjects With Clinical Remission at Week 8

End point title	Percentage of Subjects With Clinical Remission at Week 8[5]

End point description:

Clinical remission in subjects was defined by a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mayo score is an instrument designed to measure disease activity of UC. It consisted of 4 subscores: stool frequency, rectal bleeding, findings of centrally read flexible proctosigmoidoscopy and PGA, each graded from 0 to 3 with higher scores indicating more severe disease. These scores were summed up to give a total score range of 0 to 12; where higher scores indicating more severe disease. FAS included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID.

End point type	Secondary

End point timeframe:

Week 8

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: percentage of subjects				
number (not applicable)	18.5	8.2		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8

Statistical analysis description:

P-value based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Difference and its 95% CI based on normal approximation for the difference in binomial proportions. Missing data were imputed using NRI.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID

Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	CMH Chi-square test
Parameter estimate	Percent Difference
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	16.3

Secondary: Percentage of Subjects With Symptomatic Remission at Week 8

End point title	Percentage of Subjects With Symptomatic Remission at Week

End point description:

Symptomatic remission in subjects was defined by a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, and 0 subscore for both rectal bleeding and stool frequency. Mayo score is an instrument designed to measure disease activity of UC. It consisted of 4 subscores: stool frequency, rectal bleeding, findings of centrally read flexible proctosigmoidoscopy and PGA, each graded from 0 to 3 with higher scores indicating more severe disease. These scores were summed up to give a total score range of 0 to 12; where higher scores indicating more severe disease. FAS included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID.

End point type	Secondary

End point timeframe:

Week 8

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: percentage of subjects				
number (not applicable)	11.8	5.7		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8

Statistical analysis description:

P-value based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Difference and its 95% CI based on normal approximation for the difference in binomial proportions. Missing data were imputed using NRI.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID

Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0601
Method	CMH Chi-square test
Parameter estimate	Percent Difference
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	11.1

Secondary: Percentage of Subjects With Deep Remission at Week 8

End point title	Percentage of Subjects With Deep Remission at Week 8[7]

End point description:

Deep remission in subjects was defined by a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and 0 subscore for both rectal bleeding and endoscopic subscores. Mayo score is an instrument designed to measure disease activity of UC. It consisted of 4 subscores: stool frequency, rectal bleeding, findings of centrally read flexible proctosigmoidoscopy and PGA, each graded from 0 to 3 with higher scores indicating more severe disease. These scores were summed up to give a total score range of 0 to 12; where higher scores indicating more severe disease. These 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 randomly assigned to either tofacitinib 10 mg BID or placebo BID.

End point type	Secondary

End point timeframe:

Week 8

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: percentage of subjects				
number (not applicable)	6.5	0		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8

Statistical analysis description:

P-value based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Difference and its 95% CI based on normal approximation for the difference in binomial proportions. Missing data were imputed using NRI.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID

Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0043
Method	CMH Chi-square test
Parameter estimate	Percent Difference
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	8.7

Secondary: Partial Mayo Scores

End point title	Partial Mayo Scores[8]

End point description:

A Partial Mayo Score (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and calculated as the sum of 3 subscores (stool frequency, rectal bleeding and PGA) with each graded from 0 to 3 with higher scores indicating more severe disease. FAS included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID. Here, 'n' signifies those subjects who were evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline: (n= 475, 121)	6.3 (± 1.2)	6.5 (± 1.2)		
At Week 2: (n= 465, 122)	4.2 (± 2.2)	5.2 (± 2.1)		
At Week 4: (n= 461, 118)	3.5 (± 2.3)	4.8 (± 2.4)		
At week 8: (n= 449, 119)	3.2 (± 2.4)	4.8 (± 2.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Partial Mayo Scores at Weeks 2, 4 and 8

End point title	Change From Baseline in Partial Mayo Scores at Weeks 2, 4 and 8[9]

End point description:

Change in partial mayo scores at weeks 2, 4, 8 relative to baseline were reported. A Partial Mayo Score

(Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and calculated as the sum of 3 subscores (stool frequency, rectal bleeding and PGA) with each graded from 0 to 3 with higher scores indicating more severe disease. FAS included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID. Here, 'n' signifies those subjects who were evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 2: (n= 464, 121)	-2.1 (± 0.1)	-1.2 (± 0.2)		
Change at week 4: (n= 460, 117)	-2.8 (± 0.1)	-1.6 (± 0.2)		
Change at week 8: (n= 448, 118)	-3.1 (± 0.1)	-1.6 (± 0.2)		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 2

Statistical analysis description:

The change from baseline was analyzed using mixed effect model with treatment group, prior treatment with antiTNF, steroid use at baseline, geographic region, visit and visit by treatment group all as fixed effects, and subjects as a random effect.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-Effects Model
Parameter estimate	Least Square Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 4

Statistical analysis description:

The change from baseline was analyzed using mixed effect model with treatment group, prior treatment

with antiTNF, steroid use at baseline, geographic region, visit and visit by treatment group all as fixed effects, and subjects as a random effect.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-Effects Model
Parameter estimate	Least Square Mean Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.7
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8

Statistical analysis description:

The change from baseline was analyzed using mixed effect model with treatment group, prior treatment with antiTNF, steroid use at baseline, geographic region, visit and visit by treatment group all as fixed effects, and subjects as a random effect.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-Effects Model
Parameter estimate	Least Square Mean Difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	0.2

Secondary: Change From Baseline in Total Mayo Scores at Week 8

End point title	Change From Baseline in Total Mayo Scores at Week 8[10]

End point description:

Change in total Mayo scores at Week 8 relative to Baseline was reported. Mayo score is an instrument designed to measure disease activity of UC. It consisted of 4 subscores: stool frequency, rectal bleeding, findings of centrally read flexible proctosigmoidoscopy and physician global assessment (PGA), each graded from 0 to 3 with higher scores indicating more severe disease. These scores were summed up to give a total score range of 0 to 12; where higher score indicating more severe disease. FAS included all subjects randomly assigned to either tofacitinib 10 mg BID or placebo BID. Here, 'n' signifies those subjects who were evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 8

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Tofacitinib 10 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	122		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 472, 121)	9 (± 1.4)	9.1 (± 1.4)		
Change at Week 8 (n= 443, 117)	-3.8 (± 2.8)	-1.9 (± 2.5)		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8

Statistical analysis description:

The change from baseline at Week 8 was analyzed using an analysis of covariance (ANCOVA) model with treatment group, prior treatment with anti-TNF, steroid use at baseline and geographic region as factors and baseline as a covariate based on the observed-case data.

Comparison groups	Tofacitinib 10 mg BID v Placebo BID
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-1.4
Variability estimate	Standard error of the mean
Dispersion value	0.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 98

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and an serious adverse event (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Tofacitinib 10 mg BID

Reporting group description:

Subjects received tofacitinib 10 mg, tablets, orally, BID for 9 weeks of double blind treatment period.

Reporting group title	Placebo BID

Reporting group description:

Subjects received tofacitinib-matched placebo tablets, orally, BID for 9 weeks of double blind treatment period.

Reporting group title	Tofacitinib 15 mg BID

Reporting group description:

Subjects received tofacitinib 15 mg, tablets, orally, BID for 9 weeks of double blind treatment period.

Serious adverse events	Tofacitinib 10 mg BID	Placebo BID	Tofacitinib 15 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 476 (3.36%)	5 / 122 (4.10%)	0 / 16 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 476 (0.00%)	1 / 122 (0.82%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Aortic dissection			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Temporal arteritis			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	5 / 476 (1.05%)	2 / 122 (1.64%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vulva cyst			

subjects affected / exposed	0 / 476 (0.00%)	1 / 122 (0.82%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 476 (0.00%)	1 / 122 (0.82%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			

subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tofacitinib 10 mg BID	Placebo BID	Tofacitinib 15 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 476 (31.09%)	38 / 122 (31.15%)	12 / 16 (75.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	12 / 476 (2.52%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	12	0	1
Liver function test abnormal			
subjects affected / exposed	0 / 476 (0.00%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
White blood cell count increased			
subjects affected / exposed	0 / 476 (0.00%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	37 / 476 (7.77%)	8 / 122 (6.56%)	0 / 16 (0.00%)
occurrences (all)	42	8	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 476 (2.31%)	6 / 122 (4.92%)	1 / 16 (6.25%)
occurrences (all)	12	6	4

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 476 (2.10%)	4 / 122 (3.28%)	1 / 16 (6.25%)
occurrences (all)	10	4	1
Pyrexia			
subjects affected / exposed	14 / 476 (2.94%)	3 / 122 (2.46%)	1 / 16 (6.25%)
occurrences (all)	15	3	1
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	6 / 476 (1.26%)	3 / 122 (2.46%)	1 / 16 (6.25%)
occurrences (all)	6	3	1
Flatulence			
subjects affected / exposed	2 / 476 (0.42%)	1 / 122 (0.82%)	1 / 16 (6.25%)
occurrences (all)	2	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 476 (0.00%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	15 / 476 (3.15%)	5 / 122 (4.10%)	1 / 16 (6.25%)
occurrences (all)	16	5	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	10 / 476 (2.10%)	0 / 122 (0.00%)	3 / 16 (18.75%)
occurrences (all)	10	0	3
Alopecia			
subjects affected / exposed	5 / 476 (1.05%)	1 / 122 (0.82%)	1 / 16 (6.25%)
occurrences (all)	5	1	1
Dermatitis acneiform			
subjects affected / exposed	0 / 476 (0.00%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 476 (0.00%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			

subjects affected / exposed	0 / 476 (0.00%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	1 / 476 (0.21%)	1 / 122 (0.82%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 476 (0.21%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Haematuria			
subjects affected / exposed	0 / 476 (0.00%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 476 (0.42%)	2 / 122 (1.64%)	1 / 16 (6.25%)
occurrences (all)	2	2	1
Infections and infestations			
Folliculitis			
subjects affected / exposed	9 / 476 (1.89%)	0 / 122 (0.00%)	1 / 16 (6.25%)
occurrences (all)	9	0	1
Gastroenteritis			
subjects affected / exposed	7 / 476 (1.47%)	2 / 122 (1.64%)	1 / 16 (6.25%)
occurrences (all)	7	2	1
Nasopharyngitis			
subjects affected / exposed	34 / 476 (7.14%)	9 / 122 (7.38%)	3 / 16 (18.75%)
occurrences (all)	39	11	3
Sinusitis			
subjects affected / exposed	2 / 476 (0.42%)	1 / 122 (0.82%)	2 / 16 (12.50%)
occurrences (all)	2	1	2
Upper respiratory tract infection			
subjects affected / exposed	15 / 476 (3.15%)	1 / 122 (0.82%)	1 / 16 (6.25%)
occurrences (all)	15	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2011	Japan specific safety screening and monitoring requirements were added.
30 November 2012	Tofacitinib 15 mg BID arm was removed. Prior to this, subjects were randomized to tofacitinib 10 mg BID, tofacitinib 15 mg BID, or placebo BID (2:2:1 ratio).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported