PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

GENERIC DRUG NAME and/or COMPOUND NUMBER: Tofacitinib/CP-690,550

PROTOCOL NO.: A3921094

PROTOCOL TITLE: 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

Study Center(s): The study was conducted at 113 study centers: Australia (3), Austria (1), Belgium (1), Canada (4), Colombia (1), Croatia (1), Czech Republic (2), Denmark (2), Estonia (1), France (3), Germany (4), Hungary (4), Israel (2), Italy (4), Japan (23), Latvia (1), Netherlands (1), New Zealand (3), Poland (4), Romania (1), Russian Federation (4), Serbia (4), Slovakia (1), South Africa (2), Spain (4), Ukraine (7), United Kingdom (UK) (2), and United States (US) (23). In addition, there were 31 study centers that received study drug but did not randomize any subjects.

Study Initiation Date and Final Completion Date: 18 April 2012 to 22 May 2015.

Phase of Development: Phase 3

Study Objective(s):

The primary objective of this study was:

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

The secondary objectives of this study were:

- To evaluate the safety and tolerability of tofacitinib in subjects with moderately to severely active UC;
- To evaluate the efficacy of tofacitinib in achieving mucosal healing in subjects with moderately to severely active UC;
- To evaluate the effect of tofacitinib induction therapy on other clinical outcomes in subjects with moderately to severely active UC;
- To evaluate tofacitinib pharmacokinetic (PK) exposure during induction therapy in subjects with moderately to severely active UC.

METHODS

Study Design: This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with moderately to severely active UC.

After the screening period, subjects who met the inclusion and exclusion criteria at the baseline visit were randomly assigned to receive 9 weeks of either tofacitinib 10 mg twice a day (BID) or matched placebo BID at a 4:1 allocation ratio. This reflected a change put in place with Protocol Amendment 3, which removed the tofacitinib 15 mg BID arm from the study. Subjects who were enrolled prior to Amendment 3 were randomly assigned to receive either tofacitinib 10 mg BID, tofacitinib 15 mg BID, or matched placebo BID at a 2:2:1 allocation ratio. Subjects who were randomized under the prior protocol and who were still active in this study at the time of the approval of Protocol Amendment 3 continued to receive blinded treatment assigned at baseline for the treatment period.

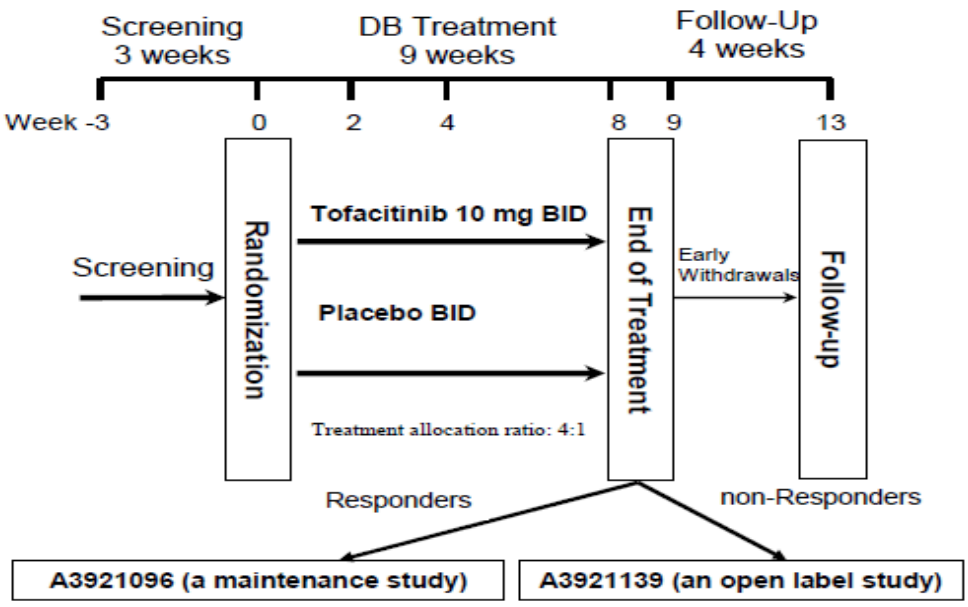
Subjects were stratified based on the status of prior treatment with tumor necrosis factor-alpha inhibitor (TNFi) therapy, corticosteroid use at baseline, and geographic region.

Subjects who completed the double-blind treatment and achieved clinical response or remission at Week 8 were eligible to enter a double-blind maintenance study (A3921096). Clinical response was defined by a decrease from baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point, or an absolute rectal bleeding subscore of 0 or 1. Remission 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.

Subjects who completed the double-blind treatment but did not achieve clinical response and did not show improvement on centrally read endoscopic subscores at Week 8 may have had an opportunity to enter an open-label study (A3921139).

Subjects who were early withdrawals from the study or who were not transferred into the maintenance study or open-label study had a 4-week safety follow-up after the last dose of study medication. A schematic of the study design is shown in Figure 1.

Figure 1 Overview of Study Design



BID = twice a day, DB = double-blind.

Number of Subjects (Planned): There were to be 545 subjects enrolled in the study and randomized in a 4:1 ratio to either tofacitinib 10 mg BID or placebo. Prior to Protocol Amendment 3, subjects were to be randomized in a 2:2:1 ratio to tofacitinib 10 mg BID, tofacitinib 15 mg BID, or placebo.

Diagnosis and Main Criteria for Inclusion: Subjects were men and women of at least 18 years of age with a diagnosis of UC that was documented at least 4 months prior to entering the study and who had moderately to severely active UC based on total Mayo score of ≥6 with a rectal bleeding score of ≥1, and an endoscopic subscore of ≥2 on the Mayo score determined within 10 days of baseline visit (Visit 2). All subjects had either failed or been intolerant of at least 1 of the following UC treatments: oral or intravenous (IV) corticosteroids, azathioprine or 6-mercaptopurine (6-MP), or TNFi therapy (infliximab or adalimumab).

Study Treatment: Subjects received their study medications as outpatients. Tofacitinib 10 mg or placebo was taken orally BID (approximately every 12 hours) for up to 9 weeks. Subjects were dispensed 2 bottles containing either 5 mg tofacitinib or placebo tablets. Subjects were instructed to take 1 tablet from each bottle in the morning and 1 tablet from each bottle in the evening, approximately 12 hours apart. Subjects were therefore taking 2 tablets BID.

Subjects enrolled prior to Protocol Amendment 3 who were randomized to 15 mg BID were dispensed 3 bottles containing either 5 mg tofacitinib or placebo tablets. These subjects were instructed to take their study medication as 1 tablet from each of the 3 bottles in the morning

and 1 tablet from each bottle in the evening, approximately 12 hours apart for a total of 3 tablets BID until they completed or were prematurely discontinued from the study.

Tofacitinib could be administered with or without food. If a tofacitinib dose was missed and the interval to the next scheduled dose was to be <6 hours, the missed dose of tofacitinib was not administered.

Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint was as follows:

- The proportion of subjects in remission at Week 8.

Key Secondary Efficacy Endpoint:

The key secondary efficacy endpoint was as follows:

- The proportion of subjects achieving mucosal healing at Week 8.

Other Secondary Efficacy Endpoints:

The other secondary efficacy endpoints were as follows:

- The proportion of subjects achieving clinical response at Week 8;
- The proportion of subjects in endoscopic remission at Week 8;
- The proportion of subjects in clinical remission at Week 8;
- The proportion of subjects in symptomatic remission at Week 8;
- The proportion of subjects achieving deep remission at Week 8;
- Partial Mayo scores and change from baseline over time;
- Change from baseline at Week 8 in total Mayo score.

Safety Evaluations: Safety was assessed by the incidence and severity of spontaneous reporting of adverse events (AEs) in all subjects who received at least 1 dose of study medication.

Statistical Methods:

The data sets summarized and analyzed in this study were the full analysis set (FAS), defined as all subjects randomly assigned to either tofacitinib 10 mg BID or placebo, and the safety analysis set, defined as all randomized subjects who received at least 1 dose of study medication.

Efficacy Analyses:

In order to control the familywise Type I error rate, a fixed sequence procedure was used. The hypothesis of no treatment effect between the tofacitinib 10 mg BID and the placebo for the primary endpoint was tested first at the 2-sided significance level 0.05. If it was significant, the hypothesis of no treatment effect between the tofacitinib 10 mg BID and the placebo for the key secondary endpoint was then tested at the significance level 0.05. The statistical significance was to be claimed for the key secondary endpoint only if the treatment effect for the primary efficacy endpoint was also significant. All other efficacy endpoints were evaluated at the 0.05 level of significance, without adjustments for multiple comparisons.

Both locally and centrally read endoscopic scores were used for the derivation of all efficacy endpoints. The primary analyses were based on the efficacy endpoints derived from the centrally read endoscopic scores and are presented in this report.

Analysis of Primary Endpoints

The primary analysis was based on the FAS. The primary endpoint was compared between treatment groups by the Cochran-Mantel-Haenszel (CMH) Chi-square test stratified by prior treatment with TNFi therapy, corticosteroid use at baseline, and geographic region; in case the cell frequencies were too small, the Fisher's exact test was to be used. The difference between treatment groups was presented along with its 95% 2-sided confidence interval (CI) in the proportion of subjects in remission at Week 8 using the normal approximation for the difference. Subjects with missing remission data at Week 8 were treated as non-responders. The non-responder imputation (NRI) method was used to handle missing values in both the summary presentations and analyses.

Analysis of Secondary Endpoints

The endpoint of mucosal healing at Week 8 was analyzed and summarized using the same methods as those for the primary endpoint, including the sensitivity analyses.

For the other secondary endpoints, the summary presentations and analyses were performed on the FAS population with no adjustments for multiple comparisons.

The binary endpoints were analyzed by the CMH Chi-square test stratified by prior treatment with TNFi therapy, corticosteroid use at baseline, and geographical region; Fisher's exact test was used in case of small cell frequencies. The difference between treatment groups was presented along with its 95% 2-sided CI using the normal approximation for the difference.

The NRI method was used to handle missing values in both the summary presentations and analyses.

Continuous secondary endpoints measured at baseline and Week 8, such as total Mayo score, were analyzed at Week 8 as changes from baseline using an analysis of covariance (ANCOVA) model with prior treatment with TNFi therapy, corticosteroid use at baseline, and geographic region as factors and baseline score as a covariate based on the observed-case data. Both the actual values and change from baseline were summarized by treatment group using descriptive statistics at each visit. Estimates of the differences and associated 95% CIs for the comparison of tofacitinib 10 mg BID to placebo were computed.

For continuous secondary endpoints that were measured repeatedly over time, such as partial Mayo score, the changes from baseline were analyzed using a linear mixed-effects model with baseline, treatment group, prior treatment with TNFi therapy, corticosteroid use at baseline, geographic region, visit, and treatment group by visit interaction as fixed effects, and subject as a random effect.

Safety Analysis:

Safety evaluations were analyzed using the safety analysis set. Missing data for safety endpoints were not imputed and were left as missing. All safety data were summarized according to the sponsor's data standards.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 1. Of 990 subjects screened for entry into the study, 614 subjects were randomized to study treatment. Of these, 598 subjects were randomized to tofacitinib 10 mg BID or placebo (FAS): 476 subjects were randomized to tofacitinib 10 mg BID, and 122 subjects were randomized to placebo. All randomized subjects received at least 1 dose of study drug (safety analysis set). There were 16 (2.4%) subjects who were randomized to and received tofacitinib 15 mg BID prior to Protocol Amendment 3.

The numbers of subjects that discontinued and completed the study are included in Table 1. The proportion of subjects who discontinued the study was low in all treatment groups.

Table 1. Subject Disposition by Treatment Group

	Tofacitinib 10 mg BID n (%)	Tofacitinib 15 mg BID n (%)	Placebo n (%)
Screened (N = 990)			
Randomized (N = 614)[a]	476 (77.5)	16 (2.6)	122 (19.9)
Prior to Protocol Amendment 3	14 (2.3)	16 (2.6)	8 (1.3)
After Protocol Amendment 3	462 (75.2)	0	114 (18.6)
Full Analysis Set	476 (100.0)	16 (100.0)	122 (100.0)
Per Protocol Analysis Set	443 (93.1)	15 (93.8)	117 (95.9)
Safety Analysis Set	476 (100.0)	16 (100.0)	122 (100.0)
Adverse events[b]	476 (100.0)	16 (100.0)	122 (100.0)
Treated	476 (100.0)	16 (100.0)	122 (100.0)
Completed	445 (93.5)	15 (93.8)	118 (96.7)
Discontinued[c]	31 (6.5)	1 (6.3)	4 (3.3)
Primary Reason for Discontinuation			
Subject died	1 (0.2)	0	0
Related to study drug	19 (4.0)	0	2 (1.6)
Adverse event	8 (1.7)	0	1 (0.8)
Insufficient clinical response[d]	11 (2.3)	0	1 (0.8)
Not related to study drug	11 (2.3)	1 (6.3)	2 (1.6)
Adverse event	1 (0.2)	0	0
No longer willing to participate in study	4 (0.8)	0	1 (0.8)
Protocol violation	4 (0.8)	1 (6.3)	1 (0.8)
Other	2 (0.4)	0	0

BID = twice a day, N = total number of subjects, n = number of subjects meeting prespecified criteria.
[a.] Percentage of randomized subjects in each treatment group and in prior and after Protocol Amendment 3 rows was calculated using the total number randomized (614) as the denominator. All other percentages were calculated using the total number randomized in each respective treatment group.
[b.] Adverse events (AEs) – all randomized subjects for which the Adverse Event case report form (CRF) was completed in the database.
[c.] One subject in the tofacitinib 10 mg BID treatment group completed the Week 8 visit and was then withdrawn for an AE. This subject was counted as discontinued instead of completed.
[d.] AEs of worsening of ulcerative colitis leading to discontinuation were designated as insufficient clinical response.

Overall, demographic characteristics were similar across treatment groups (Table 2). For all subjects randomized, there were more male than female subjects and the majority were white.

Table 2. Baseline Demographic Characteristics by Treatment Group

	Tofacitinib 10 mg BID (N = 476)	Tofacitinib 15 mg BID (N = 16)	Placebo (N = 122)
Age (years)			
Mean (SD)	41.3 (14.1)	39.9 (12.8)	41.8 (15.3)
Range	18, 77	21, 68	19, 81
Sex, n (%)			
Men	277 (58.2)	9 (56.3)	77 (63.1)
Women	199 (41.8)	7 (43.8)	45 (36.9)
Race, n (%)			
White	395 (83.0)	12 (75.0)	98 (80.3)
Black	3 (0.6)	0	3 (2.5)
Asian	54 (11.3)	3 (18.8)	14 (11.5)
Other	15 (3.2)	1 (6.3)	3 (2.5)
Unspecified	9 (1.9)	0	4 (3.3)
Weight (kg)			
Mean (SD)	72.9 (16.8)	78.1 (19.3)	72.7 (16.7)
Range	37.0, 156.5	55.0, 127	37.4, 130
Height (cm)			
Mean (SD)	171.4 (9.6)	168.1 (5.0)	172.4 (10.4)
Range	145.5, 196.0	160.0, 175.3	143.0, 199.0

Race was not collected for French subjects.
BID = twice a day, N = number of subjects randomized, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoint:

The proportion of subjects achieving remission at Week 8 (FAS, NRI) was statistically significantly greater in the tofacitinib 10 mg BID group compared with the placebo group (Table 3).

Table 3. Proportion of Subjects in Remission at Week 8 (FAS, NRI)

	Tofacitinib 10 mg BID (N = 476) n (%)	Placebo (N = 122) n (%)	Difference From Placebo	
			Difference (95% CI)[a]	P-Value[b]
Remission				
Central read	88 (18.5)	10 (8.2)	10.3 (4.3, 16.3)	0.0070

BID = twice a day, CI = confidence interval, FAS = full analysis set, N = number of subjects in the analysis set, n = number of subjects meeting prespecified criteria, TNFi = tumor necrosis factor-alpha inhibitor.
[a.] 95% CI was based on the normal approximation for the difference.
[b.] P-value was based on Cochran-Mantel-Haenszel (CMH) Chi-squared test stratified by prior treatment with TNFi, corticosteroid use at baseline, and geographical region.

Key Secondary Efficacy Endpoint:

The proportion of subjects achieving mucosal healing at Week 8 (FAS, NRI) was statistically significantly greater in the tofacitinib 10 mg BID group compared with the placebo group (Table 4).

Table 4. Proportion of Subjects With Mucosal Healing at Week 8 (FAS, NRI)

	Tofacitinib 10 mg BID (N = 476) n (%)	Placebo (N = 122) n (%)	Difference From Placebo	
			Difference (95% CI)[a]	P-Value[b]
Mucosal Healing				
Central read	149 (31.3)	19 (15.6)	15.7 (8.1, 23.4)	0.0005

Mucosal healing was defined by a Mayo endoscopic subscore of 0 or 1.
BID = twice a day, CI = confidence interval, FAS = full analysis set, N = number of subjects in the analysis set, n = number of subjects meeting specific criteria, TNFi = tumor necrosis factor-alpha inhibitor.
[a.] 95% CI was based on the normal approximation for the difference.
[b.] P-value was based on Cochran-Mantel-Haenszel (CMH) Chi-squared test stratified by prior treatment with TNFi, corticosteroid use at baseline, and geographical region.

Other Secondary Efficacy Endpoints:

For the other secondary endpoints of both clinical remission and clinical response at Week 8, tofacitinib 10 mg BID had statistically significantly higher proportions of subjects with clinical remission and clinical response at Week 8 compared with placebo (Table 5).

For the other secondary endpoints of endoscopic remission and deep remission, tofacitinib 10 mg BID had statistically significantly higher proportions of subjects with endoscopic remission and deep remission at Week 8 compared with placebo (Table 5).

Table 5. Summary of Other Secondary Binary Efficacy Endpoints at Week 8 (FAS, NRI)

	Tofacitinib 10 mg BID (N = 476) n (%)	Placebo (N = 122) n (%)	Difference From Placebo	
			Difference (95% CI)[a]	P-Value[b]
Clinical remission				
Central read	88 (18.5)	10 (8.2)	10.3 (4.3, 16.3)	0.0070
Clinical response				
Central read	285 (59.9)	40 (32.8)	27.1 (17.7, 36.5)	<0.0001
Endoscopic remission				
Central read	32 (6.7)	2 (1.6)	5.1 (1.9, 8.3)	0.0345
Symptomatic remission				
Central read	56 (11.8)	7 (5.7)	6.0 (1.0, 11.1)	0.0601
Deep remission				
Central read	31 (6.5)	0 (0)	6.5 (4.3, 8.7)	0.0043

BID = twice a day, CI = confidence interval, FAS = full analysis set, N = number of subjects in the analysis set, n = number of subjects meeting specific criteria, TNFi = tumor necrosis factor-alpha inhibitor.
[a.] 95% CI was based on the normal approximation for the difference.
[b.] P-value was based on Cochran-Mantel-Haenszel (CMH) Chi-squared test stratified by prior treatment with TNFi, corticosteroid use at baseline, and geographical region; p-value from Fisher's exact test was also provided in the source table.

The descriptive statistics (FAS, observed cases) for the partial Mayo score (range: 0 to 9) and partial Mayo score change from baseline are presented in Table 6. Baseline mean partial Mayo scores were similar for both the tofacitinib 10 mg BID and placebo groups. Reductions in partial Mayo scores were greater in the tofacitinib 10 mg BID group than the placebo group. The analysis of change from baseline for partial Mayo scores using the linear mixed-effects model (FAS, observed cases) is presented in Table 7. As early as Week 2, which was the first post-baseline timepoint assessed, the tofacitinib 10 mg BID treatment group showed a statistically significantly greater reduction from baseline in partial Mayo score than placebo. The difference between treatment groups continued to increase at Week 4 and Week 8.

Table 6. Descriptive Statistics of Partial Mayo Score and Change from Baseline (FAS, Observed Cases)

	Tofacitinib 10 mg BID		Placebo	
Partial Mayo Score	Observed Data	Change From Baseline	Observed Data	Change From Baseline
Baseline				
N	475		121	
Mean (SD)	6.3 (1.2)		6.5 (1.2)	
Week 2				
N	465	464	122	121
Mean (SD)	4.2 (2.2)	-2.1 (2.0)	5.2 (2.1)	-1.3 (1.7)
Week 4				
N	461	460	118	117
Mean (SD)	3.5 (2.3)	-2.8 (2.1)	4.8 (2.4)	-1.7 (1.8)
Week 8				
N	449	448	119	118
Mean (SD)	3.2 (2.4)	-3.2 (2.3)	4.8 (2.5)	-1.7 (2.1)

BID = twice a day, FAS = full analysis set, N = number of observations with non-missing values, SD = standard deviation.

Table 7. Analysis of Change From Baseline for Partial Mayo Score Using Linear Mixed-Effects Model (FAS, Observed Cases)

	Change From Baseline			Difference From Placebo			
	N	Adjusted Mean	SE	Diff	SE	95% CI	P-Value
Week 2							
Tofacitinib 10 mg BID	464	-2.1	0.1	-0.9	0.2	(-1.3, -0.5)	<0.0001
Placebo	121	-1.2	0.2				
Week 4							
Tofacitinib 10 mg BID	460	-2.8	0.1	-1.1	0.2	(-1.5, -0.7)	<0.0001
Placebo	117	-1.6	0.2				
Week 8							
Tofacitinib 10 mg BID	448	-3.1	0.1	-1.5	0.2	(-1.9, -1.1)	<0.0001
Placebo	118	-1.6	0.2				

P-value was obtained from the mixed-effects model: Change from baseline = treatment + prior treatment with TNFi + corticosteroid use at baseline + geographic region + week + treatment*week + baseline with subjects as random effect.
BID = twice a day, CI = confidence interval, Diff = difference, FAS = full analysis set, N = number of observations with non-missing values, SE = standard error, TNFi = tumor necrosis factor-alpha inhibitor.

The analysis of change from baseline for total Mayo scores at Week 8 using the ANCOVA (FAS, observed cases) is presented in Table 8. At Week 8, the tofacitinib 10 mg BID group showed statistically significantly greater reduction from baseline in total Mayo score compared with the placebo group.

Table 8. Analysis of Change From Baseline for Total Mayo Score at Week 8 Using the ANCOVA Model (FAS, Observed Cases)

	Change From Baseline			Difference From Placebo			
	N	Adjusted Mean	SE	Diff	SE	95% CI	P-Value
Week 8							
Tofacitinib 10 mg BID	446	-3.8	0.1	-1.9	0.3	(-2.5, -1.4)	<0.0001
Placebo	117	-1.8	0.3				

Adjusted means and p-value were obtained from the ANCOVA model: change from baseline = treatment + baseline total Mayo score + prior treatment with TNFi + corticosteroid use at baseline + geographic region.
ANCOVA = analysis of covariance, BID = twice a day, CI = confidence interval, Diff = difference, FAS = full analysis set, N = number of observations with non-missing values, SE = standard error, TNFi = tumor necrosis factor-alpha inhibitor.

Safety Results:

All-Causality Treatment-Emergent Non-Serious Adverse Events

The incidence (>5% of subjects) of all-causality non-serious treatment-emergent adverse events (TEAEs) was similar for subjects treated with tofacitinib 10 mg BID compared with subjects treated with placebo (Table 9). The most frequent non-serious TEAEs by preferred term (PT) reported were headache and nasopharyngitis in the tofacitinib 10 mg BID and placebo groups.

Table 9. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in >5% of Subjects

	Tofacitinib 10 mg BID n (%)	Tofacitinib 15 mg BID n (%)	Placebo n (%)
Number (%) of Subjects			
Evaluable for adverse events	476	16	122
With adverse events	148 (31.1)	12 (75.0)	38 (31.1)
Subjects with AEs by: SOCs and MedDRA PTs			
Blood and Lymphatic System Disorders	11 (2.3)	1 (6.3)	6 (4.9)
Anaemia	11 (2.3)	1 (6.3)	6 (4.9)
Gastrointestinal Disorders	23 (4.8)	3 (18.8)	9 (7.4)
Colitis ulcerative	6 (1.3)	1 (6.3)	3 (2.5)
Flatulence	2 (0.4)	1 (6.3)	1 (0.8)
Gastrooesophageal reflux disease	0	1 (6.3)	0
Nausea	15 (3.2)	1 (6.3)	5 (4.1)
General Disorders and Administration Site Conditions	24 (5.0)	2 (12.5)	7 (5.7)
Fatigue	10 (2.1)	1 (6.3)	4 (3.3)
Pyrexia	14 (2.9)	1 (6.3)	3 (2.5)
Infections and Infestations	65 (13.7)	6 (37.5)	13 (10.7)
Folliculitis	9 (1.9)	1 (6.3)	0
Gastroenteritis	7 (1.5)	1 (6.3)	2 (1.6)
Nasopharyngitis	34 (7.1)	3 (18.8)	9 (7.4)
Sinusitis	2 (0.4)	2 (12.5)	1 (0.8)
Upper respiratory tract infection	15 (3.2)	1 (6.3)	1 (0.8)
Investigations	12 (2.5)	3 (18.8)	0
Blood creatine phosphokinase increased	12 (2.5)	1 (6.3)	0
Liver function test abnormal	0	1 (6.3)	0
White blood cell count increased	0	1 (6.3)	0
Musculoskeletal and Connective Tissue Disorders	2 (0.4)	1 (6.3)	2 (1.6)
Myalgia	2 (0.4)	1 (6.3)	2 (1.6)
Nervous System Disorders	37 (7.8)	0	8 (6.6)
Headache	37 (7.8)	0	8 (6.6)
Psychiatric Disorders	1 (0.2)	2 (12.5)	1 (0.8)
Anxiety	0	1 (6.3)	0
Depressed Mood	1 (0.2)	1 (6.3)	1 (0.8)
Renal and Urinary Disorders	1 (0.2)	1 (6.3)	0
Dysuria	1 (0.2)	1 (6.3)	0
Haematuria	0	1 (6.3)	0
Skin and Subcutaneous Tissue Disorder	15 (3.2)	6 (37.5)	1 (0.8)
Acne	10 (2.1)	3 (18.8)	0
Alopecia	5 (1.1)	1 (6.3)	1 (0.8)
Dermatitis acneiform	0	1 (6.3)	0
Night sweats	0	1 (6.3)	0

Subjects were only counted once per treatment for each row.
Includes events from study database, even those that occurred after last dose of study drug.
MedDRA (v18.0) coding dictionary applied.
AE = adverse event, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities, n = number of subjects meeting prespecified criteria, PT = preferred term, SOC = system organ class.

All-Causality Treatment-Emergent Serious Adverse Events

The incidence of all-causality serious TEAEs was similar for subjects treated with tofacitinib 10 mg BID compared with subjects treated with placebo (Table 10). No subjects treated with tofacitinib 15 mg BID experienced serious TEAEs.

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Tofacitinib 10 mg BID			Tofacitinib 15 mg BID			Placebo		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of Subjects									
Evaluable for adverse events	476			16			122		
With adverse events	16 (3.4)			0			5 (4.1)		
Subjects with AEs by: SOCs and MedDRA PTs									
Cardiac Disorders	1 (0.2)	1	0	0	0	0	0	0	0
Acute coronary syndrome	1 (0.2)	1	0	0	0	0	0	0	0
Gastrointestinal Disorders	6 (1.3)	6	2	0	0	0	2 (1.6)	2	0
Colitis ulcerative	5 (1.1)	5	1	0	0	0	2 (1.6)	2	0
Intestinal perforation	1 (0.2)	1	1	0	0	0	0	0	0
General Disorders and Administration Site Conditions	1 (0.2)	1	0	0	0	0	0	0	0
Malaise	1 (0.2)	1	0	0	0	0	0	0	0
Immune System Disorders	1 (0.2)	1	0	0	0	0	0	0	0
Drug hypersensitivity	1 (0.2)	1	0	0	0	0	0	0	0
Infections and Infestations	6 (1.3)	6	2	0	0	0	0	0	0
Anal abscess	1 (0.2)	1	0	0	0	0	0	0	0
Cellulitis	1 (0.2)	1	0	0	0	0	0	0	0
Clostridium difficile infection	1 (0.2)	1	0	0	0	0	0	0	0
Febrile infection	1 (0.2)	1	1	0	0	0	0	0	0
Otitis externa	1 (0.2)	1	0	0	0	0	0	0	0
Pneumonia	1 (0.2)	1	1	0	0	0	0	0	0
Injury, Poisoning and Procedural Complications	1 (0.2)	1	0	0	0	0	1 (0.8)	1	0
Animal bite	0	0	0	0	0	0	1 (0.8)	1	0
Joint injury	1 (0.2)	1	0	0	0	0	0	0	0
Musculoskeletal and Connective Tissue Disorders	1 (0.2)	1	0	0	0	0	0	0	0
Arthralgia	1 (0.2)	1	0	0	0	0	0	0	0
Reproductive system and Breast Disorders	0	0	0	0	0	0	1 (2.2)	1	0
Vulva cyst	0	0	0	0	0	0	1 (2.2)	1	0
Respiratory, Thoracic, and Mediastinal Disorders	0	0	0	0	0	0	1 (0.8)	1	1
Pulmonary embolism	0	0	0	0	0	0	1 (0.8)	1	1
Skin and Subcutaneous Tissue Disorders	1 (0.2)	1	0	0	0	0	0	0	0
Drug eruption	1 (0.2)	1	0	0	0	0	0	0	0

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Tofacitinib 10 mg BID			Tofacitinib 15 mg BID			Placebo		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Vascular Disorders	2 (0.4)	2	1	0	0	0	0	0	0
Aortic dissection	1 (0.2)	1	0	0	0	0	0	0	0
Temporal arteritis	1 (0.2)	1	1	0	0	0	0	0	0

Except for n1 and n2, subjects were only counted once per treatment for each row.
Includes events from study database, even those that occurred after last dose of study drug.
Percentages of gender-specific events were calculated using the corresponding gender count as the denominator.
MedDRA (v18.0) coding dictionary applied.
AE = adverse event, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities, n = number of subjects in this reporting group affected by an occurrence of this all-causality AE, n1 = number of occurrences of all-causality TEAEs, n2 = number of occurrences of treatment-related TEAEs, PT = preferred term, SOC = system organ class.

Withdrawals of Subjects from the Study

Discontinuations from the study are listed in Table 11. A greater proportion of subjects in the tofacitinib 10 mg BID group discontinued from the study compared with the placebo group.

Table 11. Discontinuations from Study

	Tofacitinib 10 mg BID n (%)	Tofacitinib 15 mg BID n (%)	Placebo n (%)
Number (%) of Subjects	476	16	122
Completed	445 (93.5)	15 (93.8)	118 (96.7)
Discontinuations	31 (6.5)	1 (6.3)	4 (3.3)
Reason for Discontinuation			
Subject died	1 (0.2)	0	0
Related to study drug	19 (4.0)	0	2 (1.6)
Adverse event	8 (1.7)	0	1 (0.8)
Insufficient clinical response	11 (2.3)	0	1 (0.8)
Not Related to Study Drug	11 (2.3)	1(6.3)	2 (1.6)
Adverse event	1 (0.2)	0	0
No longer willing to participate in study	4 (0.8)	0	1 (0.8)
Other	2 (0.4)	0	0
Protocol violation	4 (0.8)	1 (6.3)	1 (0.8)

Insufficient clinical response includes subjects who discontinued due to AE of worsening UC.
AE = adverse event, BID = twice daily, n = number of subjects meeting prespecified criteria, UC = ulcerative colitis.

Deaths: One death occurred during the study in the tofacitinib 10 mg BID group due to aortic dissection, which was assessed by the investigator as not related to the study drug.

CONCLUSIONS:

This Phase 3 study demonstrated efficacy of tofacitinib 10 mg BID as an induction therapy for subjects with moderate to severe UC.

- Treatment effects for the tofacitinib 10 mg BID group were statistically significantly greater compared with the placebo group for both remission (primary endpoint) and mucosal healing (key secondary endpoint).

- Significant improvements in partial Mayo score from treatment with tofacitinib 10 mg BID were observed as early as Week 2.

The tofacitinib 10 mg BID dose appeared to be well tolerated.

- The most frequent all-causality TEAEs were headache and nasopharyngitis, with similar rates between the tofacitinib 10 mg BID and placebo groups.

- The most frequent all-causality SAE was colitis ulcerative (worsening of UC), with similar rates between the tofacitinib 10 mg BID and placebo groups. One death occurred during the study in the tofacitinib 10 mg BID group due to aortic dissection, which was assessed by the investigator as not related to the study drug.