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

PROTOCOL NO.: A3921063

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Investigate the Safety and Efficacy of CP-690,550 in Subjects With Moderate to Severe Ulcerative Colitis

Study Centers: A total of 51 centers (12 centers in Hungary; 4 centers in France; 3 centers each in Belgium, Brazil, the Czech Republic, Poland, Slovakia, South Africa, and Spain; 2 centers each in Chile, Denmark, Israel, Mexico, Sweden, and the United Kingdom; and 1 center each in Italy and the Netherlands.

Study Initiation and Final Completion Dates: 19 January 2009 to 06 September 2010

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To demonstrate efficacy of CP-690,550 (tofacitinib) in inducing a clinical response in subjects with moderate-to-severe ulcerative colitis (UC).

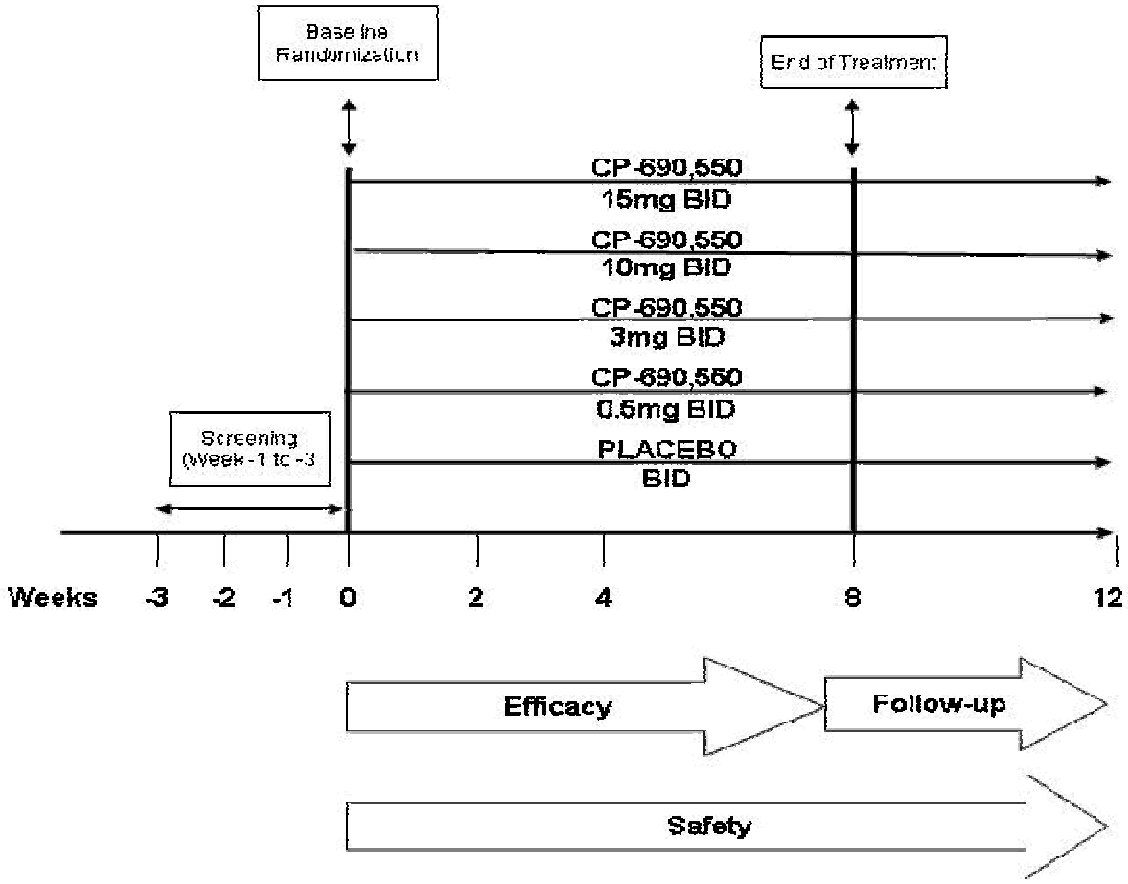
Secondary Objectives:

- To evaluate the safety and tolerability of oral tofacitinib in subjects with moderate-to-severe UC;
- To evaluate the efficacy of tofacitinib in inducing clinical remission in subjects with moderate-to-severe UC;
- To characterize the pharmacokinetics (PK) of tofacitinib in subjects with moderate-to-severe UC;
- To evaluate the effect of treatment with tofacitinib on quality-of-life in subjects with moderate-to-severe UC; and
- To demonstrate the change from Baseline in biomarkers C-reactive protein (CRP) and fecal calprotectin.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study in which a total of 192 subjects (estimated 180 subjects evaluable) were to be randomized. Subjects were to be screened between 7 and 21 days prior to the Baseline visit. At Baseline, subjects with moderate-to-severe UC (Mayo score ≥6 and endoscopic subscore ≥2) and fulfilling all inclusion/exclusion criteria were to be randomized into 1 of the 5 treatment arms: 0.5 mg, 3 mg, 10 mg, and 15 mg of tofacitinib twice daily (BID) or placebo BID. Subjects were stratified according to whether or not they had previous exposure to anti-tumor necrosis factor (TNF) α treatment. The double-blind treatment period lasted 8 weeks. All subjects were followed up for 4 weeks after the end of the study treatment or early withdrawal (Figure 1 and Table 1). The total duration of the study was 85 weeks.

Figure 1. Study Design Schematic



BID = Twice daily; CP-690,550 = Tofacitinib.

Table 1. Schedule of Activities

Protocol Activity	Screening	Baseline	Weeks		End-of-Treatment/ Early Withdrawal	Follow-Up
	Week -1 to -3	Day 1	Week 2	Week 8	Week 8	Week 12
Visit Number	**1**	**2**	**3**	**5**	**5**	**6**
Study Day	**-7 to -21 days**	**1**	**±3 days**	**±3 days**	**±3 days**	**±7 days**
Informed consent	X					
Medical history	X					
Complete physical examination	X	X			X	X
Targeted physical examination			X	X		
Vital signs	X	X	X	X	X	X
Laboratory:						
Hematology	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X
Stool culture/microscopy	X					
Lipid profile (fasting)		X			X	X
HBsAg, HCV Ab	X					
FSH[a]	X					
β–HCG (blood)[b]	X					
Serum IgG, IgM, IgA		X			X	
Urine pregnancy test		X	X	X	X	X
Mantoux PPD or QuantiFERON[c]	X					
Chest radiograph[d]	X					
Electrocardiogram	X			X	X	X
Endoscopy (flexible sigmoidoscopy or colonoscopy)		X[e]			X	
Pharmacokinetic sampling		X[f]	X[g]	X[g]	X[f]	
Pharmacogenomic sampling[h]		X				
Randomization		X				
Study medication dispensing		X		X		
Study drug accountability				X	X	
Assessments:						
Patient diary	X	X	X	X	X	X
Mayo score		X			X	
Partial Mayo score		X	X	X	X	X

Table 1. Schedule of Activities

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	Week -1 to -3	Day 1	Week 2	Week 8	Week 8	Week 12
Visit Number	**1**	**2**	**3**	**5**	**5**	**6**
Study Day	**-7 to -21 days**	**1**	**±3 days**	**±3 days**	**±3 days**	**±7 days**
IBDQ		X			X	
Patient-reported treatment impact					X	
Adverse events		X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Biomarker analysis:						
C-reactive protein		X		X	X	
Fecal calprotectin	X	X	X	X	X	X

BCG = Bacille Calmette Guérin; β-HCG = Beta human chorionic gonadotropin; DNA = Deoxyribonucleic acid; FSH = Follicle-stimulating hormone; HBsAg = Hepatitis B surface antigen; HCV Ab = Hepatitis C virus antibody; IBDQ = Inflammatory bowel disease questionnaire; IgA = Immunoglobulin A; IgG = Immunoglobulin G; IgM = Immunoglobulin M; PPD = Purified protein derivative.

a. FSH was performed in postmenopausal females only.
b. β-HCG was performed in females of childbearing potential only.
c. Only for subjects who had not had a tuberculin skin test within 3 months prior to Screening. Subjects who had a Mantoux PPD test were required to have a 48- to 72-hour post-test skin induration evaluation by a health care professional (nurse or doctor). Subjects who had previously received a BCG vaccination could have been tested by QuantiFERON Gold test in place of Mantoux PPD and used these results to determine subject eligibility for participation.
d. Chest radiograph was required if not performed within 3 months prior to Screening.
e. Colonoscopy was required at Baseline only, instead of flexible sigmoidoscopy, if not performed within the last 10 years. The duration of the time between endoscopy and Baseline was not to exceed 7 days.
f. Study medication dose was taken in the clinic and blood samples were taken prior to dosing and at 0.25, 0.5, 1, and 2- to 3- hours post-dose (or if not possible, as close to 2 hours post-dose as feasible).
g. Two blood samples were collected at the clinic at least 1 hour apart. The date and time of the last 6 study drug doses were to be documented.
h. For de-identified pharmacogenomic (DNA) sampling, a separate molecular profiling consent was to be obtained.

Number of Subjects (Planned and Analyzed): The study planned to enroll a total of 192 subjects. A total of 275 subjects were screened, 195 subjects (6 in Belgium, 14 in Brazil, 2 in Chile, 11 in the Czech Republic, 12 each in Denmark and France, 65 in Hungary, 6 in Israel, 3 each in Italy and Mexico, 2 in the Netherlands, 14 in Poland, 12 in Slovakia, 22 in South Africa, 5 in Spain, 3 each in Sweden and the United Kingdom) were randomized and assigned to study medication (49 subjects in the placebo BID group and 146 subjects in the tofacitinib BID group). One of the 49 subjects in the placebo group was randomized but discontinued from the study on the same day and did not receive any study drug treatment. All 194 subjects who were treated with tofacitinib and placebo were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Subjects were healthy male or female subjects aged at least 18 years. Subjects were to have a clinical diagnosis of active moderate-to-severe UC with a Mayo score of ≥6 for ≥3 months prior to study entry, and an endoscopic subscore of ≥2 for the Mayo score determined within 7 days of baseline. Subjects currently receiving 5-aminosalicylic acid, sulfasalazine, or oral corticosteroids for UC were eligible provided they were on a stable dose for the required period of time.

Exclusion Criteria: Subjects with a diagnosis of indeterminate colitis, clinical findings suggestive of Crohn's disease, or with UC, which was confined to a proctitis (distal 15 cm or less). Treatment-naïve subjects diagnosed with UC (without previous exposure to treatment) and subjects displaying clinical signs of ischemic colitis, fulminant colitis, or toxic megacolon. Subjects who had surgery as a treatment for UC or were likely to require surgery during the study period. Subjects that were receiving immunosuppressants, anti-TNFα therapy, or interferon at the time of study enrollment.

Study Treatment: Tofacitinib and matching placebo tablets were provided by the Sponsor and dispensed for oral administration. Subjects were randomized to receive 0.5 mg, 3 mg, 10 mg, or 15 mg of tofacitinib or placebo (2:2:2:3:3, respectively). Study medication was self-administered by the subject, BID. However, at Baseline (Day 1) the first dose was taken in the clinic. At the end of the treatment (Week 8), subjects were to take their morning oral dose at the clinic. In case the study visit was in the afternoon, subjects were to take the morning dose at home and take the evening dose at the clinic. Study medication could have been taken with or without food: and the two daily doses were to be taken approximately 12 hours apart.

Efficacy and Safety Endpoints:

Primary Efficacy Endpoint:

- Clinical response at Week 8 (decrease from Baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1).

Secondary Efficacy Endpoint:

- Clinical remission at Week 8 (total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point);
- Change from Baseline in partial Mayo score at Week 2, 4, 8 and 12;
- Endoscopic response at Week 8 (decrease from Baseline of at least 1 point in the Mayo endoscopic subscore);
- Endoscopic remission at Week 8 (Mayo endoscopic subscore equals 0);
- Improvement in quality of life measured by Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 8;
- Change from Baseline in the following biomarker levels: CRP, fecal calprotectin.

Safety Endpoints:

- Incidence and severity of adverse events (AEs);
- Incidence and severity of clinical laboratory abnormalities.

Safety Evaluations: Standard safety assessments included physical examination, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory evaluations (hematology, chemistry, urinalysis), and AE monitoring in all subjects who received at least 1 dose of study medication. Other safety evaluations included flexible sigmoidoscopy/colonoscopy, chest radiograph, tuberculosis test, and QuantiFERON test.

Statistical Methods:

Full Analysis Set: The Full Analysis Set (FAS) included all randomized subjects who had either withdrawn as a treatment failure or had completed at least 1 week of dosing and had at least 1 valid Mayo score during the active double-blind phase of the study. The FAS was the primary analysis set of interest in all efficacy analyses.

Per Protocol Analysis Set: Per Protocol Analysis Set (PPAS) was the subset of subjects from the FAS who had no major protocol violations. Protocol deviations were assessed by the project team prior to unblinding the study. The primary analysis was supported by a sensitivity analysis that was performed using the PPAS population.

Safety Analysis Set: The Safety Analysis Set (SAS) consisted of all randomized subjects who received at least 1 dose of study medication. The SAS was to be used in the analysis of all safety endpoints.

Summary statistics including the counts and percentages were presented by treatment group for all binary variables. Baseline stratification based on exposure to anti-TNFα treatment

was to be included in the models used for analyzing binary endpoints if a sufficient number of subjects had previous exposure to anti-TNFα treatment.

If a subject had a lack of response or loss of response to treatment, the subject was considered a "treatment failure" and classified as a non-responder for all binary endpoints from the time of change in treatment or medication, regardless of whether a Mayo score had been recorded or data were missing.

The total number of subjects evaluated may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg, discontinuation of a subject that was not classified as treatment failure or the visit falling outside of the predefined window, had their binary response treated as missing; therefore, these subjects were not included in the evaluation.

The primary efficacy endpoint was the proportion of clinical responders at Week 8. The primary analysis was performed on the FAS. A summary of the number of responders in each treatment arm at Week 8 was produced by treatment group.

In the design of this study, the shape of the dose-response curve was assumed to be a 3-parameter maximal pharmacological effect (E_{max}) model which described a dose-response that started at E_0 (the logit of the placebo response rate) and smoothly increased to an asymptote. The plan was to analyze clinical response, clinical remission, endoscopic response, and endoscopic remission using this model. For clinical response and endoscopic response, a problem with the fit of the E_{max} model was that the effect appeared to be in the steep part of the dose-response curve. As the model was over-parameterized, alternative model fits were explored and a model linear in dose was selected, as this gave a reasonable approximation to the E_{max} model fit over the range of doses in the study. The final models fitted were a linear-in-dose model for clinical response and endoscopic response and a 3-parameter E_{max} model for clinical remission and endoscopic remission.

The fitted curve was to be shown graphically with confidence intervals (CIs) for each dose. Estimates of the treatment differences in response function and associated 90% CIs for each active dose against placebo were calculated from the model. These results were back-transformed to give point estimates of the difference in proportions and associated 90% CIs using the δ-method.

For the analysis of continuous endpoints, if a subject was considered a "treatment failure," the Baseline value was carried forward (Baseline observation carried forward) from the time of change in treatment or medication, regardless of whether a score had been recorded or data were missing.

Total Mayo scores (0 to 12 scale) and partial Mayo scores (0 to 9 scale) were listed and summarized as continuous data. Changes from Baseline were summarized across time for each dose. Week 8 changes from Baseline were plotted and summarized by dose to visually assess dose-related changes. Week 8 data were analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, Baseline scores, and anti-TNFα treatment stratification (if a sufficient number of subjects had previous exposure to anti-TNFα

treatment). Estimates of the treatment differences in response function and associated 95% CIs for each active dose versus placebo were calculated. The longitudinal analysis of the change from Baseline in partial Mayo scores was to be performed by means of a Mixed-Effect Model Repeated Measures (MMRM) analysis using statistical analysis system Proc Mixed.

All data for inflammatory bowel disease questionnaire (IBDQ) were listed and data for the 4 dimensions and total score were summarized by time postdose for each dose. Week 8 changes from Baseline for the 4 dimensions and total score were to be plotted and summarized by dose to visually assess dose-related changes. All IBDQ data (Baseline and Week 8) were summarized across time. The Week 8 change from Baseline was analyzed using an analysis of variance that allows for variation due to dose group and Baseline value.

Biomarker data (CRP and fecal calprotectin) were log-transformed (natural logarithm) for the analyses. Descriptive summary statistics for continuous variables were presented.

Reticulocyte counts were reported within the standard presentations of hematology data. Changes from Baseline were also plotted and summarized across time. Week 8 changes in reticulocyte counts were plotted and summarized by dose to visually assess dose-related changes.

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product were reported. AEs (serious and non-serious) were to be recorded on the case report form (CRF) from the time the subject had taken at least 1 dose of study treatment through the last subject visit. In addition to standard AE data, AE data were also to be collected for significant infections (on unique CRF pages). Any AEs that started or increased in severity following the start of treatment were counted as treatment-emergent.

Safety laboratory tests data were explored through the use of standard presentations of descriptive statistics. Serum creatinine was reported within the standard presentations of chemistry data. The Cockcroft-Gault glomerular filtration rate calculation was used as an estimate of creatinine clearance. Serum lipids, including total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides were reported within the standard presentations of chemistry data. Week 8 changes from Baseline were plotted and summarized by dose to visually assess dose-related changes.

Vital signs, ECGs, and other safety parameters were explored through the use of standard presentations of descriptive statistics.

RESULTS

Subject Disposition and Demography:

A total of 195 subjects were assigned to study treatment and 194 subjects received study drug. One subject assigned to placebo was discontinued from the study before receiving treatment. A total of 157 subjects completed the study and 37 subjects discontinued from the study. All 194 subjects who were treated with tofacitinib and placebo were analyzed for

efficacy in the FAS. In the PPAS (FAS subjects with no major protocol violations), only 185 subjects were analyzed for efficacy.

All subjects who were treated with tofacitinib were analyzed for AEs and laboratory data. All 48 subjects who were treated with placebo were analyzed for AEs and 47 placebo-treated subjects were analyzed for laboratory data (one subject was discontinued from the study due to an AE). Subject disposition is summarized in Table 2.

Table 2. Subject Disposition

Number of Subjects, n (%)	Placebo	Tofacitinib BID				Total
		0.5 mg	3 mg	10 mg	15 mg	
Screened						**275**
Assigned to Study Treatment	**49**	**31**	**33**	**33**	**49**	**195**
Treated	48[a]	31	33	33	49	194
Completed	35 (71.4)	20 (64.5)	26 (78.8)	31 (93.9)	45 (91.8)	157 (80.5)
Discontinued	13 (26.5)	11 (35.5)	7 (21.2)	2 (6.1)	4 (8.2)	37 (19.0)
Related to study drug	6	6	5	2	1	-
Adverse event	1	0	0	0	0	-
Insufficient clinical response	5	6	5	2	1	-
Not related to study drug	7	5	2	0	3	-
Adverse event	2	2	0	0	2	-
Lost to follow-up	1	0	0	0	0	-
No longer willing to participate in the study	2	2	2	0	0	-
Analyzed for pharmacokinetics						
Pharmacokinetics	0	31 (100)	33 (100)	33 (100)	49 (100)	146 (74.9)
Analyzed for efficacy						
Full analysis set	48 (98.0)	31 (100)	33 (100)	33 (100)	49 (100)	194 (99.5)
Per protocol set	46 (93.9)	30 (96.8)	31 (93.9)	30 (90.9)	48 (98.0)	185 (94.9)
Analyzed for safety						
Adverse events	48 (98.0)	31 (100)	33 (100)	33 (100)	49 (100)	194 (99.5)
Laboratory data	47 (95.9)	31 (100)	33 (100)	33 (100)	49 (100)	193 (99.0)

BID = Twice daily; n = Number of subjects with a response.

a. One subject was randomized but discontinued from the study on the same day and did not receive any study drug treatment.

All subjects were male or female adults with a clinical diagnosis of UC ≥3 months prior to entry in the study; the majority of subjects were White. Subjects ranged in age from 19 to 77 years, with a mean body mass index of 25.5, 26.3, 24.8, 25.4, and 25.6 kg/m^2 for placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg, respectively. Demographic characteristics were similar between treatment groups.

Of the total number of subjects that were evaluated (195 subjects), the majority of subjects never smoked (66.0%), while 7.2% of the subjects were smokers and 26.8% of the subjects were ex-smokers. A summary of the demographic characteristics and smoking classification is provided in Table 3.

Table 3. Demographic Characteristics and Smoking Classification

Characteristic	Placebo N = 49	Tofacitinib BID			
		0.5 mg N = 31	3 mg N = 33	10 mg N = 33	15 mg N = 49
Gender, n:	49	31	33	33	49
Male	23	17	19	21	26
Female	26	14	14	12	23
Age (years):	49	31	33	33	49
Mean (SD)	42.8 (14.7)	43.8 (13.4)	42.5 (14.3)	43.2 (12.8)	41.2 (13.5)
Range	21-77	20-73	21-72	21-65	19-66
Race, n:	49	31	33	33	49
White	43	28	30	30	45
Black	1	0	1	0	1
Other	5	3	2	3	3
Weight (kg):	49	31	33	33	49
Mean (SD)	74.6 (15.6)	75.6 (13.3)	73.8 (16.4)	75.9 (13.2)	74.1 (17.7)
Range	46.3-112.3	50.8-105.0	46.8-119.7	56.0-97.7	41.4-126.0
BMI (kg/m^2):	49	31	33	33	49
Mean (SD)	25.5 (4.1)	26.3 (3.7)	24.8 (3.9)	25.4 (4.0)	25.6 (5.2)
Range	17.3-38.2	20.1-34.7	17.2-36.1	18.5-36.6	16.8-37.4
Height (cm):	49	31	33	33	49
Mean (SD)	170.7 (11.2)	169.3 (8.2)	172.0 (10.2)	172.8 (9.8)	169.7 (8.4)
Range	150.0-194.0	151.0-187.0	158.0-194.0	152.0-196.0	155.0-189.0
Smoking status, n (%):	49	31	33	33	49
Never smoked	35 (71.4)	16 (51.6)	19 (57.6)	24 (75.0)	34 (69.4)
Smoker	2 (4.1)	3 (9.7)	4 (12.1)	1 (3.1)	4 (8.2)
Ex-smoker	12 (24.5)	12 (38.7)	10 (30.3)	7 (21.9)	11 (22.4)
Duration since subject started smoking (years):	14	15	12	8	15
Mean (SD)	30.5 (14.8)	27.0 (16.5)	27.6 (17.6)	24.0 (14.8)	24.2 (15.3)
Range	4.0-52.0	0.4-59.0	5.0-54.0	0.0-41.0	0.3-46.0
Duration since subject stopped smoking (years):	12	12	9	7	11
Mean (SD)	8.2 (9.8)	12.6 (11.7)	12.3 (14.2)	7.7 (4.3)	13.6 (7.7)
Range	0.1-34.0	1.0-35.0	0.3-46.0	2.0-13.0	4.0-32.0

N was the total number of subjects evaluated (subjects assigned to study treatment).
n was the total number of subjects that met the criteria.
Body mass index was calculated as $weight/(height \times 0.01)^2$.
BID = Twice daily; BMI = Body mass index; SD = Standard deviation.

Efficacy Results:

Primary Evaluations:

In the analysis with a FAS population, 47.5%, 29.6%, 51.6%, 63.3%, and 80% of subjects in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg treatment groups, respectively, achieved a clinical response at Week 8. Similar results were observed in the prior TNF-α, no prior TNF-α, failed prior TNF-α, no failed prior TNF-α, failed immunosuppressants, and no failed immunosuppressants study populations. The number of subjects who were clinical responders at Week 8 is summarized in Table 4.

Table 4. Clinical Response at Week 8 (FAS)[a]

Subject Population Responders	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
All subjects, N	40	27	31	30	45
n (%)	19 (47.5)	8 (29.6)	16 (51.6)	19 (63.3)	36 (80)
Prior TNF-α, N	13	7	9	10	12
n (%)	5 (38.5)	1 (14.3)	3 (33.3)	6 (60)	8 (66.7)
No prior TNF-α, N	27	20	22	20	33
n (%)	14 (51.9)	7 (35)	13 (59.1)	13 (65)	28 (84.8)
Failed TNF-α, N	11	1	5	6	9
n (%)	4 (36.4)	0	1 (20)	3 (50)	7 (77.8)
No failed TNF-α, N	29	26	26	24	36
n (%)	15 (51.7)	8 (30.8)	15 (57.7)	16 (66.7)	29 (80.6)
Failed immunosuppressants, N	17	11	11	15	16
n (%)	6 (35.3)	4 (36.4)	2 (18.2)	9 (60)	12 (75)
No failed immunosuppressants, N	23	16	20	15	29
n (%)	13 (56.5)	4 (25)	14 (70)	10 (66.7)	24 (82.8)

N was the total number subjects evaluated.
n was the number of subjects that were clinical responders.
If a subject was a treatment failure, the 4 Mayo components at the post-withdrawal visits were imputed with the Baseline scores, regardless of whether data were recorded or were missing. The endoscopic component was imputed at Week 8 only. Such subjects were classified as non-responders at the post-withdrawal visit for binary analysis.
Responder was defined as a subject with a 3-point improvement in total Mayo score, with at least 30% improvement in total Mayo score, and with at least 1-point improvement in rectal bleeding or an absolute score of 0 or 1.
BID = Twice daily; FAS = Full analysis set; TNF-α = Tumor necrosis factor alpha.
a. The total number of subjects evaluated for efficacy may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg, discontinuation of a subject that was not classified as a treatment failure, a visit fell outside of the predefined window, their binary response was treated as missing; therefore, these subjects were not included in the evaluation.

Statistics were performed for Week 8 clinical response (FAS) using a logistic regression that was linear in dose. From the dose-response modeling of the data, the predefined proof-of-concept criteria of a 20% difference from placebo with a 90% 2-sided lower confidence limit >0 at Week 8 for clinical response (FAS) were met for both tofacitinib 10 mg and 15 mg BID doses. The estimated rates for clinical response were 0.400, 0.413, 0.484, 0.675, and 0.786 for all subjects in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg,

and 15 mg treatment groups, respectively. For clinical response the model results showed differences from placebo of 8.4% for tofacitinib 3 mg, 27.5% for tofacitinib 10 mg, and 38.6% for tofacitinib 15 mg BID with 90% 2-sided lower confidence limits of 5.2%, 16.9%, and 25.0%, respectively. The statistical analysis for clinical response at Week 8 is summarized in Table 5 and a plot of the fitted logistic regression (linear in dose) dose-response model of clinical response at Week 8 is presented in Figure 2.

Table 5. Summary of Statistical Analysis for Clinical Response at Week 8 (FAS)[a] - Logistic Regression Linear in Dose

Category Treatment Group	Estimated Response Rate	90% CI	Difference From Placebo	90% CI
All subjects:[b]				
Placebo	0.400	0.311, 0.488		
Tofacitinib 0.5 mg	0.413	0.327, 0.499	0.014	0.009, 0.019
Tofacitinib 3 mg	0.484	0.410, 0.557	0.084	0.052, 0.116
Tofacitinib 10 mg	0.675	0.600, 0.750	0.275	0.169, 0.382
Tofacitinib 15 mg	0.786	0.698, 0.873	0.386	0.250, 0.522
No prior TNF-α:				
Placebo	0.454	0.355, 0.553		
Tofacitinib 0.5 mg	0.468	0.372, 0.564	0.014	0.009, 0.020
Tofacitinib 3 mg	0.539	0.455, 0.623	0.085	0.051, 0.119
Tofacitinib 10 mg	0.722	0.642, 0.801	0.268	0.163, 0.373
Tofacitinib 15 mg	0.821	0.738, 0.903	0.367	0.237, 0.497
Prior TNF-α:				
Placebo	0.289	0.171, 0.406		
Tofacitinib 0.5 mg	0.300	0.183, 0.418	0.012	0.008, 0.016
Tofacitinib 3 mg	0.363	0.244, 0.482	0.075	0.047, 0.102
Tofacitinib 10 mg	0.559	0.430, 0.688	0.270	0.166, 0.374
Tofacitinib 15 mg	0.691	0.555, 0.827	0.402	0.257, 0.548

If a subject was a treatment failure, the 4 Mayo components at the post-withdrawal visits were imputed with the Baseline scores, regardless of whether data were recorded or were missing. The endoscopic component was imputed at Week 8 only. Such subjects were classified as non-responders at the post-withdrawal visit for binary analysis.

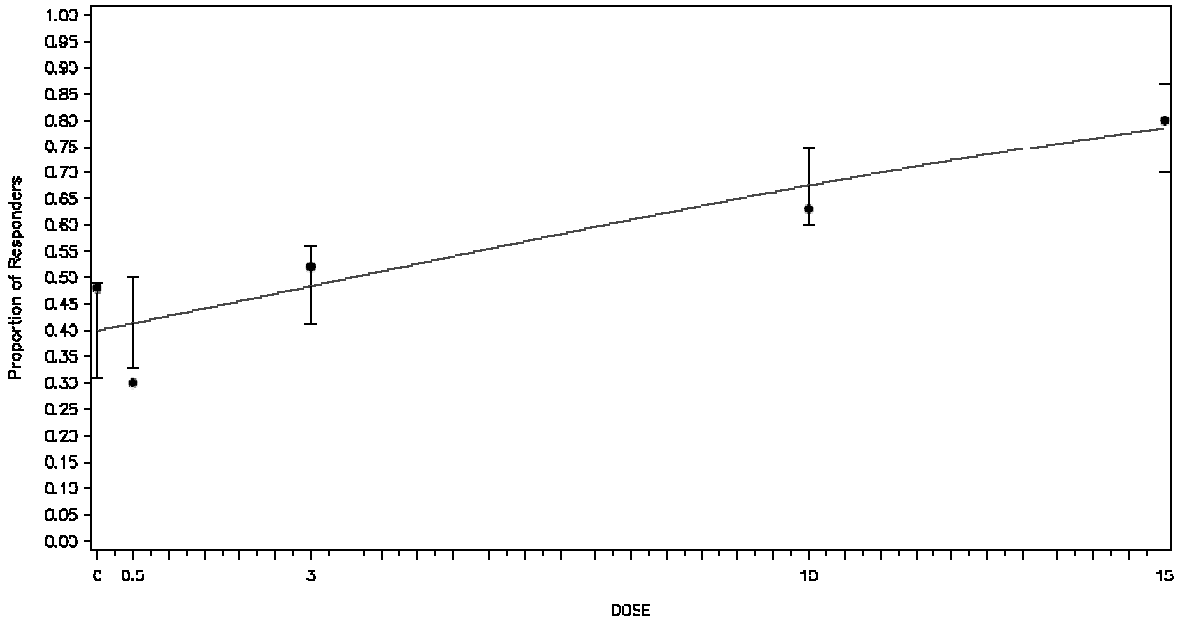
Responder was defined as a subject with a 3-point improvement in total Mayo score, with at least 30% improvement in total Mayo score, and with at least 1-point improvement in rectal bleeding or an absolute score of 0 or 1.

CI = Confidence interval; FAS = Full analysis set; TNF-α= Tumor necrosis factor alpha.

a. The total number of subjects evaluated for efficacy may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg, discontinuation of a subject that was not classified as a treatment failure, a visit fell outside of the predefined window, their binary response was treated as missing; therefore, these subjects were not included in the evaluation.

b. Estimates and difference from placebo in response rates were calculated using sample proportions of subjects with each TNF-α category to weight the beta 0 estimates in the analysis.

Figure 2. Fitted Logistic Regression (linear in dose) Dose Response Model of Clinical Responders at Week 8 With Overlay of Raw Data Responses at Week 8 (FAS)[a]



The dotted circle represents the actual data for proportion of responders.
The line and the 90% confidence intervals represent the data for the predicted proportion of responders from the fitted E_{max} model.
E_{max} = Maximal pharmacologic effect; FAS = Full analysis set.

a. The total number of subjects evaluated for efficacy may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg, discontinuation of a subject that was not classified as a treatment failure, a visit fell outside of the predefined window, their binary response was treated as missing; therefore, these subjects were not included in the evaluation.

Secondary Evaluations:

Clinical Remission: In the FAS analysis, 12.2%, 7.4%, 35.5%, 50%, and 42.2% of subjects in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg treatment groups, respectively, were in clinical remission at Week 8. Similar results were observed in the prior TNF-α, no prior TNF-α, failed prior TNF-α, no failed prior TNF-α, failed immunosuppressants, and no failed immunosuppressants study populations. The number of subjects in clinical remission at Week 8 is summarized in Table 6.

Table 6. Clinical Remission at Week 8 (FAS)[a]

Subject Population Responders	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
All subjects, N	41	27	31	30	45
n (%)	5 (12.2)	2 (7.4)	11 (35.5)	15 (50)	19 (42.2)
Prior TNF-α, N	13	7	9	10	12
n (%)	0	0	3 (33.3)	5 (50)	3 (25)
No prior TNF-α, N	28	20	22	20	33
n (%)	5 (17.9)	2 (10)	8 (36.4)	10 (50)	16 (48.5)
Failed TNF-α, N	11	1	5	6	9
n (%)	0	0	1 (20)	2 (33.3)	3 (33.3)
No failed TNF-α, N	30	26	26	24	36
n (%)	5 (16.7)	2 (7.7)	10 (38.5)	13 (54.2)	16 (44.4)
Failed immunosuppressants, N	18	11	11	15	16
n (%)	0	1 (9.1)	2 (18.2)	7 (46.7)	4 (25)
No failed immunosuppressants, N	23	16	20	15	29
n (%)	5 (21.7)	1 (6.3)	9 (45)	8 (53.3)	15 (51.7)

N was the total number subjects evaluated.
n was the number of subjects that were in clinical remission.
If a subject was a treatment failure, the 4 Mayo components at the post-withdrawal visits were imputed with the Baseline scores, regardless of whether data were recorded or were missing. The endoscopic component was imputed at Week 8 only.
Remission was defined as a subject with a total Mayo score of 2 or lower, with no component score exceeding 1 point.
BID = Twice daily; FAS = Full analysis set; TNF-α= Tumor necrosis factor alpha.
a. The total number of subjects evaluated for efficacy may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg, discontinuation of a subject that was not classified as a treatment failure, a visit fell outside of the predefined window, their binary response was treated as missing; therefore, these subjects were not included in the evaluation.

The estimated rates for clinical remission were 0.093, 0.144, 0.307, 0.436, and 0.464 for subjects in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg treatment groups, respectively, at Week 8. The model-predicted differences from placebo were 5.1%, 21.5%, 34.3%, and 37.2% for the tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg treatment groups, respectively. The statistical analysis for clinical remission at Week 8 is summarized in Table 7 and a plot of the fitted E_{max} dose-response model of clinical remission at Week 8 is presented in Figure 3.

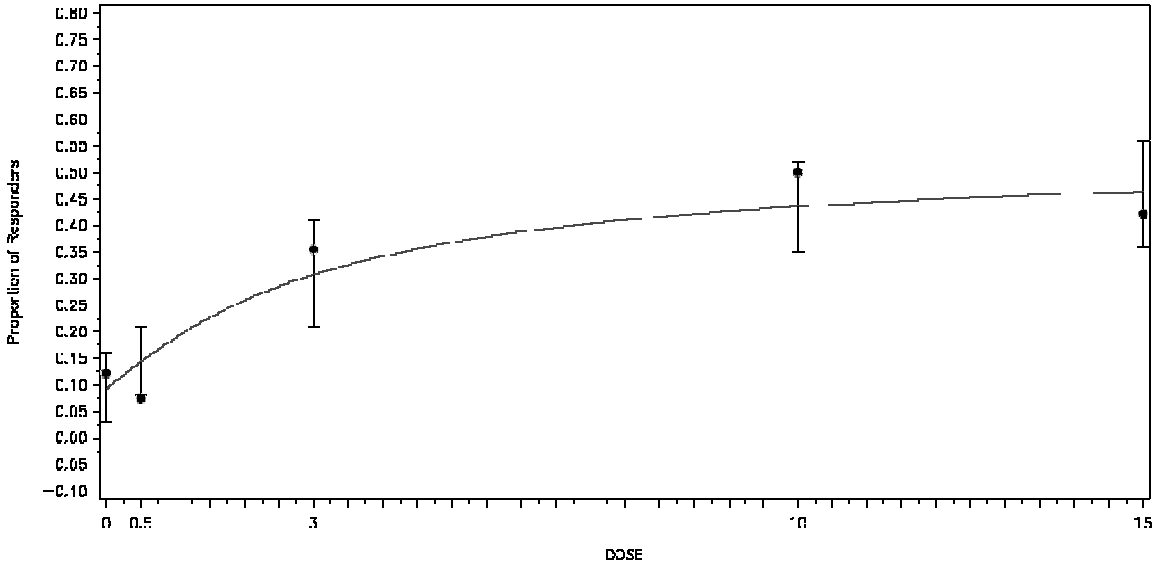
Table 7. Summary of Statistical Analysis for Clinical Remission at Week 8 (FAS)[a] - E_{max} Model

Category Treatment Group	Estimated Response Rate	90% CI	Difference From Placebo	90% CI
All subjects:[b]				
Placebo	0.093	0.029, 0.156		
Tofacitinib 0.5 mg	0.144	0.077, 0.211	0.051	0.001, 0.102
Tofacitinib 3 mg	0.307	0.209, 0.406	0.215	0.097, 0.333
Tofacitinib 10 mg	0.436	0.350, 0.521	0.343	0.234, 0.453
Tofacitinib 15 mg	0.464	0.365, 0.563	0.372	0.253, 0.490
No prior TNF-α:				
Placebo	0.111	0.035, 0.187		
Tofacitinib 0.5 mg	0.171	0.092, 0.249	0.060	0.001, 0.118
Tofacitinib 3 mg	0.352	0.241, 0.464	0.241	0.109, 0.374
Tofacitinib 10 mg	0.486	0.389, 0.584	0.375	0.253, 0.498
Tofacitinib 15 mg	0.515	0.405, 0.625	0.404	0.274, 0.534
Prior TNF-α:				
Placebo	0.061	0.007, 0.114		
Tofacitinib 0.5 mg	0.096	0.030, 0.163	0.036	-0.003, 0.074
Tofacitinib 3 mg	0.220	0.101, 0.339	0.159	0.052, 0.267
Tofacitinib 10 mg	0.329	0.195, 0.464	0.268	0.148, 0.389
Tofacitinib 15 mg	0.355	0.209, 0.501	0.294	0.163, 0.425

If a subject was a treatment failure, the 4 Mayo components at the post-withdrawal visits were imputed with the Baseline scores, regardless of whether data were recorded or were missing. The endoscopic component was imputed at Week 8 only.
Remission was defined as a subject with a total Mayo score of 2 or lower, with no component score exceeding 1 point.
CI = Confidence interval; E_{max} = Maximal pharmacologic effect; FAS = Full analysis set;
TNF-α = Tumor necrosis factor alpha.

a. The total number of subjects evaluated for efficacy may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg discontinuation of a subject that was not classified as a treatment failure, a visit fell outside of the predefined window, their binary response was treated as missing; therefore, these subjects were not included in the evaluation
b. Estimates and difference from placebo in response rates were calculated using sample proportions of subjects with each TNF-α category to weight the beta 0 estimates in the analysis.

Figure 3. Fitted E_{max} Dose Response Model of Clinical Remission at Week 8 With Overlay of Raw Data Responses at Week 8 (FAS)[a]



The dotted circle represents the actual data for proportion of subjects in clinical remission.
The line and the 90% confidence intervals represent the data for the predicted proportion of subjects in clinical remission from the fitted E_{max} model.
E_{max} = Maximal pharmacologic effect; FAS = Full analysis set.

a. The total number of subjects evaluated for efficacy may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg, discontinuation of a subject that was not classified as a treatment failure, a visit fell outside of the predefined window, their binary response was treated as missing; therefore, these subjects were not included in the evaluation.

Total Mayo Score: The median Mayo score at Baseline was 8 for all treatment groups with the exception of tofacitinib 0.5 mg BID where the median Mayo score at Baseline was 9. The adjusted mean change from Baseline ranged from -1.98 (tofacitinib 0.5 mg BID) to -4.45 (tofacitinib 15 mg BID).

A statistically significant difference in mean change from Baseline versus placebo of -2.01 was observed for tofacitinib 10 mg BID treatment group (p=0.003) and -2.37 for tofacitinib 15 mg BID treatment group (p<0.001). Similar results were observed in the FAS last observation carried forward (LOCF) data set. The summary of the statistical analysis for the total Mayo score at Week 8 (FAS) is presented in Table 8.

Table 8. Summary of Statistical Analysis for Total Mayo Score at Week 8 (FAS) - ANCOVA

Treatment Group	n	Baseline Mean	Adjusted Mean Change From Baseline	Standard Error	95% CI
All subjects	173	8.21			
Placebo	40	8.35	-2.08	0.440	-2.95, -1.21
Tofacitinib 0.5 mg	27	8.63	-1.98	0.542	-3.05, -0.91
Tofacitinib 3 mg	31	8.32	-3.35	0.501	-4.34, -2.36
Tofacitinib 10 mg	30	7.93	-4.09	0.505	-5.09, -3.09
Tofacitinib 15 mg	45	7.96	-4.45	0.422	-5.28, -3.61

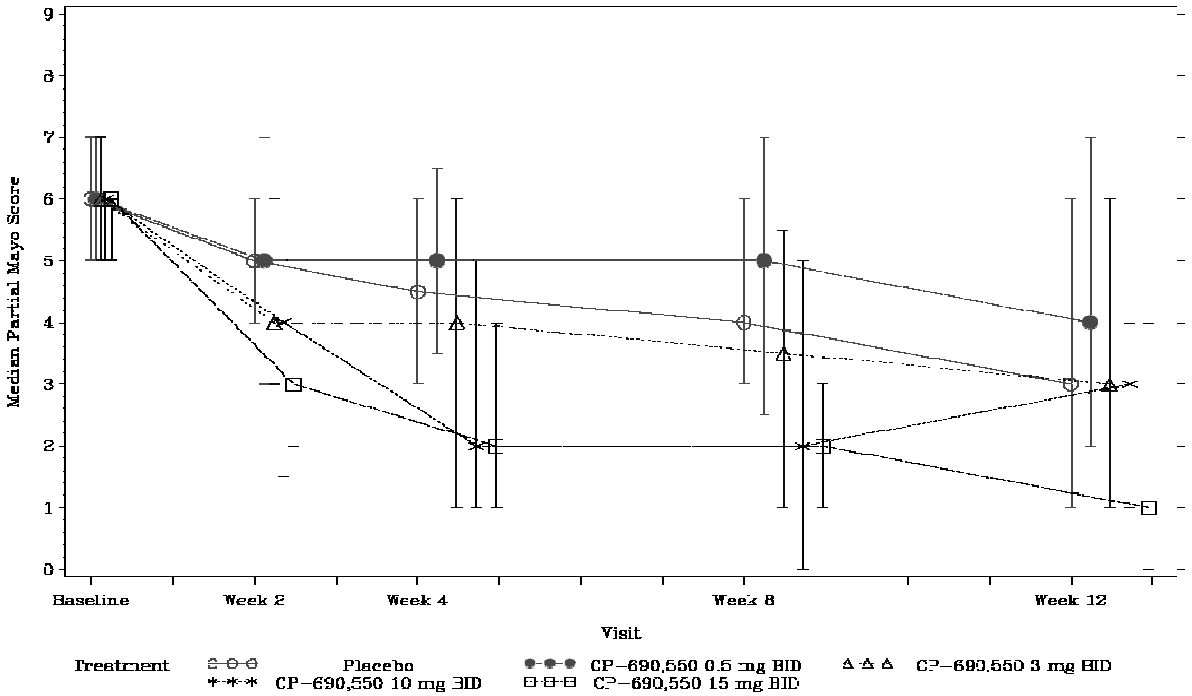
Treatment Group	Difference From Placebo			
	Treatment Difference	Standard Error	95% CI	p-Value
Tofacitinib 0.5 mg	0.09	0.683	-1.25, 1.44	0.892
Tofacitinib 3 mg	-1.27	0.654	-2.56, 0.02	0.054
Tofacitinib 10 mg	-2.01	0.663	-3.32, -0.70	0.003
Tofacitinib 15 mg	-2.37	0.597	-3.55, -1.19	0.000[a]

n was the number of subjects that were included in the analysis.
ANCOVA = Analysis of covariance; CI = Confidence interval; FAS = Full analysis set.
a. The p-value was reported as 0.000 due to the programming limitations; however, the actual value should be reported as <0.001.

Partial Mayo Score: Based on the MMRM analysis of the partial Mayo scores, a statistically significant difference from placebo was observed as early as Week 2 in the tofacitinib 10 mg and 15 mg BID treatment groups. The adjusted mean change from Baseline at Week 8 ranged from -1.29 (tofacitinib 0.5 mg BID) to -3.23 (tofacitinib 15 mg BID).

A statistically significant difference in mean change from Baseline was observed for tofacitinib 10 mg and 15 mg treatment groups versus placebo (differences of -1.28 and -1.76 and p-values of 0.010 and <0.001, respectively). Similar results were observed in the FAS LOCF data set. Median partial Mayo scores are presented in Figure 4.

Figure 4. Median Partial Mayo Score by Week and Dose



Week 12 was the Follow-up Visit after double-blind treatment when subjects could have been on concomitant medication for the primary diagnosis.
BID = Twice daily; CP-690,550 = Tofacitinib.

Endoscopic Response: In the FAS analysis, 55%, 51.9%, 61.3%, 70%, and 82.2% of subjects in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg treatment groups, respectively, had an endoscopic response at Week 8. Similar results were observed in the prior TNF-α, no prior TNF-α, failed prior TNF-α, no failed prior TNF-α, failed immunosuppressants, and no failed immunosuppressants study populations. The results of endoscopic response at Week 8 are summarized in Table 9**.**

Table 9. Number of Subjects With Endoscopic Response at Week 8 (FAS)[a]

Subject Population	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
All subjects, N	40	27	31	30	45
n (%)	22 (55)	14 (51.9)	19 (61.3)	21 (70)	37 (82.2)
Prior TNF-α, N	13	7	9	10	12
n (%)	5 (38.5)	3 (42.9)	4 (44.4)	7 (70)	8 (66.7)
No prior TNF-α, N	27	20	22	20	33
n (%)	17 (63)	11 (55)	15 (68.2)	14 (70)	29 (87.9)
Failed TNF-α, N	11	1	5	6	9
n (%)	4 (36.4)	0	2 (40)	4 (66.7)	7 (77.8)
No failed TNF-α, N	29	26	26	24	36
n (%)	18 (62.1)	14 (53.8)	17 (65.4)	17 (70.8)	30 (83.3)
Failed immunosuppressants, N	17	11	11	15	16
n (%)	6 (35.3)	7 (63.6)	4 (36.4)	10 (66.7)	13 (81.3)
No failed immunosuppressants, N	23	16	20	15	29
n (%)	16 (69.6)	7 (43.8)	15 (75)	11 (73.3)	24 (82.8)

N was the total number subjects evaluated.
n was the number of subjects that had an endoscopic response.
If a subject was a treatment failure, the 4 Mayo components at the post-withdrawal visits were imputed with the Baseline scores, regardless of whether data were recorded or were missing. The endoscopic component was imputed at Week 8 only.
Endoscopic response was defined as a decrease from Baseline in the findings on the endoscopy subscore of 1 point or more.
BID = Twice daily; FAS = Full analysis set; TNF-α = Tumor necrosis factor alpha.

a. The total number of subjects evaluated for efficacy may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg, discontinuation of a subject that was not classified as a treatment failure, a visit fell outside of the predefined window, their binary response was treated as missing; therefore, these subjects were not included in the evaluation.

Endoscopic Remission: In the FAS analysis, 2.4%, 7.4%, 19.4%, 30%, and 26.7% of subjects in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg treatment groups, respectively, were in endoscopic remission at Week 8. Similar results were observed in the prior TNF-α, no prior TNF-α, failed prior TNF-α, no failed prior TNF-α, failed immunosuppressants, and no failed immunosuppressants study populations. The number of subjects in endoscopic remission at Week 8 is summarized in Table 10.

Table 10. Endoscopic Remission at Week 8 (FAS)[a]

Subject Population	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
All subjects, N	41	27	31	30	45
n (%)	1 (2.4)	2 (7.4)	6 (19.4)	9 (30)	12 (26.7)
Prior TNF-α, N	13	7	9	10	12
n (%)	0	0	2 (22.2)	3 (30)	3 (25)
No prior TNF-α, N	28	20	22	20	33
n (%)	1 (3.6)	2 (10)	4 (18.2)	6 (30)	9 (27.3)
Failed TNF-α, N	11	1	5	6	9
n (%)	0	0	1 (20)	1 (16.7)	3 (33.3)
No failed TNF-α, N	30	26	26	24	36
n (%)	1 (3.3)	2 (7.7)	5 (19.2)	8 (33.3)	9 (25)
Failed immunosuppressants, N	18	11	11	15	16
n (%)	0	1 (9.1)	1 (9.1)	4 (26.7)	4 (25)
No failed immunosuppressants, N	23	16	20	15	29
n (%)	1 (4.3)	1 (6.3)	5 (25)	5 (33.3)	8 (27.6)

N was the total number subjects evaluated.
n was the number of subjects that were in endoscopic remission.
If a subject was a treatment failure, the 4 Mayo components at the post-withdrawal visits were imputed with the Baseline scores, regardless of whether data were recorded or were missing. The endoscopic component was imputed at Week 8 only.
Endoscopic remission was defined as a finding on the endoscopy subscore equal to 0.
BID = Twice daily; FAS = Full analysis set; TNF-α = Tumor necrosis factor alpha.

a. The total number of subjects evaluated for efficacy may not have been equal to the total number of subjects in the FAS. Subjects in the FAS with missing Week 8 binary data, for reasons other than treatment failure, eg, discontinuation of a subject that was not classified as a treatment failure, a visit falling outside of the predefined window, their binary response was treated as missing; therefore, these subjects were not included in the evaluation

Inflammatory Bowel Disease Questionnaire: For the IBDQ, each domain (bowel function, emotional status, systemic symptoms, and social functions) demonstrated a trend towards dose-related improvements, with the largest improvements being seen in the tofacitinib 15 mg group. The change from Baseline in IBDQ score for each domain is presented in Table 11.

Table 11. Change From Baseline in IBDQ Score at Week 8 (FAS)

Domain Parameter	Placebo N = 48	Tofacitinib BID			
		0.5 mg N = 31	3 mg N = 33	10 mg N = 33	15 mg N = 49
Bowel function, n	34	18	24	26	42
Mean (SD)	9.15 (10.59)	11.06 (10.48)	11.46 (9.65)	13.19 (14.18)	18.96 (11.60)
Range	-10 to 36	-3 to 34	-2 to 36	-8 to 47	-3 to 43
Emotional status, n	34	18	24	26	42
Mean (SD)	9.49 (11.89)	6.33 (14.09)	9.21 (10.60)	7.88 (14.70)	16.48 (14.75)
Range	-7 to 41	-18 to 37	-6 to 34	-12 to 52	-13 to 48
Systematic symptoms, n	34	18	24	26	42
Mean (SD)	4.44 (5.86)	4.89 (5.81)	4.79 (4.62)	3.85 (6.39)	7.24 (5.88)
Range	-4 to 17	-7 to 16	-2 to 16	-8 to 22	-3 to 19
Social functions, n	34	18	24	26	42
Mean (SD)	4.67 (6.49)	5.44 (7.45)	4.83 (5.72)	5.46 (6.96)	8.04 (7.07)
Range	-13 to 21	-7 to 23	-6 to 16	-4 to 24	-4 to 20

N was the number subjects in the subject population.
n was the number of subjects that were included in the analysis.
For IBDQ scores, a positive change from Baseline indicated improvement.
BID = Twice daily; FAS = Full analysis set; IBDQ = Inflammatory bowel disease questionnaire;
SD = Standard deviation.

The mean (standard deviation) change from Baseline in total IBDQ score at Week 8 was 27.75 (29.75) for placebo, 27.72 (33.37) for tofacitinib 0.5 mg, 30.29 (27.29) for tofacitinib 3 mg, 30.38 (39.76) for tofacitinib 10 mg, and 50.71 (35.55) for tofacitinib 15 mg.

The adjusted mean change from Baseline ranged from 25.76 (tofacitinib 0.5 mg BID) to 49.85 (tofacitinib 15 mg BID). A statistically significant difference in mean change from Baseline was observed for the tofacitinib 15 mg treatment group versus placebo (p=0.001). A summary of statistical analysis for change from Baseline in the total IBDQ score at Week 8 (ANCOVA) is presented in Table 12.

Table 12. Summary of Statistical Analysis for Change From Baseline in Total IBDQ Score at Week 8 (FAS) - ANCOVA

Treatment Group	n	Baseline Mean	Adjusted Mean Change From Baseline	Standard Error	95% CI
All subjects	144	126.60			
Placebo	34	123.56	26.50	5.260	16.10, 36.90
Tofacitinib 0.5 mg	18	121.83	25.76	7.232	11.46, 40.06
Tofacitinib 3 mg	24	133.83	33.28	6.279	20.86, 45.69
Tofacitinib 10 mg	26	130.55	32.01	6.017	20.11, 43.90
Tofacitinib 15 mg	42	124.52	49.85	4.731	40.50, 59.21

Treatment Group	Difference From Placebo			
	Treatment Difference	Standard Error	95% CI	p-Value
Tofacitinib 0.5 mg	-0.74	8.933	-18.41, 16.92	0.934
Tofacitinib 3 mg	6.78	8.207	-9.45, 23.01	0.410
Tofacitinib 10 mg	5.51	8.001	-10.31, 21.33	0.492
Tofacitinib 15 mg	23.35	7.069	9.37, 37.33	0.001

n was the number of subjects that were included in the analysis.
ANCOVA = Analysis of covariance; CI = Confidence interval; IBDQ = Inflammatory bowel disease questionnaire; FAS = Full analysis set.

Biomarkers:

C-Reactive Protein:

Geometric mean CRP levels at Baseline were 4.53 mg/L for placebo, 6.60 mg/L for tofacitinib 0.5 mg BID, 6.34 mg/L for tofacitinib 3 mg BID, 4.74 mg/L for tofacitinib 10 mg BID, and 5.70 mg/L for tofacitinib 15 mg BID. The geometric mean change from Baseline in CRP to Week 8 was 0.73 for placebo, 0.75 for tofacitinib 0.5 mg BID, 0.41 for tofacitinib 3 mg BID, 0.59 for tofacitinib 10 mg BID, and 0.27 for tofacitinib 15 mg BID. A summary of change from Baseline in CRP (mg/L) by visit for the FAS is provided in Table 13.

Table 13. Baseline and Change From Baseline in C-Reactive Protein by Visit (FAS)

Visit / Parameter	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
Baseline, N	48	31	33	32	49
Geometric mean (SD) (mg/L)	4.53 (12.84)	6.60 (29.43)	6.34 (13.21)	4.74 (16.45)	5.70 (26.44)
Natural log-transformed data:					
Arithmetic mean (SD)	1.51 (1.40)	1.89 (1.58)	1.85 (1.38)	1.56 (1.44)	1.74 (1.67)
Week 4, N	38	22	25	30	46
Change from Baseline:					
Geometric mean	0.82	0.88	0.47	0.31	0.24
Natural log-transformed data:					
Arithmetic mean (SD)	-0.20 (1.01)	-0.13 (1.04)	-0.76 (1.24)	-1.17 (1.47)	-1.42 (1.21)
Week 8, N	37	21	27	28	44
Change from Baseline:					
Geometric mean	0.73	0.75	0.41	0.59	0.27
Natural log-transformed data:					
Arithmetic mean (SD)	-0.31 (1.02)	-0.28 (1.37)	-0.89 (1.29)	-0.53 (1.50)	-1.31 (1.62)

N was the total number of subjects evaluated.
The back-transformed adjusted mean provided an estimate of the geometric mean and the back-transformed treatment differences provided an estimate of the ratio between the geometric means.
BID = Twice daily; FAS = Full analysis set; SD = Standard deviation.

The adjusted mean changes from Baseline in CRP to Week 8 were decreases in all treatment groups. The adjusted mean change from Baseline in CRP to Week 8 was -0.40 for the placebo group, -0.26 for the tofacitinib 0.5 mg BID group, -0.80 for the tofacitinib 3 mg BID group, -0.54 for the tofacitinib 10 mg BID group, and -1.30 for the tofacitinib 15 mg BID group. A statistically significant difference in the adjusted mean change from Baseline at Week 8 was observed for the tofacitinib 15 mg treatment group versus placebo (p=0.002). A summary of the statistical analysis for CRP at Week 8 for the FAS is provided in Table 14.

Table 14. Summary of Statistical Analysis for C-Reactive Protein at Week 8 (FAS)

Visit / Parameter	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
Baseline, N	37	21	27	28	44
Baseline geometric mean	3.75	4.90	5.93	4.61	4.85
Week 8					
Anti-log					
Adjusted mean ratio	0.67	0.77	0.45	0.58	0.27
95% confidence interval	0.45, 1.01	0.45, 1.32	0.28, 0.73	0.36, 0.94	0.19, 0.40
Treatment ratio[a]		1.14	0.67	0.87	0.40
95% confidence interval		0.58, 2.26	0.35, 1.26	0.46, 1.62	0.23, 0.71
p-Value		0.703	0.210	0.656	0.002[b]

N was the total number of subjects evaluated.
The back-transformed adjusted mean change from Baseline provided an estimate of the adjusted mean change as a ratio and the back-transformed treatment difference provided an estimate of the ratio of the ratios.
BID = Twice daily; FAS = Full analysis set.
a. Tofacitinib versus placebo.
b. Statistically significant.

Fecal Calprotectin: A clear treatment effect was seen in the levels of fecal calprotectin measured across time, with the highest decreases from Baseline observed in the tofacitinib 15 mg treatment group.

Geometric mean fecal calprotectin levels at Baseline were 635.4 mg/kg for placebo, 664.6 mg/kg for tofacitinib 0.5 mg BID, 718.1 mg/kg for tofacitinib 3 mg BID, 366.6 mg/kg for tofacitinib 10 mg BID, and 720.3 mg/kg for tofacitinib 15 mg BID. The geometric mean change from Baseline in fecal calprotectin to Week 8 was 0.81 for placebo, 0.72 for, tofacitinib 0.5 mg BID, 0.46 for tofacitinib 3 mg BID, 0.50 for tofacitinib 10 mg BID, and 0.24 for tofacitinib 15 mg BID. A summary of change from Baseline in fecal calprotectin (mg/kg) by visit for the FAS is provided in Table 15.

Table 15. Baseline and Change From Baseline in Fecal Calprotectin by Visit (FAS)

Visit / Parameter	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
Baseline, N	46	29	31	32	49
Geometric mean (SD) (mg/kg)	635.4 (2596)	664.6 (1623)	718.1 (2182)	366.6 (2001)	720.3 (2575)
Natural log-transformed data:					
Arithmetic mean (SD)	6.45 (1.56)	6.50 (1.49)	6.58 (1.26)	5.90 (1.75)	6.58 (1.24)
Week 2, N	39	24	28	31	47
Change from Baseline:					
Geometric mean	1.29	1.38	0.62	0.83	0.39
Natural log-transformed data:					
Arithmetic mean (SD)	0.25 (1.35)	0.33 (1.72)	-0.48 (2.05)	-0.18 (1.25)	-0.95 (1.66)
Week 4, N	37	22	27	28	45
Change from Baseline:					
Geometric mean	1.01	1.06	0.65	0.72	0.29
Natural log-transformed data:					
Arithmetic mean (SD)	0.01 (1.36)	0.06 (1.64)	-0.44 (2.04)	-0.32 (1.17)	-1.25 (1.48)
Week 8, N	40	25	28	31	43
Change from Baseline:					
Geometric mean	0.81	0.72	0.46	0.50	0.24
Natural log-transformed data:					
Arithmetic mean (SD)	-0.21 (1.64)	-0.34 (1.48)	-0.78 (1.67)	-0.70 (1.85)	-1.41 (1.78)
Week 12, N	33	19	24	28	42
Change from Baseline:					
Geometric mean	0.61	1.17	0.67	0.59	0.39
Natural log-transformed data:					
Arithmetic mean (SD)	-0.49 (1.67)	0.16 (1.18)	-0.41 (1.92)	-0.53 (1.55)	-0.95 (1.36)

N was the total number of subjects evaluated.
The back-transformed adjusted mean provided an estimate of the geometric mean and the back-transformed treatment differences provided an estimate of the ratio between the geometric means.
BID = Twice daily; FAS = Full analysis set; SD = Standard deviation.

A statistically significant difference in the adjusted mean change from Baseline was observed for tofacitinib 10 mg and 15 mg treatment groups versus placebo ($p = 0.035$ and $p = 0.004$, respectively). A summary of the statistical analysis for fecal calprotectin at Week 8 for the FAS is provided in Table 16.

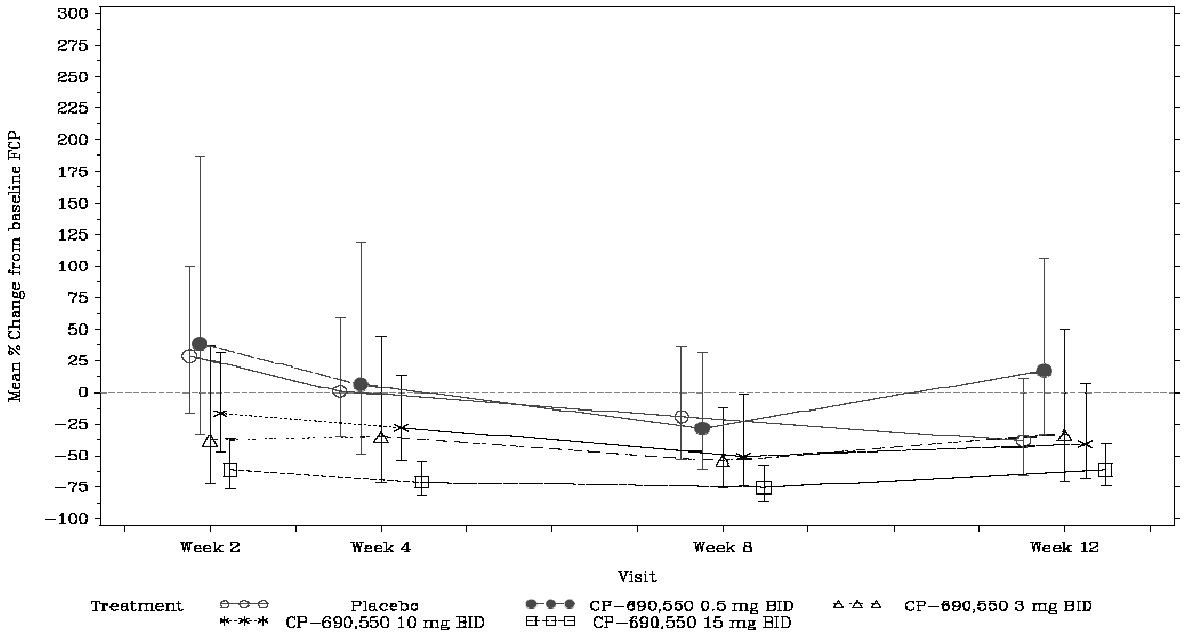
Table 16. Summary of Statistical Analysis for Fecal Calprotectin at Week 8 (FAS)

Visit / Parameter	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
Baseline, N	40	25	28	31	43
Baseline geometric mean	515.97	520.87	604.17	353.38	783.00
Week 8					
Anti-log					
Adjusted mean ratio	0.77	0.69	0.49	0.38	0.31
95% confidence interval	0.50, 1.21	0.39, 1.21	0.29, 0.83	0.22, 0.62	0.20, 0.47
Treatment ratio[a]		0.89	0.63	0.48	0.39
95% confidence interval		0.43, 1.83	0.31, 1.26	0.25, 0.95	0.21, 0.74
p-Value		0.751	0.192	0.035[b]	0.004[b]

N was the total number of subjects evaluated.
The back-transformed adjusted mean change from Baseline provided an estimate of the adjusted mean change as a ratio and the back-transformed treatment difference provided an estimate of the ratio of the ratios.
BID = Twice daily; FAS = Full analysis set.
a. Tofacitinib versus placebo.
b. Statistically significant.

The mean percent change from Baseline (with 95% CI) in fecal calprotectin (FAS) by visit is presented in Figure 5.

Figure 5. Mean (With 95% CI) Percent Change From Baseline Fecal Calprotectin by Visit (FAS)



Week 12 was the Follow-up Visit after double-blind treatment when subjects could have been on concomitant medication for the primary diagnosis.
BID = Twice daily; CI = Confidence interval; CP-690,550 = Tofacitinib; FAS = Full analysis set; FCP = Fecal calprotectin.

Safety Results:

All-Causality and Treatment-Related TEAEs: The most frequently reported all-causality TEAEs in the tofacitinib BID group were headache, colitis ulcerative, dizziness, and nasopharyngitis. In the placebo group, the most frequently reported treatment-emergent and treatment-related AEs were colitis ulcerative and influenza.

The overall incidence of treatment-related TEAEs was similar between the subjects in both treatment groups. The most frequently reported treatment-related TEAEs in the tofacitinib BID group were headache and dizziness. In the placebo group, the most frequently reported treatment-related and TEAEs was colitis ulcerative. The all-causality and treatment-related/TEAEs by body system and preferred term are presented in Table 17.

Table 17. TEAEs Occurred in ≥5% Subjects in Any Treatment Group, All-Causality and Treatment-Related - Safety Population

	Placebo			Tofacitinib 0.5 mg BID			Tofacitinib 3 mg BID			Tofacitinib 10 mg BID			Tofacitinib 15 mg BID		
	n (%)	n1[a]	n2[b]	n (%)	n1[a]	n2[b]	n (%)	n1[a]	n2[b]	n (%)	n1[a]	n2[b]	n (%)	n1[a]	n2[b]
Evaluable for Adverse Events	**48**			**31**			**33**			**33**			**49**		
With Adverse Events, n (%)	**12 (25.0)**			**17 (54.8)**			**8 (24.2)**			**9 (27.3)**			**12 (24.5)**		
System organ class Preferred term															
Gastrointestinal disorders	7 (14.6)	7	2	8 (25.8)	8	2	3 (9.1)	3	1	1 (3.0)	1	0	4 (8.2)	4	0
Abdominal pain	1 (2.1)	1	0	1 (3.2)	1	1	0	0	0	0	0	0	3 (6.1)	3	0
Colitis ulcerative	6 (12.5)	6	2	5 (16.1)	5	1	2 (6.1)	2	1	1 (3.0)	1	0	1 (2.0)	1	0
Dyspepsia	0	0	0	2 (6.5)	2	0	1 (3.0)	1	0	0	0	0	0	0	0
Infections and infestations	4 (8.3)	5	1	6 (19.4)	6	1	1 (3.0)	1	0	1 (3.0)	1	0	2 (4.1)	2	0
Influenza	3 (6.3)	4	1	2 (6.5)	2	0	0	0	0	0	0	0	1 (2.0)	1	0
Nasopharyngitis	1 (2.1)	1	0	2 (6.5)	2	0	1 (3.0)	1	0	1 (3.0)	1	0	1 (2.0)	1	0
Sinusitis	0	0	0	2 (6.5)	2	1	0	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (3.2)	1	1	0	0	0	3 (9.1)	4	0	2 (4.1)	2	0
Arthralgia	0	0	0	0	0	0	0	0	0	2 (6.1)	2	0	2 (4.1)	2	0
Pain in extremity	0	0	0	1 (3.2)	1	1	0	0	0	2 (6.1)	2	0	0	0	0
Nervous system disorders	2 (4.2)	3	1	4 (12.9)	4	2	3 (9.1)	3	1	4 (12.1)	5	2	5 (10.2)	12	10
Dizziness	1 (2.1)	1	1	2 (6.5)	2	1	0	0	0	1 (3.0)	1	0	2 (4.1)	2	2
Headache	2 (4.2)	2	0	2 (6.5)	2	1	3 (9.1)	3	1	3 (9.1)	4	2	4 (8.2)	10	8
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	2 (6.1)	2	1	1 (3.0)	1	0	0	0	0
Rash	0	0	0	0	0	0	2 (6.1)	2	1	1 (3.0)	1	0	0	0	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 13.0) coding dictionary applied.
BID = Twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = The number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities; TEAE = Treatment-emergent adverse event.

a. The number of occurrences of treatment-emergent all-causalities adverse events.
b. The number of occurrences of treatment-emergent causally-related to treatment adverse events.

All-Causality and Treatment-Related Treatment Emergent SAEs:

The most frequently reported all causality treatment emergent SAE in both tofacitinib BID and placebo group was colitis ulcerative. The overall incidence of all causality treatment emergent SAE was similar between the subjects in both treatment groups. The all causality and treatment related treatment emergent SAE by body system and preferred term are presented in Table 18.

Table 18. Treatment Emergent SAEs in Any Treatment Group, All-Causality and Treatment-Related - Safety Population

	Placebo			Tofacitinib 0.5 mg BID			Tofacitinib 3 mg BID			Tofacitinib 10 mg BID			Tofacitinib 15 mg BID		
	n (%)	n1[a]	n2[b]	n (%)	n1[a]	n2[b]	n (%)	n1[a]	n2[b]	n (%)	n1[a]	n2[b]	n (%)	n1[a]	n2[b]
Evaluable for Adverse Events	**48**			**31**			**33**			**33**			**49**		
With Adverse Events, n (%)	**4 (8.3)**			**1 (3.2)**			**1 (3.0)**			**2 (6.1)**			**2 (4.1)**		
System organ class Preferred term															
Gastrointestinal disorders	3 (6.3)	3	1	0	0	0	1 (3.0)	1	1	1 (3.0)	1	0	2 (4.1)	2	0
Colitis ulcerative	3 (6.3)	3	1	0	0	0	1 (3.0)	1	1	1 (3.0)	1	0	2 (4.1)	2	0
General disorders and administration site conditions	0	0	0	1 (3.2)	1	1	0	0	0	0	0	0	0	0	0
General physical health deterioration	0	0	0	1 (3.2)	1	1	0	0	0	0	0	0	0	0	0
Immune system disorders	0	0	0	0	0	0	0	0	0	1 (3.0)	1	0	0	0	0
Drug hypersensitivity	0	0	0	0	0	0	0	0	0	1 (3.0)	1	0	0	0	0
Infections and infestations	0	0	0	0	0	0	0	0	0	2 (6.1)	2	0	0	0	0
Anal abscess	0	0	0	0	0	0	0	0	0	1 (3.0)	1	0	0	0	0
Postoperative abscess	0	0	0	0	0	0	0	0	0	1 (3.0)	1	0	0	0	0
Nervous system disorders	1 (2.1)	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Ischaemic stroke	1 (2.1)	1	0	0	0	0	0	0	0	0	0	0	0	0	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (Version 13.0) coding dictionary applied.
BID = Twice daily; SAE = Serious adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = The number of subjects in this reporting group affected by any occurrence of this serious adverse event, all-causalities.

a. The number of occurrences of treatment-emergent all-causalities SAE.
b. The number of occurrences of treatment-emergent causally-related to treatment SAE.

Discontinuations due to AEs:

The number of subjects permanently discontinuing from the study and from study drug due to AEs were low in all treatment groups: 3 subjects in the placebo group and 2 subjects each in the tofacitinib 0.5 mg and 15 mg treatment groups. The most common AE that led to permanent discontinuation from the study was colitis ulcerative. Additionally, 2 subjects had AEs leading to permanent discontinuation from study drug but not from the study: 1 subject in the placebo group discontinued study drug due to an SAE of colitis ulcerative (permanently discontinued the study because the subject was lost to follow-up); and 1 subject in the tofacitinib 10 mg group discontinued study drug due to an SAE of anal abscess (completed the study). No discontinuations occurred due to abnormal laboratory test results. Discontinuations due to AEs are presented in Table 19.

Table 19. Discontinuations due to Adverse Events

Treatment Group[a]	Adverse Event[b]	Start/ Stop Day[c]	Severity/ Outcome	Study Drug Action	Causality	SAE	Reason for Withdrawal[d]
Placebo:							
1	Colitis ulcerative	14/22	Severe/ resolved	Permanently discontinued	Study drug	Yes	Colitis ulcerative
2	Colitis ulcerative	58/92	Severe/ resolved	Permanently discontinued	Disease under study	Yes	Lost to follow-up
3	Ischaemic stroke	8/>9[e]	Severe/still present	Permanently discontinued	Other, illness[f]	Yes	Ischaemic stroke
4	Colitis ulcerative	73/78	Moderate/ resolved	Permanently discontinued	Disease under study	No	Colitis ulcerative
Tofacitinib 0.5 mg:							
1	Colitis ulcerative	3/28	Moderate/ resolved	Permanently discontinued	Disease under study	No	Colitis ulcerative
2	Colitis ulcerative	19/26	Moderate/ resolved	Permanently discontinued	Disease under study	No	Colitis ulcerative
Tofacitinib 10 mg:							
1	Anal abscess	56/>85[e]	Moderate/ still present	Permanently discontinued	Other, illness[g]	Yes	NA/completed the study
Tofacitinib 15 mg:							
1	Colitis ulcerative	2/62	Severe/ resolved	Permanently discontinued	Disease under study	Yes	Colitis ulcerative and vomiting
	Vomiting	5/6	Severe/ resolved	Permanently discontinued	Other, due to worsening of ulcerative colitis	No	
2	Colitis ulcerative	19/29	Severe/ resolved	Permanently discontinued	Disease under study	Yes	Colitis ulcerative

SAEs were defined according to the investigator's assessment.
MedDRA (Version 13.0) coding dictionary was applied.
BID = Twice daily; ID = Identification; NA = Not applicable; MedDRA = Medical Dictionary for Regulatory Activities; SAE = Serious adverse event.

a. Dosing was BID.
b. Adverse event MedDRA preferred terms were used.
c. Day was relative to the start of study treatment (ie, first day of study treatment equals Day 1).
d. Permanent withdrawal from the study.
e. Value was imputed from incomplete dates and times.
f. Illnesses were general cerebrovascular stricture (due to age) and hypertension.
g. Illness was likely an intercurrent disease.

Dose Reductions or Temporary Discontinuations due to AEs:

Two subjects had a temporary discontinuation of study drug due to AEs. One subject in the tofacitinib 0.5 mg group experienced 3 AEs (general physical health deterioration, pain in extremity, and headache) that resulted in temporary discontinuation of the study drug. These AEs were considered treatment-related. One subject in the tofacitinib 3 mg group experienced 1 AE (headache) that resulted in temporary discontinuation of study drug. This AE was considered treatment-related.

Deaths:

There were no deaths among subjects who participated in this study.

Clinical Laboratory Test Results:

The most frequently occurring laboratory test abnormalities were elevated total neutrophils (>1.2 × upper limit of normal [ULN]), elevated low-density lipoprotein cholesterol (>1.2 × ULN), elevated total cholesterol (>1.3 × ULN), elevated white blood cells count (≥6/high-power field) for urine microscopy, and low lymphocytes (<0.8 × lower limit of normal). A total of 2 subjects had 1 laboratory abnormality each that was considered clinically significant based on the assessment of the Investigator. The incidences of laboratory test abnormalities are summarized in Table 20.

Table 20. Incidences of Laboratory Test Abnormalities in >1 Subject per Parameter (Without Regard to Baseline Abnormality)

Number of Subjects, n		Placebo N = 47	Tofacitinib BID 0.5 mg N = 31	Tofacitinib BID 3 mg N = 33	Tofacitinib BID 10 mg N = 33	Tofacitinib BID 15 mg N = 49
With Laboratory Abnormalities		**35**	**22**	**24**	**26**	**33**
Parameter	**Criteria**					
Hematology:		5	2	4	2	1
Hemoglobin (g/dL)	<0.8 × LLN	1	2	1	1	1
Hematocrit (%)	<0.8 × LLN					
Reticulocytes (abs)	>1.5 × ULN	1	0	1	0	0
Lymphocytes (abs)	<0.8 × LLN	7	2	2	3	4
	>1.2 × ULN	2	2	3	1	3
Total neutrophils (abs)	<0.8 × LLN	1	0	1	2	3
	>1.2 × ULN	6	7	5	6	7
Basophils (abs)	>1.2 × ULN	1	0	0	1	0
Eosinophils (abs)	>1.2 × ULN	4	5	2	0	2
Monocytes (abs)	>1.2 × ULN	8	1	1	0	1
Liver function:						
Total bilirubin (mg/dL)	>1.5 × ULN	1	0	0	0	1
GGT (IU/L)	>3.0 × ULN	1	0	0	1	3
Lipids:						
Cholesterol (mg/dL)	>1.3 × ULN	5	4	2	8	9
HDL cholesterol (mg/dL)	<0.8 × LLN	2	5	1	3	0
LDL cholesterol (mg/dL)	>1.2 × ULN	4	4	4	9	9
Triglycerides (mg/dL)	>1.3 × ULN	0	2	0	2	3
Electrolytes:						
Potassium (meq/L)	<0.9 × LLN	0	1	0	1	1
Bicarbonate (venous) (meq/L)	<0.9 × LLN	3	3	1	2	3
	>1.1 × ULN	3	1	4	0	2
Clinical chemistry:						
Glucose (mg/dL)	<0.6 × LLN	1	1	1	1	0
	>1.5 × ULN	1	2	0	1	1
Urinalysis (Microscopy):						
RBC (/HPF)	≥6	2	0	2	4	2
WBC (/HPF)	≥6	5	4	4	4	3

N was the total number of subjects in the treatment group in the indicated population with at least 1 observation of a given laboratory test while on study treatment or during lag time.
n was the number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
abs = Absolute; BID = Twice daily; GGT = Gamma glutamyl transferase; HDL = High-density lipoprotein; HPF = High power field; LDL = Low-density lipoprotein; LLN = Lower limit of normal; RBC = Red blood cells; ULN = Upper limit of normal; WBC = White blood cells.

Serum Lipids: There were dose-related increases compared with Baseline at Week 8 in mean LDL across all dose groups. There were increases compared with Baseline at Week 8 in mean HDL levels across all dose groups, with the largest increase occurring in the tofacitinib 15 mg treatment group. No subjects required initiation of lipid-lowering medication during the study. Changes from Baseline in LDL, HDL, and triglycerides are presented in Table 21.

Table 21. Change From Baseline in LDL, HDL, and Triglycerides by Visit

Parameter Visit	Placebo	Tofacitinib BID			
		0.5 mg	3 mg	10 mg	15 mg
LDL (mg/dL)					
Week 8, n	46	31	32	31	46
Mean (SD)	-2.14 (18.77)	2.97 (17.95)	4.63 (18.41)	9.36 (25.36)	11.81 (23.23)
Range	-53.00 - 47.10	-37.84 - 61.78	-31.27 - 53.28	-42.08 - 69.88	-31.00 - 62.93
Week 12, n	43	28	28	30	47
Mean (SD)	-3.52 (21.29)	10.67 (37.76)	-0.65 (15.61)	-5.75 (21.82)	1.52 (19.34)
Range	-45.00 - 36.00	-27.03 - 169.11	-39.00 - 34.36	-55.21 - 33.98	-41.70 - 44.02
HDL (mg/dL)					
Week 8, n	46	31	32	32	48
Mean (SD)	0.94 (8.58)	3.27 (12.07)	5.35 (8.54)	5.95 (11.14)	12.13 (12.47)
Range	-16.99 - 22.01	-30.12 - 36.29	-17.76 - 27.03	-19.69 - 24.71	-15.06 - 42.86
Week 12, n	43	28	28	31	47
Mean (SD)	1.94 (10.10)	4.52 (12.69)	3.02 (9.85)	0.89 (14.96)	0.85 (14.69)
Range	-27.03 - 26.00	-28.96 - 35.91	-12.74 - 23.94	-27.03 - 56.76	-39.77 - 52.12
Triglycerides (mg/dL)					
Week 8, n	46	31	32	32	48
Mean (SD)	-1.23 (57.23)	16.85 (52.18)	7.37 (42.98)	-6.00 (41.97)	16.45 (60.79)
Range	-204.44 - 98.24	-74.34 - 156.65	-79.65 - 114.16	-84.96 - 119.48	-75.00 - 255.77
Week 12, n	43	28	28	31	47
Mean (SD)	-3.90 (49.94)	5.83 (36.25)	-4.13 (43.55)	26.50 (159.27)	5.47 (44.04)
Range	-226.56 - 82.31	-49.56 - 109.74	-83.00 - 101.78	-215.94 - 800.04	-89.00 - 144.26

n was the number of subjects that were included in the analysis.
BID = Twice daily; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; SD = Standard deviation.

Vital Signs, Electrocardiograms, and Physical Examination:

After dosing, vital signs of clinical concern in blood pressure were observed in subjects treated with tofacitinib or placebo; the incidence of vital signs of clinical concern was similar across all treatment groups. No subjects experienced abnormalities in pulse rate (<40 or >120 beats per minute). No vital sign values were considered clinically significant.

All abnormal ECG findings were not clinically significant. The most common sites for physical examination findings at Baseline were abdomen, rectal, and skin. All subjects in the safety analysis set had a physical examination at Baseline and all but 1 subject (placebo) had a physical examination at the final visit.

CONCLUSIONS:

- In this study of subjects with moderately-to-severely active UC, the primary endpoint of clinical response at Week 8 was achieved in 47.5%, 29.6%, 51.6%, 63.3%, and 80% of subjects in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg treatment groups, respectively. From the dose-response modeling of the data, the predefined proof-of-concept criteria of a 20% difference from placebo with a 90% 2-sided lower confidence limit >0 at Week 8 for clinical response were met for both tofacitinib 10 mg BID and 15 mg BID doses.

- The rates of clinical remission at Week 8 were 12.2%, 7.4%, 35.5%, 50%, and 42.2% in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg groups, respectively. The E_{max} dose-response model results showed differences from placebo of 5.1%, 21.5%, 34.3%, and 37.2% for tofacitinib 0.5 mg BID, 3 mg BID, tofacitinib 10 mg BID, and tofacitinib 15 mg BID with 90% 2-sided lower confidence limits of 0.1%, 9.7%, 23.4%, and 25.3%, respectively.

- There were dose-related treatment effects with tofacitinib for all other efficacy endpoints including endoscopic response, endoscopic remission, total and partial Mayo scores, and individual components of Mayo score. A treatment effect was observed as early as Week 2 in the tofacitinib 10 mg and 15 mg treatment groups based on the partial Mayo score.

- Tofacitinib demonstrated dose-related improvements in quality-of-life, as measured by the IBDQ at Week 8. The improvements in quality-of-life were greatest for the tofacitinib 15 mg treatment group.

- There were dose-related decreases from Baseline in CRP levels at Week 4 and Week 8. A statistically significant reduction in the adjusted change from Baseline of 60% was observed at Week 8 for the tofacitinib 15 mg treatment group versus placebo ($p = 0.002$). There were also dose-related decreases from Baseline in fecal calprotectin levels at all-time points. A statistically significant reduction in the adjusted change from Baseline was observed for tofacitinib 10 mg and 15 mg treatment groups versus placebo (52%, $p = 0.035$; and 61%, $p = 0.004$; respectively).

- Tofacitinib treatment at doses up to 15 mg BID for 8 weeks were generally well-tolerated in subjects with moderately-to-severely active UC. The most common AEs were colitis ulcerative and headache. There was a dose-dependent increase from Baseline in mean LDL levels at Week 8.

- Four subjects in the placebo group, 1 subject each in the tofacitinib 0.5 mg and 3 mg treatment groups, and 2 subjects each in the tofacitinib 10 mg and 15 mg treatment groups experienced at least 1 treatment-emergent SAE. One subject each in the placebo and tofacitinib 0.5 mg and 3 mg treatment groups experienced a treatment-related SAE.

- No deaths occurred during this study.