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GENERIC DRUG NAME AND/OR COMPOUND NUMBER: Tofacitinib / CP-690,550

PROTOCOL NO.: A3921086

PROTOCOL TITLE: A Open-Label Extension Study of CP-690,550 as Maintenance Therapy in Patients with Crohn's Disease

Study Center(s):

This study was conducted at 57 sites: 1 site each in Austria, the Czech Republic, Greece, and South Africa; 2 sites each in Bulgaria, France, the Netherlands, the Republic of Korea, and the Ukraine; 3 sites each in Australia, Canada, Germany, Israel, and Spain; 5 sites each in Hungary and Japan; and 18 sites in the United States.

Study Initiation Date and Primary Completion or Final Completion Dates: Study Initiation Date: 23 April 2012; Final Completion Date: 25 July 2016

Phase of Development: Phase 2b

Study Objective(s):

Primary Objective:

The primary objective of the study was to assess the safety and tolerability of long-term open-label (OL) tofacitinib (CP-690,550) therapy in subjects with Crohn's Disease (CD).

Secondary Objectives:

- To evaluate the effect of OL tofacitinib maintenance therapy on clinical remission in subjects with CD
- To evaluate the effect of OL tofacitinib maintenance therapy on quality of life in subjects with CD
- To evaluate the effect of OL tofacitinib maintenance therapy on biomarkers as measured by C-reactive protein (CRP) and fecal calprotectin (FEC).

METHODS

Study Design:

This was a Phase 2b, multicenter, OL extension study in subjects with CD who completed the double-blind maintenance treatment in Study A3921084 or withdrew early due to Study A3921084 treatment failure. This study consisted of a 48-week OL treatment period followed by a 4-week safety follow-up. The eligibility of a subject for Study A3921086 was assessed based on study data collected at the Week 26 or Early Termination (ET) visit of

Study A3921084. The study data collected at the Week 26 visit or ET visit of Study A3921084 was recorded as the baseline data for Study A3921086.

Eligible subjects were assigned to either tofacitinib 5 mg twice daily (BID) or 10 mg BID depending on the subject's clinical remission status at the end of the Study A3921084 treatment visit. Restrictions on the use of prohibited concomitant medications were applicable throughout the study. All subjects who either withdrew early or completed the OL study were asked to return to the study site for a safety follow-up visit approximately 4 weeks after the last dose of study drug.

A schedule of study activities is provided in Table 1.

Table 1. Schedule of Activities

Study Procedure	**A3921084 Week 26/ A3921086 Baseline**	**Open-Label Treatment Period**					**Follow-up**
	Day 1[a]	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48[b] (End of Treatment/ Early Termination)**	**Week 52[c] (End of Study /Follow-up)**
Visit Number	**Visit 1**	**Visit 2 (±5 days)**	**Visit 3 (±5 days)**	**Visit 4 (±5 days)**	**Visit 5 (±5 days)**	**Visit 6 (±5 days)**	**Visit 7 (±7 days)**
Informed consent	X						
Medical history[d]	X						
Concomitant medication	X	X	X	X	X	X	X
Complete physical examination	X					X	
Targeted physical examination[e]		X	X	X	X		X
Vital signs, including height, weight and temperature[f]	X	X	X	X	X	X	X
12-lead ECG[f]	X					X	
Assessment of inclusion/exclusion criteria	X						
(Pseudo)randomization/study treatment assignment[g]	X						
AEs	X	X	X	X	X	X	X
Study drug dispensing	X	X	X	X	X		
Study drug accountability		X	X	X	X	X	
Laboratory							
Hematology[h]	X	X	X	X	X	X	X
Blood chemistry[h]	X	X	X	X	X	X	X
Lipid profile, fasting	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Urine pregnancy test[i]	X	X	X	X	X	X	X
Biomarker Analysis							
hsCRP	X	X	X	X	X	X	X
Fecal calprotectin[j]	X	X	X	X	X	X	X
CD assessments							

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Visit Number	**Visit 1**	**Visit 2 (±5 days)**	**Visit 3 (±5 days)**	**Visit 4 (±5 days)**	**Visit 5 (±5 days)**	**Visit 6 (±5 days)**	**Visit 7 (±7 days)**
Subject diaries[k]	X	X	X	X	X	X	X
CDAI[l]	X	X	X	X	X	X	X
Patient-Reported Outcome Assessments							
IBDQ	X	X		X		X	
PRTI						X	
SF-36	X			X		X	
EQ-5D/VAS	X			X		X	

Abbreviations: AE = adverse event; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; EQ-5D = EuroQOL 5 Dimensions questionnaire; hsCRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; PRTI = Patient-Reported Treatment Impact; SF-36 = 36-Item Short Form Health Survey; VAS = visual analog scale.

a. For eligible subjects who completed the double-blind treatment of Study A3921084 or fulfilled Study A3921084 treatment failure criteria and consent for Study A3921086, their Week 26/Visit 6 data from Study A3921084 served as their baseline visit data for Study A3921086.
b. If a subject discontinued early from the open-label therapy, study procedures were to be completed as per End of Treatment/Early Termination schedule. This visit could have been scheduled on the last day the subject took study drug or as soon as possible thereafter.
c. All subjects participating in the open-label extension study were asked to return to the clinic for the End of Study/Follow-up Visit.
d. Medical history for Study A3921084 was to be brought forward to Study A3921086. Resolved AEs occurring in Study A3921084 were captured as part of the medical history for Study A3921086. Ongoing AEs from Study A3921084 were brought forward to Study A3921086 and were followed as appropriate.
e. The targeted physical examination was performed at Week 8, 16, 24, 36 and Follow-up Visit (Week 52) assessing the following: general appearance, eyes, mouth, heart, lungs, abdomen, perineal, musculoskeletal ,extremities, skin and lymph nodes.
f. 12-lead ECG along with vital signs were to be performed before laboratory blood collections. Height was measured as part of vital signs at the baseline visit only.
g. (Pseudo) randomization number was generated and subjects were assigned to open-label study treatment.
h. Baseline hematology, blood chemistry, and laboratory AEs at baseline were obtained from the results of the Week 26/Visit 6 laboratory results of

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Visit Number	Visit 1	Visit 2 (±5 days)	Visit 3 (±5 days)	Visit 4 (±5 days)	Visit 5 (±5 days)	Visit 6 (±5 days)	Visit 7 (±7 days)

Study A3921084.

i Urine pregnancy testing (human chorionic gonadotropin) was required only for women of childbearing potential; testing could have been repeated more frequently if required by local practices, if a menstrual cycle was missed, or if potential pregnancy was otherwise suspected. Urine pregnancy testing was performed (using methodology with a testing sensitivity of at least 25 mIU/mL) at the study site using test assays supplied by the central laboratory.

j. Labeled stool containers and plastic bags were provided to the subjects at the preceding visit so they could bring a refrigerated or frozen stool specimen with them at that visit. While it was preferred to provide a fresh specimen, it would not have interfered with testing if the stool was immediately refrigerated or frozen. If the subject failed to bring in the stool specimen, they were to stay at the site and provide it the day of the visit if at all possible or at the earliest possible time.

k. To be consistent in diary recording, study site staff were asked to place a telephone call approximately 10 days prior to each scheduled visit to remind subjects to start entering diary data continuously.

l. Subjects were assigned to open-label study treatment based on the CDAI score calculated using the Study A3921084 Week 20 hematocrit result. When the Study A3921084 Week 26 hematocrit result became available, the Investigator or designate was required to recalculate CDAI score in order to aid the assessment of subject's Crohn's disease progress.

Number of Subjects (Planned and Analyzed):

All subjects who completed Study A3921084 or withdrew early due to Study A3921084 protocol-specified treatment failure criteria were eligible for the A3921086 OL study. It was expected that approximately 108 subjects would enroll in Study A3921084 and estimated that 40% of subjects would have dropped out from Study A3921084. It was expected that approximately 85 subjects in Study A3921084 would be enrolled in the A3921086 OL extension study. The estimated number of subjects included the number of subjects who withdrew early but met Study A3921084 treatment failure criteria.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Eligible subjects were expected to meet the following and all other qualifying criteria: Subjects who completed the 26-week maintenance treatment of Study A3921084 or subjects who withdrew early due to Study A3921084 treatment failure according to prespecified criteria; women of childbearing potential who tested negative for pregnancy prior to study enrolment; sexually active females of childbearing potential were required to use adequate contraceptive methods during the study period and until completion of the follow-up procedures. No specific contraceptive measures were required in male subjects during study participation. Subjects in Canada who were women of childbearing potential and sexually active had to use 2 contraceptive methods at the same time: a highly effective contraceptive method and an additional effective contraceptive method; subjects who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures; and evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) had been informed of all pertinent aspects of the study.

Study Treatment:

Eligible subjects were assigned to either tofacitinib 5 mg BID or 10 mg BID depending on the subject's clinical remission status at the end of the Study A3921084 treatment visit. Eligible subjects who were in clinical remission (Crohn's Disease Activity Index [CDAI] <150) at Week 26 of Study A3921084 were assigned to tofacitinib 5 mg BID. Eligible subjects who were not in clinical remission (CDAI ≥150) were assigned to receive tofacitinib 10 mg BID. There was a single study treatment dose adjustment allowed, at the discretion of the Investigator, from 5 mg BID to 10 mg BID or from 10 mg BID to 5 mg BID, after the initial 8 weeks of fixed OL treatment and for the remaining treatment period.

The first dose of study drug was to occur approximately 12 hours after the last dose of Study A3921084 medication. Tofacitinib tablets were dispensed in bottles. Subjects receiving tofacitinib 5 mg BID were instructed to take 1 tablet from their bottle in the morning and 1 tablet from their bottle in the evening, approximately 12 hours apart. Subjects receiving tofacitinib 10 mg BID were instructed to take 1 tablet from each of the 2 bottles in the morning and 1 tablet from each of the 2 bottles in the evening, approximately 12 hours apart. Tofacitinib could be administered with or without food.

Tofacitinib was not made available to subjects at the end of study treatment.

Efficacy, Pharmacodynamic, and Outcomes Research Endpoints:

Primary Efficacy Endpoint

There was no primary efficacy endpoint.

Secondary Efficacy Endpoints

All efficacy endpoints were secondary endpoints and were exploratory. Sustained clinical remission was defined as being in clinical remission (CDAI score <150) at both Week 24 and Week 48.

The secondary efficacy endpoints included:

- The proportion of all enrolled subjects in clinical remission and sustained clinical remission at Week 48
- The proportions of subjects in clinical remission and sustained clinical remission among subjects in clinical remission at the A3921086 study baseline
- Proportion of subjects in clinical remission (CDAI score <150) and sustained clinical remission among subjects in clinical response (CDAI-100 response from Study A3921083 baseline) or clinical remission at Study A3921086 baseline. CDAI-100 response from Study A3921083 baseline was defined as a decrease of at least 100 points in CDAI score from Study A3921083 baseline
- The median time to relapse among subjects in clinical remission (CDAI score <150) at baseline. Relapse was defined as an increase in CDAI of >100 points from the baseline and an absolute CDAI score of >220 points
- CDAI scores over time and change from baseline in CDAI scores
- The 8 CDAI component scores over time:
    1. Number of liquid or very soft stools
    2. Abdominal pain
    3. General well-being
    4. CD related signs and symptoms
    5. Use of anti-diarrheals (Y/N)
    6. Abdominal mass
    7. Hematocrit
    8. Body weight

- The proportion of subjects achieving a steroid-free clinical remission at Week 48 among subjects on steroids at baseline

- Corticosteroid use over time

- Proportion of subjects switching from 5 mg BID to 10 mg BID and from 10 mg BID to 5 mg BID after the initial assignment at Day 1

The CDAI is a validated instrument to measure disease activity and the response to treatment in CD studies, and clinical remission or clinical response as measured by CDAI has been used as a primary endpoint in multiple pivotal trials in the CD indication. Scores range from 0 to approximately 600. An electronic CDAI diary was provided to the subjects at baseline (Visit 1) in order for them to record the number of liquid or very soft stools, the intensity of abdominal pain, and general well-being. Subjects were requested to complete the daily diary for at least 7 days prior to each study clinic visit. The information extracted was used for calculation of the CDAI score, taking into account the continuous 7 days' data recorded prior to each study clinic visit.

Pharmacodynamic (Biomarker) Evaluations

Biomarker endpoints, serum CRP and FEC over time and change from baseline in CRP and FEC, were measured throughout the study at protocol-specified times and analyzed by a central laboratory. FEC was obtained from stool samples, and high sensitivity CRP (hsCRP) was obtained from serum samples.

Patient-Reported Outcomes (PRO) Research Endpoints

PRO endpoints were:

- Absolute scores and change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total score and domain scores (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) over time

- The proportion of subjects with IBDQ total score ≥170 at Week 48 (clinical remission)

- The absolute scores for the Patient-Reported Treatment Impact (PRTI) assessment at Week 48

- The absolute scores and change from baseline in the 36-Item Short Form Health Survey (SF-36), version 2, acute (physical and mental component summary scores, and 8 domain scores) over time

- The absolute scores and change from baseline in EuroQOL 5 Dimensions Questionnaire (EQ-5D) and visual analog scale (VAS) over time

- The number of subjects hospitalized and the total length of hospitalizations related to CD

PRO measurements were collected and evaluated in a different manner than the observed or volunteered adverse events (AEs). Given these differences, no attempt was made to resolve

any apparent discrepancies between observed or volunteered AEs and PRO data collected from subjects.

The IBDQ is a psychometrically validated PRO instrument with 32 items (grouped into 4 domains: bowel function, emotional status, systemic symptoms and social function) for measuring the disease-specific quality of life in subjects with inflammatory bowel disease, including CD. Total possible IBDQ scores ranged from 32 to 224. For each domain, a higher score indicated a better quality of life. An IBDQ total score ≥170 indicates clinical remission.

At the Week 48 or ET visit, subjects completed the PRTI at the clinic prior to any procedures being performed or the administration of study drug. The inflammatory bowel disease PRTI survey is a validated instrument completed by the subject designed to assess their preference, willingness to use and satisfaction with therapy. The PRTI questionnaire comprises 3 individual questions (subject satisfaction with study treatment, subject preference for study drug over prior treatment, and subject willingness to re-use the study treatment again), each of which was scored on a 5-point Likert scale.

The SF-36 (version 2 with a 1-week recall) is a widely used general health status questionnaire that assesses 8 domains of functional health and well-being. On the specified study visit days, subjects completed the SF-36 at the clinic prior to any procedures being performed or the administration of study drug.

The EQ-5D and VAS is a standardized instrument completed by the subject designed to assess impact on quality of life in 5 domains (including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and 1 question on the subject's current health state "today". The VAS records the respondent's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). On the specified study visit days, subjects completed the EQ-5D/VAS at the clinic prior to any procedures being performed or the administration of study drug.

Safety Evaluations:

Safety endpoints in this study were:

- Incidence and severity of AEs
- Incidence and severity of clinical laboratory abnormalities, and change from baseline in clinical laboratory values
- Incidence of clinically significant changes in physical examination from baseline
- Incidence of vital sign abnormalities and changes from baseline in vital sign measures
- Incidence of electrocardiogram (ECG) abnormalities and change from baseline in ECG measurements during treatment

- Summary of adjudicated clinical safety endpoints of special interest (major adverse cardiovascular events, hepatic injury, opportunistic infection, malignancy, gastrointestinal [GI] perforation, and interstitial lung disease [ILD])

- Summary of malignancies confirmed by central laboratory pathologist over-read of biopsies

An AE was defined as any untoward medical event in a clinical investigation subject administered a product or medical device, whether or not the event had a causal relationship with the treatment or usage. Examples of AEs included, but were not limited to, abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, progression/worsening of underlying disease, drug abuse, and drug dependency. AEs could also include signs or symptoms resulting from drug overdose, drug withdrawal, drug misuse, drug interactions, extravasation, exposure during pregnancy, exposure via breast feeding, and medication errors.

A serious AE (SAE) was defined as an untoward medical event at any dose that resulted in death, was life-threatening (immediate risk of death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions), or resulted in a congenital anomaly/birth defect.

As part of safety data collection, the study closely monitored serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials. Subjects were monitored for the development of conditions that increased the risk of infection and the risk of the development of infection. A subject who experienced a serious infection was discontinued from the study and the serious infection was reported as an SAE.

The Investigator was required to assess the causality of all AEs (both serious and nonserious), record the causal relationship in the case report form (CRF), as appropriate, and report the assessment in accordance with SAE reporting requirements as applicable. In addition, if the Investigator determined an SAE was associated with study procedures, the Investigator recorded this causal relationship in the source documents and CRF, as appropriate, and reported this assessment in accordance with SAE reporting requirements as applicable.

To help assess specific safety events in this and other studies in the tofacitinib program, adjudication committees, including a Cardiovascular Endpoint Adjudication Committee, Malignancy Adjudication Committee, Opportunistic Infection Review Committee, Hepatic Event Review Committee, and GI Perforation Review Committee, were established to harmonize and standardize selected safety event assessment. All biopsies of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder, and all bowel biopsies containing suspicious dysplasia or malignancy were also to be submitted to the central laboratory for review by central laboratory pathologists. In addition to these external committees, an internal committee of medically qualified Pfizer

personnel with expertise in the assessment and diagnosis of respiratory disease, the ILD Review Committee, were to review and categorize potential events of ILD.

Statistical Methods:

The Full Analysis Set (FAS) was defined as all subjects enrolled in this OL extension study and was the primary analysis set. No protocol deviations were used to define a per-protocol analysis set. All analyses were performed for the FAS. The Safety Analysis Set (SAS) was defined as all subjects who received at least 1 dose of study drug and was consistent with the FAS, as all enrolled subjects received a minimum of 1 dose of study drug.

Descriptive summary statistics were calculated based on all subjects and the initial assignment of dose groups. If a treatment different from the initial assigned treatment was taken on Day 1, the actual treatment taken was used. All summaries were obtained based on the observed data. Missing data were not imputed.

There was no primary efficacy endpoint. All efficacy endpoints were exploratory. CDAI was measured at baseline, Weeks 8, 16, 24, 36, 48, and 52 (follow-up) and was calculated based on the hematocrit measured at the same visits. Sustained clinical remission was defined as being in clinical remission (CDAI score <150) at both Week 24 and Week 48.

Summary statistics such as number of subjects, proportions, 95% 2-sided confidence intervals (CIs) for binary endpoints and number of subjects, means, median, minimum, maximum, and 95% CIs for continuous endpoints including changes from baseline, were reported by study visit.

Kaplan-Meier estimates and the median time for the time to relapse among subjects in clinical remission at baseline were also summarized.

The 8 CDAI component scores were descriptively summarized. Six component scores (the number of liquid or very soft stools, the intensity of abdominal pain, general well-being, the occurrence of extraintestinal symptoms or signs, hematocrit and body weight) were all treated as continuous data and the observed scores and changes from baseline were summarized. The other 2 component scores (the need for antidiarrheal drugs and the presence of abdominal mass) were treated as categorical variables and the frequency and percentage of subjects in each category was summarized.

PRO Analyses: IBDQ was assessed at baseline, Week 8, Week 24, Week 48, and Week 48/ET. The IBDQ total score and the 4 IBDQ domain scores were summarized as observed scores and changes from baseline. The IBDQ derived binary response endpoint at Week 48 was descriptively summarized as frequencies and percentages.

The categorical PRTI data collected at Week 48/ET was descriptively summarized using frequencies and percentages.

SF-36 was assessed at baseline, Week 24, Week 48, and Week 48/ET. The 2 component summaries (physical and mental component scores) and the 8 domain scores were summarized as observed scores and changes from baseline. The additional SF-36

Health-Transition score is a 5-point ordered categorical endpoint. This was summarized as number of subjects and percent per category.

The EQ-5D was assessed at baseline, Week 24, Week 48, and Week 48/ET. The EQ-5D utility index score and the EQ-5D VAS score were summarized as observed scores and changes from baseline. The 5 EQ-5D domain scores are all scored on a 3-point scale. The number of subjects in each category was summarized as number of subjects and percent per category.

Other Evaluations: Demographics and baseline characteristics were summarized by the initial assignment dose group as well as the combined group. For continuous variables such as age; number of subjects meeting the criteria (n), mean, median, standard deviation (SD), minimum, and maximum were reported. For categorical variables such as gender, the frequency and the percentage in each category was reported. The summaries were performed for the FAS population.

The number of subjects and length of hospitalizations were also descriptively summarized using mean and median.

Pharmacodynamic (Biomarker) Analyses: The biomarker endpoints; hsCRP (mg/L) and FEC (mg/kg), were measured at baseline (Day 1) and Weeks 8, 16, 24, 36, 48 and 52 (follow-up). Concentrations were summarized descriptively by dose group assigned at baseline as well as the combined group. Summaries included both the median and geometric mean concentrations. Changes from baseline were summarized as medians and the back-transformed results from the log-transformed change gave the estimates of the relative changes from baseline. Values below any limits of quantification were replaced; otherwise missing data were not imputed. The summaries were performed for the FAS population.

Safety: Long-term safety evaluation was the primary objective of this study.

AEs, vital signs, ECGs, laboratory tests data, and adjudicated events were summarized. Treatment-emergent AEs were tabulated by body system and by preferred term (PT). The proportion of AEs as reported was presented for the combined group as well as by the initial assignment of dose group.

In addition, significant infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials were summarized. The proportion of AEs as reported, was presented for the combined group as well as by the initial assignment of dose group.

A 3-tier approach classified AEs into 1 of 3 tiers. Tier-1 events were prespecified events of clinical importance that were maintained in a list in the product's safety review plan; this list could have been updated as more was understood about the drug. Tier-2 events were not Tier-1 events but were "common." A Medical Dictionary for Regulatory Activities PT was defined as a Tier-2 event if there were at least 4 subjects with the same event in any group. Tier-3 events were events that were neither Tier-1 nor Tier-2 events. The analysis of AEs under this 3-tier approach was considered exploratory. There was no adjustment for multiple comparisons or stratification factors in the analyses. The proportions of Tier-1 and Tier-2

AEs observed in each group were presented along with the point estimates and associated 95% CIs of the risk difference between the 2 active treatments.

RESULTS

Subject Disposition and Demography:

There were 150 subjects assigned to study treatment (Table 2). Of the 150 subjects treated, 88 subjects (43 subjects in the tofacitinib 5 mg BID group and 45 subjects in the tofacitinib 10 mg BID group) completed the study.

All assigned subjects (n=150) were included in the FAS population, which was used as the primary analysis population, and in the SAS population used for the safety analyses.

Table 2. Subject Evaluation Groups

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Total
Number (%) of subjects			
Assigned to study treatment	62	88	150
Treated	62	88	150
Completed	43 (69.4)	45 (51.1)	88 (58.7)
Discontinued	19 (30.6)	43 (48.9)	62 (41.3)
Analyzed for Efficacy:			
Full Analysis Set	62 (100.0)	88 (100.0)	150 (100.0)
Analyzed for Safety:			
Adverse events	62 (100.0)	88 (100.0)	150 (100.0)
Laboratory data	62 (100.0)	88 (100.0)	150 (100.0)
Safety Analysis Set	62 (100.0)	88 (100.0)	150 (100.0)

Subjects were analyzed as per their initial dose assignment.
Abbreviation: BID = twice daily.

There were 19 subjects who discontinued from the study in the tofacitinib 5 mg BID group and 43 subjects who discontinued the study in the tofacitinib 10 mg BID group. The reasons for discontinuation from study are provided in Table 3.

Table 3. Discontinuations from Study

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Total
Number (%) of subjects	62	88	150
Discontinuations			
Related to Study Drug	8 (12.9)	32 (36.4)	40 (26.7)
Adverse event	2 (3.2)	5 (5.7)	7 (4.7)
Insufficient clinical response	6 (9.7)	27 (30.7)	33 (22.0)
Not Related to Study Drug	11 (17.7)	11 (12.5)	22 (14.7)
Adverse event	1 (1.6)	5 (5.7)	6 (4.0)
Does not meet entrance criteria	1 (1.6)	0	1 (0.7)
Lost to follow-up	2 (3.2)	1 (1.1)	3 (2.0)
No longer willing to participate in study	3 (4.8)	4 (4.5)	7 (4.7)
Other	1 (1.6)	0	1 (0.7)
Protocol violation	3 (4.8)	1 (1.1)	4 (2.7)
Total	19 (30.6)	43 (48.9)	62 (41.3)

Subjects were analyzed as per their initial dose assignment.
The 'Other' reason was that the subject in the tofacitinib 5 mg BID group was unable to return for the follow-up visit.
Abbreviation: BID = twice daily.

The mean age of subjects across treatment groups in this study was 39.4 years (SD 12.1 years), and ages ranged from 18 to 67 years. Most subjects (80.0%) were white. There were no notable differences in demographic characteristics between the 2 groups (Table 4).

Table 4. Demographic Characteristics

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Total
Number (%) of subjects	62	88	150
Gender, n			
Male	32	47	79
Female	30	41	71
Age (years):			
<18	0	0	0
18-44	37 (59.7)	64 (72.7)	101 (67.3)
45-64	24 (38.7)	23 (26.1)	47 (31.3)
≥65	1 (1.6)	1 (1.1)	2 (1.3)
Mean (SD)	41.0 (12.6)	38.2 (11.6)	39.4 (12.1)
Range	18-67	19-66	18-67
Race:			
White	49 (79.0)	71 (80.7)	120 (80.0)
Black	2 (3.2)	1 (1.1)	3 (2.0)
Asian	11 (17.7)	14 (15.9)	25 (16.7)
Other	0	2 (2.3)	2 (1.3)
Weight (kg):			
N	62 (100.0)	88 (100.0)	150 (100.0)
Mean (SD)	75.5 (19.2)	71.2 (20.3)	73.0 (19.9)
Range	49.8-167.6	45.3-141.8	45.3-167.6
Body Mass Index(kg/m^2):			
N	62 (100.0)	88 (100.0)	150 (100.0)
Mean (SD)	25.9 (5.5)	24.5 (6.0)	25.1 (5.8)
Range	15.0-46.2	16.0-50.4	15.0-50.4
Height (cm):			
N	62 (100.0)	88 (100.0)	150 (100.0)
Mean (SD)	170.3 (9.2)	170.0 (10.3)	170.1 (9.9)
Range	154.9-190.5	150.0-205.0	150.0-205.0

Abbreviations: BID = twice daily; N = number of subjects; n = number of subjects meeting the criteria; SD = standard deviation.
Subjects were analyzed as per their initial dose assignment.

Efficacy Results:

Clinical Remission and Sustained Clinical Remission at Week 48

At baseline, the number of subjects who met clinical remission criteria based on recalculated baseline CDAI scores was 61/62 subjects in the tofacitinib 5 mg BID group (98.4%) and 4/88 subjects in the tofacitinib 10 mg BID group (4.6%). Baseline CDAI scores were recalculated using baseline hematocrit results received after treatment assignment was determined. Therefore, 1 subject in the tofacitinib 5 mg BID group and 4 subjects in the tofacitinib 10 mg BID group had remission status that did not correspond to their initial dose assignment.

For subjects in the tofacitinib 5 mg BID group, a slight decrease in the proportion of subjects remaining in the study who met clinical remission criteria was observed at Week 8 (41/54 subjects, 75.9%) with the observed rate remaining fairly similar over time with 29/33 subjects (87.9%) in clinical remission at Week 48. Notably for subjects in the tofacitinib 10 mg BID group, who were intended to be, by protocol design, those who entered the study not in remission, the proportion of subjects remaining in the study at a given study

visit who met clinical remission generally increased at each study visit, with 55.6% (20/36 subjects) at Week 48 in remission.

The proportion of subjects who met sustained clinical remission was 75.0% for the tofacitinib 5 mg BID group and 34.3% for the tofacitinib 10 mg BID group (Table 5).

Table 5. Proportion of Subjects Who Met Clinical Remission Criteria by Week, and Sustained Clinical Remission Criteria (FAS)

	Observed			
	N	**n**	**Rate (%)**	**95%[a] CI**
Baseline				
Tofacitinib 5 mg BID	62	61	98.39	91.34, 99.96
Tofacitinib 10 mg BID	88	4	4.55	1.25, 11.23
Total	150	65	43.33	35.27, 51.66
Week 8				
Tofacitinib 5 mg BID	54	41	75.93	62.36, 86.51
Tofacitinib 10 mg BID	75	28	37.33	26.43, 49.27
Total	129	69	53.49	44.50, 62.31
Week 16				
Tofacitinib 5 mg BID	53	45	84.91	72.41, 93.25
Tofacitinib 10 mg BID	66	23	34.85	23.53, 47.58
Total	119	68	57.14	47.75, 66.17
Week 24				
Tofacitinib 5 mg BID	49	41	83.67	70.34, 92.68
Tofacitinib 10 mg BID	59	27	45.76	32.72, 59.25
Total	108	68	62.96	53.14, 72.06
Week 36				
Tofacitinib 5 mg BID	41	37	90.24	76.87, 97.28
Tofacitinib 10 mg BID	48	24	50.00	35.23, 64.77
Total	89	61	68.54	57.83, 77.97
Week 48				
Tofacitinib 5 mg BID	33	29	87.88	71.80, 96.60
Tofacitinib 10 mg BID	36	20	55.56	38.10, 72.06
Total	69	49	71.01	58.84, 81.31
Follow-up				
Tofacitinib 5 mg BID	38	25	65.79	48.65, 80.37
Tofacitinib 10 mg BID	43	19	44.19	29.08, 60.12
Total	81	44	54.32	42.87, 65.44
Sustained Clinical Remission				
Tofacitinib 5 mg BID	32	24	75.00	56.60, 88.54
Tofacitinib 10 mg BID	35	12	34.29	19.13, 52.21
Total	67	36	53.73	41.12, 66.00

Subjects were analyzed as per their initial dose assignment.
Clinical remission was defined as CDAI <150. Sustained clinical remission was defined as being in clinical remission at both Week 24 and Week 48.
Abbreviations: BID = twice daily; CDAI = Crohn's Disease Activity Index; CI = confidence interval; FAS = Full Analysis Set; N=number of subjects with non-missing data (at Week 24 and Week 48 for sustained clinical remission); n = number of subjects meeting the binary endpoint criteria.
a. 95% Clopper-Pearson exact CI reported for the proportions.

Clinical Remission and Sustained Clinical Remission Among Subjects in Clinical Remission at Baseline of the OL Study

Among subjects in clinical remission at baseline who remained in the study at a given time point, the proportion of subjects who met clinical remission in the tofacitinib 5 mg BID group decreased slightly at Week 8 with 40/53 (75.5%) subjects but remained fairly similar at each subsequent time point, with 28/32 (87.5%) subjects at Week 48 (Table 6).

The proportion of subjects with sustained clinical remission among subjects in clinical remission at baseline was 77.4% for subjects in the tofacitinib 5 mg BID group (24/31 subjects) and 33.3% (1/3 subjects) in the tofacitinib 10 mg BID group.

Table 6. Proportion of Subjects Who Met Clinical Remission Criteria by Week Among Subjects in Clinical Remission at A3921086 Baseline (FAS)

	Observed			
	N	n	Rate (%)	95%[a] CI
Baseline				
Tofacitinib 5 mg BID	61	61	100.00	94.13, 100.00
Tofacitinib 10 mg BID	4	4	100.00	39.76, 100.00
Total	65	65	100.00	94.48, 100.00
Week 8				
Tofacitinib 5 mg BID	53	40	75.47	61.72, 86.24
Tofacitinib 10 mg BID	4	2	50.00	6.76, 93.24
Total	57	42	73.68	60.34, 84.46
Week 16				
Tofacitinib 5 mg BID	52	44	84.62	71.92, 93.12
Tofacitinib 10 mg BID	4	3	75.00	19.41, 99.37
Total	56	47	83.93	71.67, 92.38
Week 24				
Tofacitinib 5 mg BID	48	41	85.42	72.24, 93.93
Tofacitinib 10 mg BID	4	1	25.00	0.63, 80.59
Total	52	42	80.77	67.47, 90.37
Week 36				
Tofacitinib 5 mg BID	40	37	92.50	79.61, 98.43
Tofacitinib 10 mg BID	3	1	33.33	0.84, 90.57
Total	43	38	88.37	74.92, 96.11
Week 48				
Tofacitinib 5 mg BID	32	28	87.50	71.01, 96.49
Tofacitinib 10 mg BID	3	3	100.00	29.24, 100.00
Total	35	31	88.57	73.26, 96.80
Follow-up				
Tofacitinib 5 mg BID	37	24	64.86	47.46, 79.79
Tofacitinib 10 mg BID	3	1	33.33	0.84, 90.57
Total	40	25	62.50	45.80, 77.27
Sustained Clinical Remission				
Tofacitinib 5 mg BID	31	24	77.42	58.90, 90.41
Tofacitinib 10 mg BID	3	1	33.33	0.84, 90.57
Total	34	25	73.53	55.64, 87.12

Subjects were analyzed as per their initial dose assignment.
Clinical remission was defined as CDAI <150
Abbreviations: BID = twice daily; CDAI = Crohn's Disease Activity Index; CI = confidence interval; FAS = Full Analysis Set; N=number of subjects with non-missing data (at Week 24 and Week 48 for sustained clinical remission); n = number of subjects meeting the binary endpoint criteria.
a. 95% Clopper-Pearson exact CI reported for the proportions.

Clinical Remission and Sustained Clinical Remission Among Subjects in Clinical Response or Clinical Remission at Baseline of the OL Study

Clinical response-100 was defined as a CDAI score decrease of at least 100 points from the Study A3921083 baseline. At baseline, the proportion of subjects who met clinical response or clinical remission criteria was 98.4% for subjects in the tofacitinib 5 mg BID group (61/62 subjects) and 17.4% in the tofacitinib 10 mg BID group (4/23 subjects; Table 7).

For subjects in the tofacitinib 5 mg BID group, a decrease in the proportion of subjects who met clinical remission criteria among those in clinical response or clinical remission at baseline was observed at Week 8 (41/54 subjects, 75.9%) but the observed proportion remained fairly consistent over time from Week 16 with 87.9% (29/33) of subjects in clinical remission at Week 48. A slight increase from baseline in the number of subjects in clinical remission was observed at each time point among those in clinical response or clinical remission at baseline for subjects in the tofacitinib 10 mg BID group, although the number of subjects meeting the criteria remained low (≤7).

Among subjects in clinical response or clinical remission at baseline of this study, the proportion of subjects who met sustained clinical remission was 75.0% for subjects in the tofacitinib 5 mg BID group (24/32 subjects) and 30.0% for subjects in the tofacitinib 10 mg BID group (3/10 subjects).

Table 7. Proportion of Subjects Who Met Clinical Remission Criteria by Week Among Subjects in Clinical Response or Clinical Remission at A3921086 Baseline (FAS)

	Observed			
	N	n	Rate (%)	95%[a] CI
Baseline				
Tofacitinib 5 mg BID	62	61	98.39	91.34, 99.96
Tofacitinib 10 mg BID	23	4	17.39	4.95, 38.78
Total	85	65	76.47	66.03, 85.00
Week 8				
Tofacitinib 5 mg BID	54	41	75.93	62.36, 86.51
Tofacitinib 10 mg BID	20	7	35.00	15.39, 59.22
Total	74	48	64.86	52.89, 75.61
Week 16				
Tofacitinib 5 mg BID	53	45	84.91	72.41, 93.25
Tofacitinib 10 mg BID	19	7	36.84	16.29, 61.64
Total	72	52	72.22	60.41, 82.14
Week 24				
Tofacitinib 5 mg BID	49	41	83.67	70.34, 92.68
Tofacitinib 10 mg BID	16	7	43.75	19.75, 70.12
Total	65	48	73.85	61.46, 83.97
Week 36				
Tofacitinib 5 mg BID	41	37	90.24	76.87, 97.28
Tofacitinib 10 mg BID	13	5	38.46	13.86, 68.42
Total	54	42	77.78	64.40, 87.96
Week 48				
Tofacitinib 5 mg BID	33	29	87.88	71.80, 96.60
Tofacitinib 10 mg BID	10	5	50.00	18.71, 81.29
Total	43	34	79.07	63.96, 89.96
Follow-up				
Tofacitinib 5 mg BID	38	25	65.79	48.65, 80.37
Tofacitinib 10 mg BID	12	5	41.67	15.17, 72.33
Total	50	30	60.00	45.18, 73.59
Sustained Clinical Remission				
Tofacitinib 5 mg BID	32	24	75.00	56.60, 88.54
Tofacitinib 10 mg BID	10	3	30.00	6.67, 65.25
Total	42	27	64.29	48.03, 78.45

Subjects were analyzed as per their initial dose assignment.
Clinical remission was defined as CDAI <150. Clinical response was defined as CDAI-100 response from Study A3921083 baseline. Sustained clinical remission was defined as being in clinical remission at both Week 24 and Week 48.
Abbreviations: BID = twice daily; CDAI = Crohn's Disease Activity Index; CI = confidence interval; FAS = Full Analysis Set; N = number of subjects with non-missing data (at Week 24 and Week 48 for sustained clinical remission); n = number of subjects meeting the binary endpoint criteria.
a. 95% Clopper-Pearson exact CI reported for the proportions.

Time to Relapse

Relapse was defined as increase in CDAI of >100 points from baseline and an absolute CDAI score of >220 points. For subjects in the tofacitinib 5 mg BID group, the estimated relapse rate among subjects in clinical remission at baseline gradually increased over time and was greatest at Week 48 (24.7%; 95% CI: 17.21%, 32.89%). For subjects in the

tofacitinib 10 mg BID group, of whom only 4 subjects were in remission at baseline, there was no notable change from Week 16 to 36 (Table 8). The estimated median time to relapse was 366 days.

Table 8. Time to Relapse Among Subjects in Clinical Remission at Baseline (FAS)

Visit	Treatment	Cumulative Number of Events	Number of Subjects Remaining at Risk	Estimated Rate (%)			
				Rate[a]	SE	95% CI[b]	
						Lower	Upper
Baseline	Tofacitinib 5 mg BID	0	61				
	Tofacitinib 10 mg BID	0	4				
Week 8	Tofacitinib 5 mg BID	4	55	6.78	3.27	3.38	11.78
	Tofacitinib 10 mg BID	0	4				
Week 16	Tofacitinib 5 mg BID	7	51	11.86	4.21	7.15	17.87
	Tofacitinib 10 mg BID	1	3	25.00	21.65	4.56	53.66
Week 24	Tofacitinib 5 mg BID	9	46	15.46	4.75	9.98	22.05
	Tofacitinib 10 mg BID	1	3	25.00	21.65	4.56	53.66
Week 36	Tofacitinib 5 mg BID	12	38	21.42	5.52	14.82	28.83
	Tofacitinib 10 mg BID	1	3	25.00	21.65	4.56	53.66
Week 48	Tofacitinib 5 mg BID	13	7	24.69	6.18	17.21	32.89
	Tofacitinib 10 mg BID	1	0				

Subjects were analyzed as per their initial dose assignment.
Relapse was defined as increase in CDAI of >100 points from the baseline and an absolute CDAI score of >220 points.
Subjects who dropped out due to lack of efficacy were treated as a relapse event with an event time at the time of drop out.
The actual days were used as the event time or censored time. The number of events/subjects at risk and event rate at each post baseline visit was estimated from the scheduled visit target day + 10 days.
Abbreviations: BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; SE = standard error.
a. Estimated from the Kaplan-Meier curve
b. Calculated from the product-limit method / Calculated from the log[-log(x-<year, month> survival probability)] using a normal approximation and back transformation

CDAI Scores Over Time and CDAI Score Changes from Baseline

Mean (SD) baseline CDAI scores were 77.13 (43.22) for subjects in the tofacitinib 5 mg BID group (subjects in remission) and 291.19 (95.78) for subjects in the tofacitinib 10 mg BID group (subjects not in remission).

For subjects in the tofacitinib 5 mg BID group, mean CDAI scores increased from baseline at Weeks 8, 16, and 24 with the highest mean score and greatest mean increase from baseline observed at Week 8 (mean [SD] 105.39 [75.82]; mean [SD] change from baseline: 26.96 [62.68]). A decrease in mean CDAI scores was subsequently observed from Weeks 36 to 48, returning to near baseline scores with a mean (SD) CDAI score of 73.91 (70.23) at Week 48.

In the tofacitinib 10 mg BID group, the mean CDAI scores at Week 8 through Week 48 for subjects who still remained in the study decreased over 100 points from baseline (Table 9).

Table 9. Descriptive Statistics of Observed CDAI Score and Change From Baseline CDAI Score by Week (FAS)

	Observed Data							Change from Baseline					
	N	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Baseline													
Tofacitinib 5 mg BID	62	62	77.13	43.22	83.00	-2	156						
Tofacitinib 10 mg BID	88	88	291.19	95.78	270.00	138	551						
Total	150	150	202.71	131.56	190.50	-2	551						
Week 8													
Tofacitinib 5 mg BID	62	54	105.39	75.82	106.00	-10	313	54	26.96	62.68	10.00	-82	185
Tofacitinib 10 mg BID	88	75	176.96	82.39	163.00	11	410	75	-114.31	112.44	-96.00	-445	96
Total	150	129	147.00	86.95	143.00	-10	410	129	-55.17	117.61	-25.00	-445	185
Week 16													
Tofacitinib 5 mg BID	62	53	86.58	65.23	77.00	-10	278	53	11.72	52.25	5.00	-98	172
Tofacitinib 10 mg BID	88	66	178.94	72.25	181.00	7	367	66	-112.02	111.09	-100.50	-477	114
Total	150	119	137.81	82.92	132.00	-10	367	119	-56.91	108.70	-23.00	-477	172
Week 24													
Tofacitinib 5 mg BID	62	49	85.12	56.67	75.00	-10	192	49	6.33	44.48	1.00	-91	92
Tofacitinib 10 mg BID	88	59	163.66	79.73	160.00	-10	407	59	-122.69	117.65	-103.00	-494	140
Total	150	108	128.03	80.18	124.00	-10	407	108	-64.16	112.05	-32.00	-494	140
Week 36													
Tofacitinib 5 mg BID	62	41	73.34	59.52	58.00	-2	230	41	-10.78	40.35	-15.00	-72	105
Tofacitinib 10 mg BID	88	48	158.67	89.15	150.00	-10	376	48	-139.81	126.18	-116.00	-494	19
Total	150	89	119.36	87.66	100.00	-10	376	89	-80.37	115.87	-42.00	-494	105
Week 48													
Tofacitinib 5 mg BID	62	33	73.91	70.23	67.00	-10	332	33	-4.79	60.09	-13.00	-125	201
Tofacitinib 10 mg BID	88	36	154.11	71.47	147.50	49	334	36	-121.94	129.21	-84.50	-460	114
Total	150	69	115.75	81.11	108.00	-10	334	69	-65.91	117.33	-36.00	-460	201
Follow-up													
Tofacitinib 5 mg BID	62	38	129.32	114.82	102.00	-10	467	38	47.66	109.73	15.00	-80	413
Tofacitinib 10 mg BID	88	43	180.65	98.80	162.00	17	429	43	-107.42	119.05	-106.00	-392	87
Total	150	81	156.57	109.03	141.00	-10	467	81	-34.67	138.11	-22.00	-392	413

Subjects were analyzed as per their initial dose assignment.

Abbreviations: BID = twice daily; CDAI = Crohn's Disease Activity Index; FAS = Full Analysis Set; Max = maximum; Min = minimum; N = number of subjects in the analysis set; n = number of subjects with non-missing data; SD = standard deviation.

Steroid-Free Clinical Remission

Among subjects on steroids at baseline, 1 of 2 subjects (50.0%, 95% CI: 1.26%, 98.74%) in the tofacitinib 5 mg BID group and 1/11 subjects (9.1%, 95% CI: 0.23%, 41.28%) in the tofacitinib 10 mg BID achieved steroid-free clinical remission at Week 48 (Table 10).

Table 10. Proportion of Subjects Achieving a Steroid-Free Clinical Remission at Week 48 (FAS) - Among Subjects on Steroids at A3921086 Baseline

	Observed			
	N	n	Rate (%)	95%[a] CI
Tofacitinib 5 mg BID	2	1	50.00	1.26, 98.74
Tofacitinib 10 mg BID	11	1	9.09	0.23, 41.28
Total	13	2	15.38	1.92, 45.45

Subjects were analyzed as per their initial dose assignment.
Clinical remission was defined as CDAI <150.
Abbreviations: BID = twice daily; CDAI = Crohn's Disease Activity Index; CI = confidence interval; FAS = Full Analysis Set; N = number of subjects with non-missing data; n = number of subjects meeting the binary endpoint criteria.
a. 95% Clopper-Pearson exact CI reported for the proportions.

Corticosteroid Use Over Time

Corticosteroid use over time is shown in Table 11. Notably for subjects in the tofacitinib 5 mg BID group, steroid use at baseline given that subjects were already in clinical remission was expectedly very low. For subjects in the tofacitinib 10 mg BID group, corticosteroid use generally decreased over time.

Table 11. Corticosteroid Use Over Time

	Tofacitinib 5 mg BID N=62	Tofacitinib 10 mg BID N=88	Total N=150
	n (%)	n (%)	n (%)
Baseline	1 (1.61)	18 (20.45)	19 (12.67)
Week 8	3 (4.84)	19 (21.59)	22 (14.67)
Week 16	3 (4.84)	12 (13.64)	15 (10.00)
Week 24	3 (4.84)	11 (12.50)	14 (9.33)
Week 36	2 (3.23)	9 (10.23)	11 (7.33)
Week 48	1 (1.61)	7 (7.95)	8 (5.33)

Subjects were analyzed as per their initial dose assignment.
Summary statistics of dose reported in mg.
Abbreviations: BID = twice daily; n = number of subjects taking corticosteroid at visit; N = number of subjects with non-missing data.

Study Treatment Dose Adjustment

Per the protocol, a single study treatment dose adjustment was allowed, at the discretion of the Investigator, from 5 mg BID to 10 mg BID or from 10 mg BID to 5 mg BID, after the initial 8 weeks of fixed OL treatment (Table 12).

Table 12. Proportion of Subjects Switching from 5 mg to 10 mg or 10 mg to 5 mg After Initial Assignment by Visit (FAS)

	Tofacitinib 5 mg BID N=62	Tofacitinib 10 mg BID N=88	Total N=150
	n (%)	n (%)	n (%)
Baseline	0	0	0
Week 8	16 (25.81)	0	16 (10.67)
Week 16	4 (6.45)	0	4 (2.67)
Week 24	2 (3.23)	2 (2.27)	4 (2.67)
Week 36	0	1 (1.14)	1 (0.67)
Week 48	0	0	0

Subjects were analyzed as per their initial dose assignment.
Abbreviations: BID = twice daily; FAS = Full Analysis Set; n=number of subjects switching dose; N = number of subjects with non-missing data.

The majority of dose adjustments occurred for subjects in the tofacitinib 5 mg BID group (subjects who were in clinical remission at baseline) up to 10 mg BID at Week 8; 4 additional subjects switched by Week 16 and 2 additional subjects switched by Week 24.

PRO Results:

Mean (SD) IBDQ total scores at baseline were 187.23 (20.38) in the tofacitinib 5 mg BID group and 127.32 (34.17) in the tofacitinib 10 mg BID group. The IBDQ mean total score remained high (≥170) at Week 48/ET for subjects in the tofacitinib 5 mg BID group and did not decrease greatly from baseline. For subjects remaining in the study in the tofacitinib 10 mg BID group, the overall mean (SD) IBDQ total score was 144.42 (42.16) at Week 48/ET, corresponding to a mean (SD) change from the baseline score of 18.84 (40.45), although no statistical testing was performed (Table 13).

Table 13. Descriptive Statistics of Observed and Change From Baseline of Total IBDQ and Domain Scores, at Week 48/ET (FAS)

	Observed Data							Change from Baseline					
	N	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
IBDQ Total Score													
Baseline													
Tofacitinib 5 mg BID	62	62	187.23	20.38	188.00	144	224						
Tofacitinib 10 mg BID	88	87	127.32	34.17	125.00	61	193						
Total	150	149	152.25	41.56	160.00	61	224						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	179.26	29.89	180.00	91	224	57	-7.98	24.93	-1.00	-81	43
Tofacitinib 10 mg BID	88	83	144.42	42.16	148.00	44	217	83	18.84	40.45	11.00	-70	140
Total	150	140	158.61	41.28	165.00	44	224	140	7.92	37.29	3.50	-81	140
Bowel Function Score													
Baseline													
Tofacitinib 5 mg BID	62	62	58.56	6.86	59.00	40	70						
Tofacitinib 10 mg BID	88	87	40.71	9.90	41.00	18	60						
Total	150	149	48.14	12.42	49.00	18	70						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	55.70	9.82	56.00	30	70	57	-2.72	8.30	0.00	-26	8
Tofacitinib 10 mg BID	88	83	46.70	12.38	49.00	18	66	83	6.37	12.41	5.00	-27	37
Total	150	140	50.36	12.21	52.00	18	70	140	2.67	11.78	3.00	-27	37
Emotional Status Score													
Baseline													
Tofacitinib 5 mg BID	62	62	69.68	8.58	72.00	48	84						
Tofacitinib 10 mg BID	88	87	48.61	14.42	47.00	20	80						
Total	150	149	57.38	16.12	60.00	20	84						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	66.98	12.27	69.00	32	84	57	-3.07	10.48	-1.00	-30	29
Tofacitinib 10 mg BID	88	83	53.19	17.32	54.00	13	83	83	5.36	15.00	3.00	-24	48
Total	150	140	58.81	16.85	61.50	13	84	140	1.93	13.94	1.00	-30	48
Systemic Symptoms Score Baseline													
Baseline													
Tofacitinib 5 mg BID	62	62	26.95	5.36	27.00	12	35						
Tofacitinib 10 mg BID	88	87	17.20	5.55	17.00	6	29						
Total	150	149	21.26	7.28	22.00	6	35						

Table 13. Descriptive Statistics of Observed and Change From Baseline of Total IBDQ and Domain Scores, at Week 48/ET (FAS)

	Observed Data							Change from Baseline					
	N	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Week 48/ET													
Tofacitinib 5 mg BID	62	57	25.82	6.28	26.00	10	35	57	-1.00	4.83	0.00	-15	8
Tofacitinib 10 mg BID	88	83	20.35	7.07	21.00	6	34	83	3.45	7.43	2.00	-10	27
Total	150	140	22.58	7.26	23.00	6	35	140	1.64	6.84	1.00	-15	27
Social Function Score													
Baseline													
Tofacitinib 5 mg BID	62	62	32.03	3.59	33.00	16	35						
Tofacitinib 10 mg BID	88	87	20.80	8.96	21.00	5	35						
Total	150	149	25.48	9.10	29.00	5	35						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	30.75	5.17	31.00	10	35	57	-1.19	4.24	0.00	-15	9
Tofacitinib 10 mg BID	88	83	24.18	8.98	27.00	5	35	83	3.66	8.89	1.00	-21	30
Total	150	140	26.86	8.30	30.00	5	35	140	1.69	7.72	0.00	-21	30

Subjects were analyzed as per their initial dose assignment.

Baseline assessments were performed at Week 26 of Study A3921084.

Abbreviations: BID = twice daily; ET = Early Termination; IBDQ = Inflammatory Bowel Disease Questionnaire; FAS = Full Analysis Set; Max = maximum; Min = minimum; N = number of subjects in the analysis set; n = number of subjects with non-missing data; SD = standard deviation.

The proportion of subjects with an IBDQ total score ≥170 at baseline was 79.0% in the tofacitinib 5 mg BID group and 11.5% of subjects in the tofacitinib 10 mg BID group, with a gradual increase in the proportion of subjects with an IBDQ total score ≥170 observed for those in the tofacitinib 10 mg BID group at Week 48 (Table 14).

Table 14. Proportion of Subjects With IBDQ Total Score ≥170 at Week 48/ET (FAS)

			Observed	
	N	n	Rate (%)	95%[a] CI
Baseline				
Tofacitinib 5 mg BID	62	49	79.03	66.82, 88.34
Tofacitinib 10 mg BID	87	10	11.49	5.65, 20.12
Total	149	59	39.60	31.69, 47.93
Week 48/ET				
Tofacitinib 5 mg BID	57	40	70.18	56.60, 81.57
Tofacitinib 10 mg BID	83	26	31.33	21.59, 42.44
Total	140	66	47.14	38.66, 55.75

Subjects were analyzed as per their initial dose assignment.
Abbreviations: BID = twice daily; CI = confidence interval; ET = Early Termination; IBDQ = Inflammatory Bowel Disease Questionnaire; FAS = Full Analysis Set; N = number of subjects at baseline in the analysis set; n = number of subjects meeting the binary endpoint criteria of IBDQ total score ≥170.
a. 95% Clopper-Pearson exact CI reported for the proportions.

Most subjects in both treatment groups reported positive outcomes of “extremely satisfied” or “satisfied” for the endpoint of patient satisfaction assessment, with 66.7% and 33.3% of subjects, respectively in the tofacitinib 5 mg BID group and 32.6% and 41.3% of subjects, respectively in the tofacitinib 10 mg BID group. The majority of subjects (ie, >50%) in both treatment groups also reported positive outcomes for the endpoints of patient preference assessment (‘yes, I definitely prefer the drug that I am receiving now’; 88.1% and 56.5% of subjects in the tofacitinib 5 mg BID and 10 mg BID group, respectively) and patient willingness assessment (‘yes, I would definitely want to use the same drug again’; 83.3% and 60.9% of subjects in the tofacitinib 5 mg BID and 10 mg BID group, respectively), with slightly higher proportions of subjects in the tofacitinib 5 mg BID group compared to subjects in the tofacitinib 10 mg BID group, respectively (Table 15).

Table 15. Summary of PRTI Data (FAS)

	Tofacitinib 5 mg BID N=62	Tofacitinib 10 mg BID N=88	Total N=150
Patient Satisfaction Assessment, number (%) of subjects			
n	42	46	88
Extremely dissatisfied	0	0	0
Dissatisfied	0	4 (8.7)	4 (4.5)
Neither satisfied nor dissatisfied	0	8 (17.4)	8 (9.1)
Satisfied	14 (33.3)	19 (41.3)	33 (37.5)
Extremely satisfied	28 (66.7)	15 (32.6)	43 (48.9)
Patient Previous Treatment Assessment, number (%) of subjects			
n	42	46	88
Injectable prescription medicines	17 (40.5)	15 (32.6)	32 (36.4)
Prescription medicines taken by mouth	19 (45.2)	20 (43.5)	39 (44.3)
Surgery	1 (2.4)	0	1 (1.1)
Prescription medicines and surgery	3 (7.1)	6 (13.0)	9 (10.2)
No treatment	2 (4.8)	5 (10.9)	7 (8.0)
Patient Preference Assessment, number (%) of subjects			
n	42	46	88
Yes, I definitely prefer the drug that I am receiving now	37 (88.1)	26 (56.5)	63 (71.6)
I have a slight preference for the drug that I am receiving now	2 (4.8)	10 (21.7)	12 (13.6)
I have no preference either way	3 (7.1)	8 (17.4)	11 (12.5)
I have a slight preference for my previous treatment	0	2 (4.3)	2 (2.3)
No, I definitely prefer my previous treatment	0	0	0
Patient Willingness Assessment, number (%) of subjects			
n	42	46	88
Yes, I would definitely want to use the same drug again	35 (83.3)	28 (60.9)	63 (71.6)
I might want to use the same drug again	6 (14.3)	11 (23.9)	17 (19.3)
I am not sure	1 (2.4)	5 (10.9)	6 (6.8)
I might not want to use the same drug again	0	0	0
No, I definitely would not want to use the same drug again	0	2 (4.3)	2 (2.3)

Subjects were analyzed as per their initial dose assignment.
Percent based on number of subjects with non-missing values within the analysis set.
Previous treatment refers to treatments prior to the A3921086 study.
Abbreviations: BID = twice daily; FAS = Full Analysis Set; N = number of subjects in the analysis set; n = number of responders; PRTI = Patient-Reported Treatment Impact.

SF-36 component values and change from baselines scores are shown in Table 16. In general, for subjects remaining in the study, component scores decreased from baseline in the tofacitinib 5 mg BID group and increased from baseline in the tofacitinib 10 mg BID group at Week 48. However, mean changes from baseline were generally small across all domains for both tofacitinib groups.

Table 16. Descriptive Statistics of Observed and Change From Baseline Mean in SF-36 Domain and Component Scores, at Week 48/ET (FAS)

	Observed Data							Change from Baseline					
	N	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Physical Component Score													
Baseline													
Tofacitinib 5 mg BID	62	62	50.15	6.73	50.72	26.9	61.1						
Tofacitinib 10 mg BID	88	86	37.80	9.53	39.21	12.8	54.3						
Total	150	148	42.97	10.43	44.25	12.8	61.1						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	48.43	8.22	51.27	23.5	59.6	57	-1.47	7.17	-0.84	-24.4	12.3
Tofacitinib 10 mg BID	88	83	41.87	10.06	43.58	20.1	58.9	82	4.47	11.06	2.80	-19.2	43.8
Total	150	140	44.54	9.87	46.08	20.1	59.6	139	2.03	10.06	0.68	-24.4	43.8
Mental Component Score													
Baseline													
Tofacitinib 5 mg BID	62	62	50.25	9.11	51.78	20.3	62.0						
Tofacitinib 10 mg BID	88	86	37.17	11.94	36.59	7.3	58.2						
Total	150	148	42.65	12.60	45.51	7.3	62.0						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	48.79	10.64	50.88	20.1	64.4	57	-1.88	9.05	-1.60	-33.6	20.4
Tofacitinib 10 mg BID	88	83	39.60	12.87	41.27	12.7	59.9	82	3.07	11.53	2.51	-26.7	28.4
Total	150	140	43.34	12.80	47.03	12.7	64.4	139	1.04	10.83	-0.10	-33.6	28.4
Physical Functioning Domain													
Baseline													
Tofacitinib 5 mg BID	62	62	53.35	5.50	55.07	32.6	57.1						
Tofacitinib 10 mg BID	88	86	43.50	10.37	45.86	18.2	57.1						
Total	150	148	47.63	9.93	50.97	18.2	57.1						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	51.40	8.59	55.07	18.2	57.1	57	-1.80	7.50	0.00	-36.8	14.3
Tofacitinib 10 mg BID	88	83	46.81	10.22	50.97	22.3	57.1	82	3.49	10.74	0.00	-28.7	38.9
Total	150	140	48.68	9.83	53.02	18.2	57.1	139	1.33	9.87	0.00	-36.8	38.9
Role Physical Domain													
Baseline													
Tofacitinib 5 mg BID	62	62	50.97	8.22	54.24	23.2	56.6						
Tofacitinib 10 mg BID	88	86	35.93	11.30	35.15	18.4	56.6						
Total	150	148	42.23	12.54	44.69	18.4	56.6						

Table 16. Descriptive Statistics of Observed and Change From Baseline Mean in SF-36 Domain and Component Scores, at Week 48/ET (FAS)

	Observed Data							Change from Baseline					
	N	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Week 48/ET													
Tofacitinib 5 mg BID	62	57	49.38	8.78	54.24	28.0	56.6	57	-1.38	7.87	0.00	-21.5	19.1
Tofacitinib 10 mg BID	88	83	40.04	12.99	42.31	18.4	56.6	82	4.60	12.62	2.39	-38.2	38.2
Total	150	140	43.84	12.32	47.08	18.4	56.6	139	2.15	11.28	0.00	-38.2	38.2
Bodily Pain Domain													
Baseline													
Tofacitinib 5 mg BID	62	62	51.32	8.55	50.05	28.4	60.9						
Tofacitinib 10 mg BID	88	87	35.31	9.14	32.56	19.2	60.9						
Total	150	149	41.98	11.89	40.47	19.2	60.9						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	49.57	10.30	52.55	23.4	60.9	57	-1.60	7.90	0.00	-21.7	12.5
Tofacitinib 10 mg BID	88	83	41.04	12.69	40.47	19.2	60.9	83	6.15	12.92	4.17	-30.0	41.7
Total	150	140	44.51	12.47	45.06	19.2	60.9	140	2.99	11.75	0.00	-30.0	41.7
General Health Domain													
Baseline													
Tofacitinib 5 mg BID	62	62	41.60	9.51	41.18	23.8	63.7						
Tofacitinib 10 mg BID	88	87	31.74	8.41	30.84	16.8	57.6						
Total	150	149	35.84	10.11	35.54	16.8	63.7						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	40.39	10.08	38.83	19.1	63.7	57	-1.42	10.00	-2.35	-30.5	21.1
Tofacitinib 10 mg BID	88	83	33.45	10.16	30.84	16.8	63.7	83	2.25	7.99	0.00	-14.1	24.4
Total	150	140	36.27	10.66	34.84	16.8	63.7	140	0.75	9.01	0.00	-30.5	24.4
Vitality Domain													
Baseline													
Tofacitinib 5 mg BID	62	62	52.78	10.68	54.95	22.0	69.9						
Tofacitinib 10 mg BID	88	87	36.92	9.88	36.99	22.0	57.9						
Total	150	149	43.52	12.85	42.97	22.0	69.9						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	51.06	11.38	51.95	22.0	69.9	57	-1.63	10.39	-2.99	-35.9	23.9
Tofacitinib 10 mg BID	88	83	41.03	12.38	39.98	22.0	66.9	83	4.47	12.16	2.99	-15.0	44.9
Total	150	140	45.11	12.93	45.97	22.0	69.9	140	1.99	11.82	0.00	-35.9	44.9

Table 16. Descriptive Statistics of Observed and Change From Baseline Mean in SF-36 Domain and Component Scores, at Week 48/ET (FAS)

	Observed Data							Change from Baseline					
	N	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Social Functioning Domain													
Baseline													
Tofacitinib 5 mg BID	62	62	51.81	7.21	56.40	24.1	56.4						
Tofacitinib 10 mg BID	88	87	36.38	12.29	34.89	13.4	56.4						
Total	150	149	42.80	12.94	45.65	13.4	56.4						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	49.42	9.64	56.40	18.8	56.4	57	-2.92	9.09	0.00	-37.6	32.3
Tofacitinib 10 mg BID	88	83	39.82	13.39	40.27	13.4	56.4	83	3.69	13.46	5.38	-43.0	37.6
Total	150	140	43.73	12.87	45.65	13.4	56.4	140	1.00	12.28	0.00	-43.0	37.6
Role Emotional Domain													
Baseline													
Tofacitinib 5 mg BID	62	62	50.12	8.85	55.68	10.2	55.7						
Tofacitinib 10 mg BID	88	86	38.55	12.73	40.54	10.2	55.7						
Total	150	148	43.40	12.61	44.32	10.2	55.7						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	47.97	10.78	55.68	21.6	55.7	57	-2.26	10.29	0.00	-30.3	30.3
Tofacitinib 10 mg BID	88	83	41.13	13.15	44.32	10.2	55.7	82	3.28	11.38	0.00	-26.5	30.3
Total	150	140	43.92	12.66	48.11	10.2	55.7	139	1.01	11.24	0.00	-30.3	30.3
Mental Health Domain													
Baseline													
Tofacitinib 5 mg BID	62	62	49.89	9.84	52.35	21.9	63.4						
Tofacitinib 10 mg BID	88	87	37.61	11.98	38.50	8.0	60.7						
Total	150	149	42.72	12.66	44.04	8.0	63.4						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	49.24	10.27	52.35	21.9	63.4	57	-1.02	8.63	0.00	-24.9	30.5
Tofacitinib 10 mg BID	88	83	40.13	12.52	41.27	10.8	63.4	83	2.87	11.72	2.77	-24.9	30.5
Total	150	140	43.84	12.46	46.81	10.8	63.4	140	1.29	10.71	0.00	-24.9	30.5

Subjects were analyzed as per their initial dose assignment.

Abbreviations: BID = twice daily; ET = Early Termination; FAS = Full Analysis Set; Max = maximum; Min = minimum; N = number of subjects in the analysis set; n = number of subjects with non-missing data; SD = standard deviation; SF-36 = 36-Item Short Form Health Survey.

Mean baseline EQ-5D Utility and VAS scores were 0.85 and 77.98, respectively for subjects in the tofacitinib 5 mg BID group and 0.57 and 48.60, respectively for subjects in the tofacitinib 10 mg BID group. No notable changes from baseline in EQ-5D utility were noted for either treatment group. A notable increase from baseline in VAS scores was observed for subjects remaining in the tofacitinib 10 mg group at Week 48, with a mean (SD) change from baseline of 10.16 (26.57) observed at Week 48/ET (Table 17).

Table 17. Descriptive Statistics of Observed and Change From Baseline Mean in EQ-5D Utility and VAS Score, by Visit (FAS)

	Observed Data							Change from Baseline					
	N	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Utility Score													
Baseline													
Tofacitinib 5 mg BID	62	62	0.85	0.21	1.00	0.05	1.00						
Tofacitinib 10 mg BID	88	85	0.57	0.28	0.69	-0.32	1.00						
Total	150	147	0.69	0.29	0.73	-0.32	1.00						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	0.84	0.16	0.85	0.19	1.00	57	-0.02	0.21	0.00	-0.53	0.74
Tofacitinib 10 mg BID	88	83	0.66	0.31	0.73	-0.24	1.00	81	0.10	0.36	0.07	-0.76	1.32
Total	150	140	0.73	0.27	0.76	-0.24	1.00	138	0.05	0.31	0.00	-0.76	1.32
VAS Score													
Baseline													
Tofacitinib 5 mg BID	62	62	77.98	16.18	80.00	20.00	100.00						
Tofacitinib 10 mg BID	88	86	48.60	19.21	50.00	8.00	80.00						
Total	150	148	60.91	23.10	65.00	8.00	100.00						
Week 48/ET													
Tofacitinib 5 mg BID	62	57	73.40	18.54	75.00	30.00	100.00	57	-3.79	20.56	-1.00	-60.00	47.00
Tofacitinib 10 mg BID	88	83	57.60	24.60	61.00	9.00	100.00	82	10.16	26.57	10.00	-40.00	92.00
Total	150	140	64.04	23.59	70.00	9.00	100.00	139	4.44	25.16	0.00	-60.00	92.00

Subjects were analyzed as per their initial dose assignment.

Abbreviations: BID = twice daily; ET = Early Termination; EQ-5D = EuroQOL 5 Dimensions questionnaire; FAS = Full Analysis Set; Max = maximum; Min = minimum; N = number of subjects in the analysis set; n = number of subjects with non-missing data; SD = standard deviation; VAS = visual analog scale.

Overall, 7 subjects (11.3%) and 14 subjects (15.9%) in the tofacitinib 5 mg BID and 10 mg BID groups, respectively were hospitalized due to CD during the study. The mean length of hospitalization related to CD was 3.8 days for subjects in the tofacitinib 5 mg BID group and 7.1 days for subjects in the tofacitinib 10 mg BID group (Table 18).

Table 18. Number and Length of Hospitalizations due to Crohn's Disease

	Tofacitinib 5 mg BID (N=62)	Tofacitinib 10 mg BID (N=88)	Total (N=150)
Number of Subjects Hospitalized, n(%)	7 (11.3)	14 (15.9)	21 (14.0)
Length of Hospitalization (days, %)			
<3	1 (1.6)	2 (2.3)	3 (2.0)
3-6	4 (6.5)	9 (10.2)	13 (8.7)
7-10	0	3 (3.4)	3 (2.0)
>10	0	3 (3.4)	3 (2.0)
Mean (SD)	3.80 (1.64)	7.06 (5.15)	6.32 (4.76)
Median	4.00	5.00	4.50
Range	1-5	2-20	1-20

Subjects were analyzed as per their initial dose assignment.
Subjects were only counted once in the row "Number of Subjects Hospitalized".
Abbreviations: BID = twice daily; N = number of subjects in the analysis set; n = number of subjects with non-missing data; SD = standard deviation.

Pharmacodynamic (Biomarker) Results:

The changes from baseline in serum CRP values by week are presented in Table 19. Mean (SD) baseline hsCRP values were 10.28 (18.58) mg/L for subjects in the tofacitinib 5 mg BID group and 20.72 (30.51) mg/L for subjects in the tofacitinib 10 mg BID group.

A decrease from baseline values in CRP was observed at each time point in both treatment groups with the greatest decrease from baseline at Week 48 (mean [SD] change of -4.55 [17.81] mg/L) for subjects remaining in the tofacitinib 5 mg BID group and at Week 36 (mean [SD] change of -12.09 [30.61] mg/L) for subjects remaining in the tofacitinib 10 mg BID group.

Table 19. Change From Baseline in CRP (mg/L), by Week (FAS)

	n	Mean	SD	Median	Min	Max
Baseline						
Tofacitinib 5 mg BID	62	10.28	18.58	3.62	0.1	98.4
Tofacitinib 10 mg BID	85	20.72	30.51	8.82	0.1	166.2
Total	147	16.32	26.58	6.12	0.1	166.2
Week 8						
Tofacitinib 5 mg BID	61	-0.44	14.78	-0.12	-45.9	59.2
Tofacitinib 10 mg BID	82	-4.81	26.76	-1.37	-122.7	102.1
Total	143	-2.95	22.48	-0.32	-122.7	102.1
Week 16						
Tofacitinib 5 mg BID	58	-2.46	14.54	-0.07	-90.4	21.7
Tofacitinib 10 mg BID	72	-7.96	25.11	-1.18	-144.9	43.9
Total	130	-5.51	21.17	-0.58	-144.9	43.9
Week 24						
Tofacitinib 5 mg BID	54	-2.76	17.59	-0.58	-92.2	29.8
Tofacitinib 10 mg BID	61	-9.26	30.20	-1.68	-159.9	59.1
Total	115	-6.21	25.19	-0.96	-159.9	59.1
Week 36						
Tofacitinib 5 mg BID	46	-4.42	22.29	-0.27	-88.8	80.7
Tofacitinib 10 mg BID	51	-12.09	30.61	-1.70	-157.7	36.5
Total	97	-8.45	27.13	-0.91	-157.7	80.7
Week 48						
Tofacitinib 5 mg BID	43	-4.55	17.81	-0.64	-91.1	22.6
Tofacitinib 10 mg BID	44	-11.45	31.30	-1.54	-155.3	51.1
Total	87	-8.04	25.63	-0.83	-155.3	51.1
Follow-up						
Tofacitinib 5 mg BID	54	3.86	21.57	0.34	-84.3	72.7
Tofacitinib 10 mg BID	71	-4.72	31.34	0.26	-154.4	44.4
Total	125	-1.01	27.78	0.34	-154.4	72.7

Subjects were analyzed as per their initial dose assignment.
Abbreviations: BID = twice daily; CRP = C-reactive protein; FAS = Full Analysis Set; Max = maximum; Min = minimum; n = number of subjects with non-missing data; SD = standard deviation.

The changes from baseline in FEC values by week are presented in Table 20. Mean (SD) baseline FEC values were 431.52 (483.37) mg/kg for subjects in the tofacitinib 5 mg BID group and 486.06 (309.75) mg/kg for subjects in the tofacitinib 10 mg BID group.

Mean concentrations of FEC decreased at each time point in both treatment groups. The greatest mean change from baseline in FEC was observed at Week 48 (mean [SD] change of -189.61 [462.61] mg/kg) for subjects remaining in the tofacitinib 5 mg BID group and at Week 36 (mean [SD] change of -133.82 [364.51] mg/kg) for subjects remaining in the tofacitinib 10 mg BID group.

Table 20. Change From Baseline in Fecal Calprotectin (mg/kg), by Week (FAS)

	n	Mean	SD	Median	Min	Max
Baseline						
Tofacitinib 5 mg BID	61	431.52	483.37	274.00	25.2	3128.0
Tofacitinib 10 mg BID	80	486.06	309.75	528.00	25.2	1065.0
Total	141	462.46	393.71	442.00	25.2	3128.0
Week 8						
Tofacitinib 5 mg BID	53	-105.51	436.41	-13.00	-2291	654.0
Tofacitinib 10 mg BID	71	-102.82	310.10	-47.00	-959.0	528.0
Total	124	-103.97	367.76	-32.50	-2291	654.0
Week 16						
Tofacitinib 5 mg BID	54	-144.65	423.20	-44.90	-2393	633.0
Tofacitinib 10 mg BID	64	-35.28	718.82	-82.50	-979.0	4999.0
Total	118	-85.33	601.95	-63.50	-2393	4999.0
Week 24						
Tofacitinib 5 mg BID	49	-120.49	511.49	-54.00	-2923	827.0
Tofacitinib 10 mg BID	55	-130.68	337.23	-65.00	-1027	703.0
Total	104	-125.88	426.11	-59.00	-2923	827.0
Week 36						
Tofacitinib 5 mg BID	41	-169.92	354.30	-56.00	-1654	528.8
Tofacitinib 10 mg BID	42	-133.82	364.51	-52.00	-985.0	592.0
Total	83	-151.65	357.77	-56.00	-1654	592.0
Week 48						
Tofacitinib 5 mg BID	37	-189.61	462.61	-98.80	-2123	745.8
Tofacitinib 10 mg BID	38	-123.87	376.70	-102.00	-977.0	910.0
Total	75	-156.30	419.71	-98.80	-2123	910.0
Follow-up						
Tofacitinib 5 mg BID	48	-51.33	453.73	0.00	-2219	777.8
Tofacitinib 10 mg BID	57	-109.23	389.54	-59.00	-1019	791.0
Total	105	-82.76	419.03	-15.00	-2219	791.0

Subjects were analyzed as per their initial dose assignment.
Abbreviations: BID = twice daily; FAS = Full Analysis Set; Max = maximum; Min = minimum; n = number of subjects with non-missing data; SD = standard deviation.

Safety Results:

A summary of SAEs is provided in Table 21. SAEs were reported in 8.1% of subjects in the tofacitinib 5 mg BID group and 15.9% of subjects in the tofacitinib 10 mg BID group. The most frequently reported SAE in both treatment groups was CD, which occurred in a higher proportion of subjects in the tofacitinib 10 mg BID group (7 subjects, 8.0%) who entered the study with active disease not in remission compared to the tofacitinib 5 mg BID group, which comprised subjects who entered the study in remission (3 subjects, 4.8%).

Table 21. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Total		
	n(%)	n1	n2	n(%)	n1	n2	n(%)	n1	n2
Number (%) of Subjects:									
Evaluable for adverse events	62			88			150		
With adverse events	5 (8.06)			14 (15.91)			19 (12.67)		
Gastrointestinal disorders	**4 (6.45)**	**4**	**0**	**9 (10.23)**	**9**	**1**	**13 (8.67)**	**13**	**1**
Colon dysplasia	1 (1.61)	1	0	0	0	0	1 (0.67)	1	0
Crohn's disease	3 (4.84)	3	0	7 (7.95)	7	1	10 (6.67)	10	1
Small intestinal obstruction	0	0	0	2 (2.27)	2	0	2 (1.33)	2	0
General disorders and administration site conditions	**2 (3.23)**	**2**	**0**	**1 (1.14)**	**1**	**0**	**3 (2.00)**	**3**	**0**
Chest pain	1 (1.61)	1	0	0	0	0	1 (0.67)	1	0
Influenza like illness	1 (1.61)	1	0	0	0	0	1 (0.67)	1	0
Pyrexia	0	0	0	1 (1.14)	1	0	1 (0.67)	1	0
Hepatobiliary disorders	**0**	**0**	**0**	**1 (1.14)**	**1**	**0**	**1 (0.67)**	**1**	**0**
Biliary colic	0	0	0	1 (1.14)	1	0	1 (0.67)	1	0
Immune system disorders	**0**	**0**	**0**	**1 (1.14)**	**1**	**1**	**1 (0.67)**	**1**	**1**
Hypersensitivity	0	0	0	1 (1.14)	1	1	1 (0.67)	1	1
Infections and infestations	**2 (3.23)**	**2**	**1**	**2 (2.27)**	**2**	**0**	**4 (2.67)**	**4**	**1**
Anal abscess	0	0	0	1 (1.14)	1	0	1 (0.67)	1	0
Diarrhoea infectious	1 (1.61)	1	0	0	0	0	1 (0.67)	1	0
Pyelonephritis	1 (1.61)	1	1	0	0	0	1 (0.67)	1	1
Vulval abscess	0	0	0	1 (2.44)	1	0	1 (1.41)	1	0
Injury, poisoning and procedural complications	**0**	**0**	**0**	**1 (1.14)**	**1**	**0**	**1 (0.67)**	**1**	**0**
Incisional hernia	0	0	0	1 (1.14)	1	0	1 (0.67)	1	0
Investigations	**0**	**0**	**0**	**1 (1.14)**	**2**	**0**	**1 (0.67)**	**2**	**0**
C-reactive protein increased	0	0	0	1 (1.14)	2	0	1 (0.67)	2	0
Renal and urinary disorders	**1 (1.61)**	**1**	**0**	**0**	**0**	**0**	**1 (0.67)**	**1**	**0**
Acute kidney injury	1 (1.61)	1	0	0	0	0	1 (0.67)	1	0
Reproductive system and breast disorders	**0**	**0**	**0**	**1 (1.14)**	**1**	**0**	**1 (0.67)**	**1**	**0**
Perineal fistula	0	0	0	1 (1.14)	1	0	1 (0.67)	1	0
Respiratory, thoracic and mediastinal disorders	**1 (1.61)**	**1**	**0**	**0**	**0**	**0**	**1 (0.67)**	**1**	**0**
Dyspnoea	1 (1.61)	1	0	0	0	0	1 (0.67)	1	0
Skin and subcutaneous tissue disorders	**1 (1.61)**	**1**	**0**	**0**	**0**	**0**	**1 (0.67)**	**1**	**0**
Hyperhidrosis	1 (1.61)	1	0	0	0	0	1 (0.67)	1	0

Subjects were analyzed as per their initial dose assignment.
Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
MedDRA (version 19.0) coding dictionary applied.
Includes data up to 999 days after last dose of study drug.
Percentage cutoff based upon frequency in any treatment group.
Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in this reporting group affected by any occurrence of this adverse event, All Causalities; n1: the number of occurrences of treatment-emergent all causalities adverse events; n2: the number of occurrences of treatment-emergent causally related to treatment adverse events.

There were no deaths during the study.

A summary of treatment-emergent non-serious AEs in >2% of subjects is provided in Table 22. The most frequently reported non-serious AE in both treatment groups was CD with 19 (30.7%) subjects in the tofacitinib 5 mg BID group and 11 (12.5%) subjects in the tofacitinib 10 mg BID group.

Table 22. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term in >2% of Subjects

System Organ Class Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Total		
	n(%)	n1	n2	n(%)	n1	n2	n(%)	n1	n2
Number (%) of Subjects:									
Evaluable for adverse events	62			88			150		
With adverse events	42 (67.74)			58 (65.91)			100 (66.67)		
Blood and lymphatic system disorders	**3 (4.84)**	**5**	**3**	**4 (4.55)**	**4**	**2**	**7 (4.67)**	**9**	**5**
Anemia	3 (4.84)	5	3	4 (4.55)	4	2	7 (4.67)	9	5
Ear and labyrinth disorders	**0**	**0**	**0**	**2 (2.27)**	**2**	**0**	**2 (1.33)**	**2**	**0**
Vertigo	0	0	0	2 (2.27)	2	0	2 (1.33)	2	0
Gastrointestinal disorders	**30 (48.39)**	**50**	**5**	**34 (38.64)**	**64**	**18**	**64 (42.67)**	**114**	**23**
Abdominal distension	2 (3.23)	2	0	3 (3.41)	3	0	5 (3.33)	5	0
Abdominal pain	7 (11.29)	7	1	7 (7.95)	8	1	14 (9.33)	15	2
Abdominal pain upper	1 (1.61)	1	0	2 (2.27)	2	2	3 (2.00)	3	2
Anal fissure	1 (1.61)	1	0	2 (2.27)	2	0	3 (2.00)	3	0
Aphthous ulcer	1 (1.61)	1	0	3 (3.41)	3	0	4 (2.67)	4	0
Constipation	2 (3.23)	2	0	1 (1.14)	1	1	3 (2.00)	3	1
Crohn's disease	19 (30.65)	22	4	11 (12.50)	13	3	30 (20.00)	35	7
Diarrhoea	3 (4.84)	3	0	1 (1.14)	1	0	4 (2.67)	4	0
Dyspepsia	0	0	0	3 (3.41)	6	4	3 (2.00)	6	4
Flatulence	0	0	0	2 (2.27)	2	0	2 (1.33)	2	0
Food poisoning	2 (3.23)	2	0	0	0	0	2 (1.33)	2	0
Haematochezia	1 (1.61)	1	0	2 (2.27)	2	0	3 (2.00)	3	0
Haemorrhoids	0	0	0	4 (4.55)	4	0	4 (2.67)	4	0
Nausea	2 (3.23)	2	0	9 (10.23)	9	3	11 (7.33)	11	3
Proctalgia	1 (1.61)	1	0	2 (2.27)	2	0	3 (2.00)	3	0
Toothache	3 (4.84)	3	0	0	0	0	3 (2.00)	3	0
Vomiting	1 (1.61)	2	0	6 (6.82)	6	4	7 (4.67)	8	4
General disorders and administration site conditions	**6 (9.68)**	**6**	**2**	**12 (13.64)**	**13**	**4**	**18 (12.00)**	**19**	**6**
Chest pain	2 (3.23)	2	1	2 (2.27)	2	1	4 (2.67)	4	2
Cyst	2 (3.23)	2	0	0	0	0	2 (1.33)	2	0
Fatigue	1 (1.61)	1	0	4 (4.55)	4	0	5 (3.33)	5	0
Pyrexia	1 (1.61)	1	1	6 (6.82)	7	3	7 (4.67)	8	4
Infections and infestations	**25 (40.32)**	**48**	**24**	**29 (32.95)**	**39**	**16**	**54 (36.00)**	**87**	**40**
Bartholin's abscess	0	0	0	1 (2.44)	1	0	1 (1.41)	1	0
Bartholinitis	0	0	0	2 (4.88)	2	0	2 (2.82)	2	0
Cystitis	2 (3.23)	2	1	0	0	0	2 (1.33)	2	1

Table 22. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term in >2% of Subjects

System Organ Class Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Total		
	n(%)	n1	n2	n(%)	n1	n2	n(%)	n1	n2
Folliculitis	0	0	0	2 (2.27)	2	2	2 (1.33)	2	2
Gastroenteritis	7 (11.29)	7	1	2 (2.27)	2	2	9 (6.00)	9	3
Herpes zoster	1 (1.61)	1	1	2 (2.27)	2	1	3 (2.00)	3	2
Influenza	5 (8.06)	5	1	8 (9.09)	9	4	13 (8.67)	14	5
Nasopharyngitis	8 (12.90)	11	6	7 (7.95)	7	3	15 (10.00)	18	9
Oral herpes	3 (4.84)	3	2	0	0	0	3 (2.00)	3	2
Pharyngitis	2 (3.23)	2	1	0	0	0	2 (1.33)	2	1
Upper respiratory tract infection	2 (3.23)	2	1	2 (2.27)	2	0	4 (2.67)	4	1
Urinary tract infection	8 (12.90)	14	9	7 (7.95)	8	4	15 (10.00)	22	13
Vaginal infection	1 (3.33)	1	1	0	0	0	1 (1.41)	1	1
Vaginitis bacterial	0	0	0	1 (2.44)	1	0	1 (1.41)	1	0
Vulvovaginal candidiasis	0	0	0	1 (2.44)	1	0	1 (1.41)	1	0
Vulvovaginal mycotic infection	0	0	0	2 (4.88)	2	0	2 (2.82)	2	0
Investigations	**7 (11.29)**	**14**	**10**	**8 (9.09)**	**14**	**11**	**15 (10.00)**	**28**	**21**
Blood alkaline phosphatase increased	2 (3.23)	2	2	0	0	0	2 (1.33)	2	2
Blood creatine phosphokinase increased	3 (4.84)	4	3	5 (5.68)	5	3	8 (5.33)	9	6
C-reactive protein increased	2 (3.23)	2	0	0	0	0	2 (1.33)	2	0
Gamma-glutamyltransferase increased	2 (3.23)	2	2	0	0	0	2 (1.33)	2	2
Lymphocyte count decreased	1 (1.61)	1	1	2 (2.27)	8	8	3 (2.00)	9	9
Smear cervix abnormal	1 (3.33)	1	1	0	0	0	1 (1.41)	1	1
Weight decreased	2 (3.23)	2	1	1 (1.14)	1	0	3 (2.00)	3	1
Metabolism and nutrition disorders	**0**	**0**	**0**	**5 (5.68)**	**7**	**0**	**5 (3.33)**	**7**	**0**
Dehydration	0	0	0	2 (2.27)	3	0	2 (1.33)	3	0
Hypercholesterolaemia	0	0	0	2 (2.27)	2	0	2 (1.33)	2	0
Vitamin B12 deficiency	0	0	0	2 (2.27)	2	0	2 (1.33)	2	0
Musculoskeletal and connective tissue disorders	**7 (11.29)**	**9**	**0**	**13 (14.77)**	**14**	**3**	**20 (13.33)**	**23**	**3**
Arthralgia	5 (8.06)	6	0	8 (9.09)	8	3	13 (8.67)	14	3
Back pain	1 (1.61)	1	0	4 (4.55)	4	0	5 (3.33)	5	0
Muscle spasms	2 (3.23)	2	0	2 (2.27)	2	0	4 (2.67)	4	0
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	**0**	**0**	**0**	**2 (2.27)**	**2**	**0**	**2 (1.33)**	**2**	**0**
Acrochordon	0	0	0	2 (2.27)	2	0	2 (1.33)	2	0
Nervous system disorders	**1 (1.61)**	**2**	**1**	**2 (2.27)**	**2**	**2**	**3 (2.00)**	**4**	**3**
Headache	1 (1.61)	2	1	2 (2.27)	2	2	3 (2.00)	4	3
Psychiatric disorders	**2 (3.23)**	**2**	**1**	**3 (3.41)**	**3**	**0**	**5 (3.33)**	**5**	**1**
Anxiety	0	0	0	3 (3.41)	3	0	3 (2.00)	3	0
Insomnia	2 (3.23)	2	1	0	0	0	2 (1.33)	2	1
Reproductive system and breast disorders	**2 (6.25)**	**2**	**0**	**4 (4.55)**	**14**	**1**	**6 (4.00)**	**6**	**1**
Amenorrhoea	0	0	0	1 (2.44)	1	1	1 (1.41)	1	1
Balanoposthitis	1 (3.13)	1	0	0	0	0	1 (1.27)	1	0
Erectile dysfunction	1 (3.13)	1	0	0	0	0	1 (1.27)	1	0
Oligomenorrhoea	0	0	0	1 (2.44)	1	0	1 (1.41)	1	0

Table 22. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term in >2% of Subjects

System Organ Class Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Total		
	n(%)	n1	n2	n(%)	n1	n2	n(%)	n1	n2
Testicular swelling	0	0	0	1 (2.13)	1	0	1 (1.27)	1	0
Vulvovaginal pruritus	0	0	0	1 (2.44)	1	0	1 (1.41)	1	0
Respiratory, thoracic, and mediastinal disorders	**1 (1.61)**	**1**	**1**	**2 (2.27)**	**2**	**1**	**3 (2.00)**	**3**	**2**
Cough	1 (1.61)	1	1	2 (2.27)	2	1	3 (2.00)	3	2
Skin and subcutaneous tissue disorders	**1 (1.61)**	**1**	**0**	**4 (4.55)**	**4**	**2**	**5 (3.33)**	**5**	**2**
Dermatitis	0	0	0	2 (2.27)	2	1	2 (1.33)	2	1
Rash	1 (1.61)	1	0	2 (2.27)	2	1	3 (2.00)	3	1

Subjects were analyzed as per their initial dose assignment.
Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
MedDRA (version 19.0) coding dictionary applied.
Includes data up to 999 days after last dose of study drug.
Percentage cutoff based upon frequency in any treatment group.
Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in this reporting group affected by any occurrence of this adverse event, All Causalities; n1: the number of occurrences of treatment-emergent all causalities adverse events; n2: the number of occurrences of treatment-emergent causally related to treatment adverse events.

Clinical Laboratory Evaluations

In general, a greater mean percent increase from baseline was observed for each lipid parameter across all timepoints for subjects remaining in the tofacitinib 10 mg BID group, compared to those remaining in the tofacitinib 5 mg BID group, with the exception of triglycerides in the tofacitinib 5 mg BID group, although these changes were not considered clinically meaningful and were similar to what has been observed with tofacitinib treatment in other studies of other indications.

The most common hematological abnormalities were observed for absolute neutrophil counts and absolute lymphocytes. However, AEs of neutrophil count decreased and lymphocyte count decreased were uncommon among subjects in both treatment groups (neutrophil count decreased reported in 1 subject in the tofacitinib 10 mg BID group only and lymphocyte count decreased reported in 1 and 2 subjects in the tofacitinib 5 mg BID and tofacitinib 10 mg BID groups, respectively).

Clinical chemistry abnormalities were few, with the most commonly reported abnormality observed for creatine kinase with 11 subjects in the tofacitinib 5 mg BID group and 14 subjects in the tofacitinib 10 mg BID group. AEs of blood creatine phosphokinase increased were reported in 3 subjects in the tofacitinib 5 mg BID group and 5 subjects in tofacitinib 10 mg BID group. No AEs relating to rhabdomyolysis or myositis were reported during the study.

Adjudicated AEs

There were no cases of confirmed adjudicated cardiovascular events or ILD events.

One subject in the tofacitinib 5 mg BID group had an event of Herpes zoster that met the criteria for opportunistic infection (reported as multidermatomal, nonadjacent or >2 adjacent dermatomes), and 1 subject in the tofacitinib 10 mg BID group had an event of Varicella that met the criteria for opportunistic infection, reported as systemic, disseminated and multidermatomal.

One hepatic event of Biliary colic in the tofacitinib 10 mg BID group was adjudicated and did not meet the criteria for a hepatic injury but was considered as possible Gilbert syndrome.

Two subjects in the tofacitinib 10 mg BID group had events that met adjudication criteria for GI perforation (Perineal fistula and Anal abscess). The event of Perineal fistula was attributed by the adjudication committee to concomitant medication and concurrent medical condition, and Anal abscess was attributed to concurrent medical condition.

Two subjects, 1 in each treatment group, had an event that was adjudicated for malignancy. Of those, 1 subject in the tofacitinib 10 mg BID group (11091001) had an event of Basal cell carcinoma that met adjudication criteria for malignancy events. The other event (Colon dysplasia) was also adjudicated but was determined not to meet the criteria for malignancy.

CONCLUSION(S):

- Tofacitinib appeared to be well tolerated as a long-term maintenance therapy in subjects with CD. There were no deaths during this study. A greater proportion of subjects in the tofacitinib 10 mg BID group experienced severe and serious AEs, and AEs that led to discontinuation compared to subjects in the tofacitinib 5 mg BID group with insufficient clinical response accounting for the majority of the discontinuations. Rates of serious infection and adjudicated events were low and similar between the tofacitinib dose groups.

- There were no clinically meaningful differences in mean lipid levels between the treatment groups at any time point with mean levels generally remaining stable over time with modest elevations from baseline values.

- At Week 48, the proportions of subjects in the tofacitinib 5 mg BID group in clinical remission and sustained clinical remission based on observed data were 87.9% (29/33 subjects remaining in the study) and 75.0% (24/32 subjects), respectively.

- At Week 48, the proportions of subjects in the tofacitinib 10 mg BID group in clinical remission and sustained clinical remission based on observed data were 55.6% (20/36 subjects remaining in the study) and 34.3% (12/35 subjects), respectively.

- Efficacy and safety were analyzed by initial dose assignment. Within and between dose group analyses are confounded by dose switching between treatment groups that was permitted after 8 weeks of treatment. Notably, the large majority of subjects who switched doses were those who switched from 5 mg BID to 10 mg BID.

- The IBDQ mean total score remained high (≥170) at each time point for subjects remaining in the study in the tofacitinib 5 mg BID group and did not decrease greatly

from baseline. For subjects remaining in the study in the tofacitinib 10 mg BID group there was a numerical increase in mean change from baseline in the total IBDQ score.

- Decreases in hsCRP and FEC from baseline were observed at each time point in both treatment groups, with the magnitude of the decrease in hsCRP from baseline being numerically greater at each time point for subjects in the tofacitinib 10 mg group than for those in the tofacitinib 5 mg BID group.