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	2011-004579-35
Trial protocol	GB CZ HU EE DK LV BE ES NL AT DE SK PL HR
Global end of trial date	09 June 2015

Results information

Result version number	v1 (current)
This version publication date	15 May 2016
First version publication date	15 May 2016

Trial information

Trial identification

Sponsor protocol code	A3921095

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01458951
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 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, 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	12 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 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 in compliance with all International Council on Harmonization (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-ASA 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	21 June 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: 22
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 58
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Netherlands: 37
Country: Number of subjects enrolled	New Zealand: 17

Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Slovakia: 28
Country: Number of subjects enrolled	South Africa: 18
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 95
Worldwide total number of subjects	547
EEA total number of subjects	268

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)	517
From 65 to 84 years	30
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 2, 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 tablets orally 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 tablets orally 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	429	6	112
Completed	397	5	97
Not completed	32	1	15
Consent withdrawn by subject	2	-	2
Adverse Event	7	-	2
Insufficient Clinical Response	17	-	11
Unspecified	1	-	-
Protocol deviation	5	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	429	6	112
Age categorical Units: Subjects			
18 to 44 Years	265	5	72
45 to 64 Years	139	1	35
Greater Than or Equal to (>=) 65 Years	25	0	5
Gender, Male/Female Units: Subjects			
Female	170	3	57
Male	259	3	55

Reporting group values	Total		
Number of subjects	547		
Age categorical Units: Subjects			
18 to 44 Years	342		
45 to 64 Years	175		
Greater Than or Equal to (>=) 65 Years	30		
Gender, Male/Female Units: Subjects			
Female	230		
Male	317		

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 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. Full analysis set included all subjects who were 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	429	112		
Units: percentage of subjects				
number (not applicable)	16.6	3.6		

Statistical analyses

Statistical analysis title	Tofacitinib 10 mg BID vs. Placebo BID at Week 8
Statistical analysis description:	
P-value was 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. Percentage difference and its 95 percent Confidence interval (CI) was 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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	CMH Chi-square Test
Parameter estimate	Percentage difference
Point estimate	13
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.1
upper limit	17.9

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. Full analysis set included all subjects who were 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	429	112		
Units: percentage of subjects				
number (not applicable)	28.4	11.6		

Statistical analyses

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

Statistical analysis description:

P-value was based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Percentage difference and its 95% CI was 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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	CMH Chi-square Test
Parameter estimate	Percentage difference
Point estimate	16.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.5
upper limit	24.1

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 sub score of at least 1 point or an absolute rectal bleeding sub score 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 flexible centrally read 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 score indicating more severe disease. Full analysis set included all subjects who were 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	429	112		
Units: percentage of subjects				
number (not applicable)	55	28.6		

Statistical analyses

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

Statistical analysis description:

P-value was based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Percentage difference and its 95% CI was 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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	CMH Chi-square Test
Parameter estimate	Percentage difference
Point estimate	26.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.8
upper limit	36

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. Full analysis set included all subjects who were 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	429	112		
Units: percentage of subjects				
number (not applicable)	7	1.8		

Statistical analyses

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

Statistical analysis description:

P-value was based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Percentage difference and its 95% CI was 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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0425
Method	CMH Chi-square Test
Parameter estimate	Percentage difference
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	8.6

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 flexible centrally read 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 score indicating more severe disease. Full analysis set included all subjects who were 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	429	112		
Units: percentage of subjects				
number (not applicable)	16.8	3.6		

Statistical analyses

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

Statistical analysis description:

P-value was based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Percentage difference and its 95% CI was 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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	CMH Chi-square Test
Parameter estimate	Percentage difference
Point estimate	13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.3
upper limit	18.1

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 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 flexible centrally read 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 score indicated more severe disease. Full analysis set indicating all subjects who were 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	429	112		
Units: percentage of subjects				
number (not applicable)	10.7	2.7		

Statistical analyses

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

Statistical analysis description:

P-value was based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Percentage difference and its 95% CI was 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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	CMH Chi-square Test
Parameter estimate	Percentage difference
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	12.2

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 flexible centrally read 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 score indicating more severe disease. Full analysis set included all subjects who were 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	429	112		
Units: percentage of subjects				
number (not applicable)	5.1	1.8		

Statistical analyses

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

Statistical analysis description:

P-value was based on CMH chi-square test stratified by prior treatment with anti-TNF, steroid use at baseline and geographic region. Percentage difference and its 95% CI was 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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1408
Method	CMH Chi-square Test
Parameter estimate	Percentage difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	6.6

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) and each grading from 0 to 3 with higher scores indicating more severe disease. Full analysis set included all subjects who were 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	429	112		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 428, 112)	6.4 (± 1.3)	6.4 (± 1.2)		
Week 2 (n= 419, 107)	4.4 (± 2.2)	5.4 (± 1.7)		
Week 4 (n= 412, 102)	3.7 (± 2.3)	4.8 (± 2)		
Week 8 (n= 401, 98)	3.3 (± 2.3)	4.5 (± 2.1)		

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. Full analysis set included all subjects who were 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	429	112		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 2 (n= 418, 107)	-2 (± 0.1)	-1 (± 0.2)		
Change at Week 4 (n= 411, 102)	-2.7 (± 0.1)	-1.5 (± 0.2)		
Change at Week 8 (n= 400, 98)	-3 (± 0.1)	-1.7 (± 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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.6
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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
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	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	0.2

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

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

End point description:

Change in total Mayo score 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 flexible centrally read 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 score indicating more severe disease. Full analysis set included all subjects who were 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	429	112		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=428,112)	9 (± 1.5)	8.9 (± 1.5)		
Change at Week 8 (n=396,98)	-3.7 (± 2.8)	-2 (± 2.4)		

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	541
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-1
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 non serious 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	18 / 429 (4.20%)	9 / 112 (8.04%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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
Colon neoplasm			
subjects affected / exposed	0 / 429 (0.00%)	1 / 112 (0.89%)	0 / 6 (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
Injury, poisoning and procedural complications			

Femur fracture			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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			
Hypertension			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 429 (0.00%)	1 / 112 (0.89%)	0 / 6 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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
Chills			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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			
Abdominal pain			

subjects affected / exposed	2 / 429 (0.47%)	0 / 112 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 429 (0.00%)	1 / 112 (0.89%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	8 / 429 (1.86%)	4 / 112 (3.57%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 8	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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
Crohn’s disease			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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
Intestinal perforation			
subjects affected / exposed	0 / 429 (0.00%)	1 / 112 (0.89%)	0 / 6 (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
Proctalgia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Furuncle			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	0 / 6 (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
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 429 (0.00%)	1 / 112 (0.89%)	0 / 6 (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

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	68 / 429 (15.85%)	20 / 112 (17.86%)	4 / 6 (66.67%)
Investigations			
Urine analysis abnormal			
subjects affected / exposed	0 / 429 (0.00%)	0 / 112 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 429 (0.23%)	0 / 112 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 429 (7.69%)	9 / 112 (8.04%)	0 / 6 (0.00%)
occurrences (all)	41	9	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 429 (2.56%)	2 / 112 (1.79%)	1 / 6 (16.67%)
occurrences (all)	11	2	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 429 (1.63%)	6 / 112 (5.36%)	0 / 6 (0.00%)
occurrences (all)	7	6	0
Abdominal pain upper			
subjects affected / exposed	7 / 429 (1.63%)	0 / 112 (0.00%)	1 / 6 (16.67%)
occurrences (all)	7	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	11 / 429 (2.56%)	6 / 112 (5.36%)	0 / 6 (0.00%)
occurrences (all)	12	6	0
Infections and infestations			
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 429 (0.00%)	0 / 112 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	7 / 429 (1.63%)	0 / 112 (0.00%)	1 / 6 (16.67%)
occurrences (all)	7	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 429 (0.00%)	0 / 112 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
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