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GENERIC DRUG NAME AND/OR COMPOUND NUMBER: Tofacitinib/CP-690550

PROTOCOL NO.: A3921096

PROTOCOL TITLE: A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Oral CP-690,550 as a Maintenance Therapy in Subjects With Ulcerative Colitis

Study Centers: The study was conducted at 196 study centers in 31 countries: Australia (4), Austria (1), Belgium (4), Brazil (1), Canada (5), Colombia (1), Croatia (1), Czech Republic (3), Denmark (5), Estonia (3), France (8), Germany (7), Hungary (12), Israel (3), Italy (3), Japan (20), Korea (5), Latvia (1), Netherlands (4), New Zealand (7), Poland (10), Romania (2), Russian Federation (7), Serbia (6), Slovakia (4), South Africa (5), Spain (4), Taiwan (1), Ukraine (13), United Kingdom (UK) (5), and United States (US) (40).

Study Initiation Date and Final Completion Date: 20 July 2012 to 27 May 2016

Phase of Development: Phase 3

Study Objectives:

Primary Objective

- To demonstrate the efficacy of tofacitinib as maintenance therapy in subjects with ulcerative colitis (UC).

Secondary Objectives

- To evaluate the safety and tolerability of tofacitinib as maintenance therapy in subjects with UC;
- To evaluate the efficacy of tofacitinib maintenance therapy in achieving mucosal healing in subjects with UC;
- To evaluate the tofacitinib pharmacokinetic (PK) exposure during maintenance therapy in subjects with UC;
- To evaluate the effect of tofacitinib as maintenance therapy on quality-of-life in subjects with UC.

METHODS

Study Design:

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with UC who had completed 1 of the induction studies

(A3921094 or A3921095) and had demonstrated clinical response. Clinical response was defined by a decrease from induction study baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point, or an absolute rectal bleeding subscore of 0 or 1. This study consisted of a 53 week double-blind treatment period followed by a 4 week safety follow-up for subjects who did not participate in the open-label study (A3921139).

Approximately 654 subjects were to be enrolled in the study. The eligibility of a subject for the study was assessed based on study data collected at the Week 8 visit of Study A3921094 or Study A3921095, which were considered and recorded as the baseline visit for Study A3921096. Subjects who demonstrated clinical response after completing either Study A3921094 or Study A3921095 were eligible to be randomly assigned to receive 1 of 3 treatments: tofacitinib 10 mg twice a day (BID), tofacitinib 5 mg BID, or the matching placebo BID with an allocation ratio of 1:1:1. Subjects were stratified according to the treatment assignments in the induction study (A3921094 or A3921095) and whether they were in remission or not. Subjects enrolled into this study received double-blind maintenance treatment for up to 53 weeks.

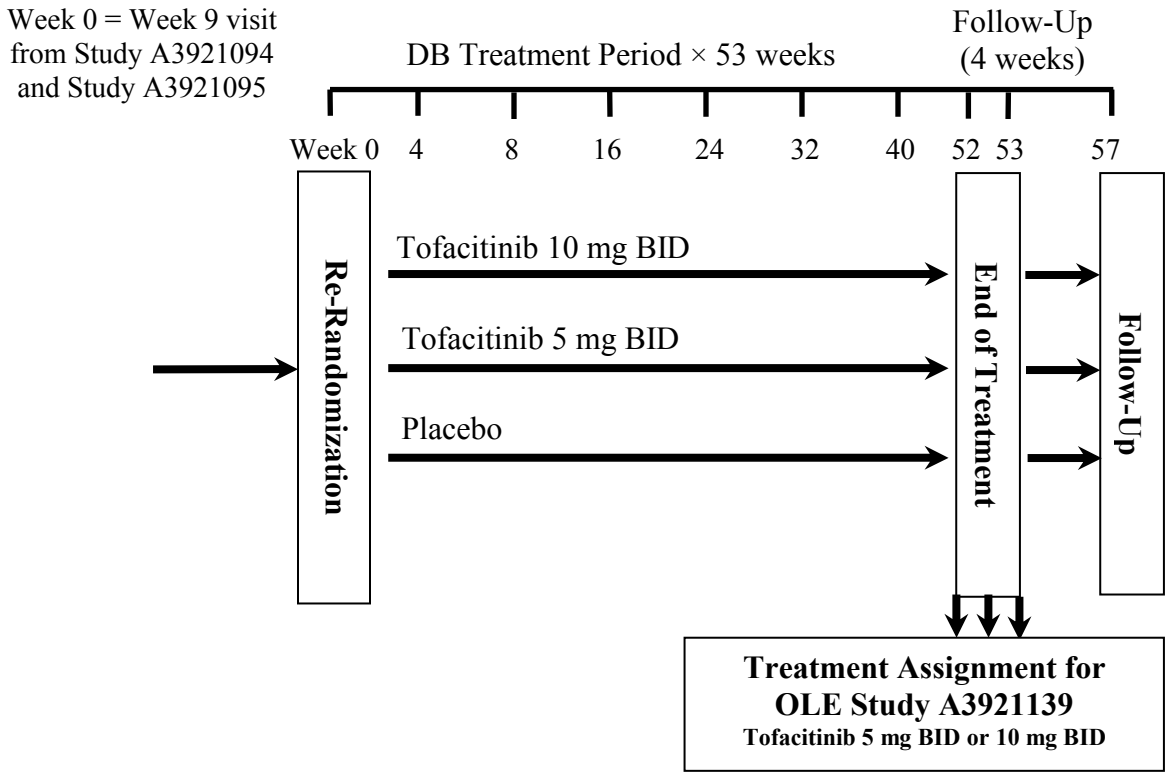
Subjects were required to remain on stable doses of their concomitant medications for UC during the study treatment period, with the exception of corticosteroids. For subjects taking corticosteroids at the baseline visit of this study, tapering of the corticosteroids was to commence from Week 0.

At the end of the double-blind treatment period, subjects who completed the study may have been eligible to enter the open-label study (A3921139). Subjects who withdrew early due to treatment failure may have also been eligible to enter the open-label study. Treatment failure was defined by an increase in Mayo score of at least 3 points from the baseline of the maintenance study, accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point yielding an absolute endoscopic subscore of at least 2 after a minimum treatment of 8 weeks in the study. Centrally-read endoscopic subscores were used to determine treatment failure.

Subjects who did not participate in the open-label study concluded this study and had a 4-week safety follow-up after the last dose of study drug. These subjects were given the post-treatment UC-Healthcare Resource Utilization questionnaires to be completed every 4 weeks and sent back to the site on a monthly basis until the anniversary of the study (Week 52).

A schematic of the study design is shown in Figure 1.

Figure 1. Study Design



BID = twice a day; DB = double-blind; OLE = open-label extension.

Number of Subjects (Planned and Analyzed):

Approximately 654 subjects were to be enrolled in the study and randomized in a 1:1:1 ratio to either tofacitinib 10 mg BID, tofacitinib 5 mg BID, or the matching placebo BID. Overall, 593 subjects were randomized to study treatment.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Eligible subjects must have met the study entry criteria, completed a 9-week induction treatment, and demonstrated a clinical response in Study A3921094 or Study A3921095. Women of childbearing potential had to have tested negative for pregnancy prior to study enrollment. Subjects must have been willing and able to comply with scheduled visits, treatment plan, laboratory tests, bowel movement diary calls, and other study procedures. Subjects were required to have an evidence of a personally signed and dated informed consent document(s) indicating that the subject (or a legally acceptable representative) had been informed of all pertinent aspects of the study.

Ineligible subjects included subjects who had a major protocol violation (as determined by the sponsor) in Study A3921094 or Study A3921095; subjects who had the presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn's disease; subjects who had surgery for UC or who, in the opinion of the investigator, were likely to require surgery for UC during the study period.

Study Treatment:

Subjects received their study medications as outpatients and were randomized into 1 of the 3 treatment groups: tofacitinib 10 mg BID, tofacitinib 5 mg BID, or placebo BID, with an allocation ratio of 1:1:1. Study drug was taken orally BID (approximately every 12 hours) for 53 weeks. Subjects were dispensed 2 bottles containing either 5 mg tofacitinib or placebo tablets and given clear dosing instructions. Subjects were instructed to take 1 tablet from each bottle in the morning and 1 tablet from each bottle in the evening, approximately 12 hours apart. Subjects were therefore taking 2 tablets BID.

At baseline (Visit 1), the first dose was taken approximately 12 hours after the last dose of study drug of Study A3921094 or Study A3921095, at home. On Week 8 (Visit 3), Week 24 (Visit 5), and Week 52 (Visit 8), the subject took the first dose of the day at the site. It was important that on the days of PK sampling, the subject took 1 dose of the study drug at the site when instructed to take the dose by a member of the investigational site to allow for timely performance of the PK sampling.

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

Efficacy Endpoints:

The primary efficacy endpoint was as follows:

- Remission at Week 52, defined by a Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0.

The key secondary endpoints were as follows:

- Mucosal healing at Week 52, defined by a Mayo endoscopic subscore of 0 or 1.

- Sustained corticosteroid-free remission among subjects in remission at baseline of this study (ie, remission and corticosteroid free at both Week 24 and 52), defined by a Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0, in addition to not requiring any treatment with corticosteroids for at least 4 weeks prior to the visit.

The other secondary endpoints were as follows:

- Remission at Week 24 and sustained remission (ie, remission at both Week 24 and Week 52);

- Remission at Week 24 and Week 52 and sustained remission, among subjects with remission at baseline of this study;

- Mucosal healing at Week 24, and sustained mucosal healing (ie, mucosal healing at both Week 24 and 52);

- Mucosal healing at Week 24 and Week 52 and sustained mucosal healing, among subjects with mucosal healing at baseline of this study;

- Corticosteroid-free remission at Week 24 and Week 52 among subjects in remission at baseline;

- Clinical response at Week 24 and Week 52 and sustained clinical response (ie, clinical response at both Week 24 and 52), defined by a decrease from induction study (A3921094 or A3921095) baseline Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or absolute subscore for rectal bleeding of 0 or 1;

- Clinical remission at Week 24 and Week 52 and sustained clinical remission (ie, clinical remission at both Week 24 and 52), defined by a Mayo score of 2 points or lower, with no individual subscore exceeding 1 point;

- Deep remission at Week 24 and Week 52 and sustained deep remission (ie, deep remission at both Week 24 and 52), defined by a Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and both absolute endoscopic and rectal bleeding subscores of 0;

- Symptomatic remission at Week 24 and Week 52 and sustained symptomatic remission (ie, symptomatic remission at both Week 24 and 52), defined by a Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, and both rectal bleeding and stool frequency subscores of 0;

- Endoscopic remission at Week 24 and Week 52 and sustained endoscopic remission (ie, endoscopic remission at both Week 24 and 52), defined by a Mayo endoscopic subscore of 0;

- Mayo score and change from baseline in Mayo score over time;

- Corticosteroid-free remission at Week 24 and Week 52 and sustained corticosteroid-free remission (ie, corticosteroid-free remission at both Week 24 and 52) among subjects receiving corticosteroids at baseline.

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

Statistical Methods:

The data sets summarized and analyzed in this study were as follows:

- Full analysis set (FAS): The primary analysis population for efficacy endpoints was the FAS defined as all subjects randomly assigned to either tofacitinib 10 mg BID, tofacitinib 5 mg BID, or placebo.

- Modified full analysis set (mFAS): The mFAS was defined as a subset of FAS including only subjects that received tofacitinib in the induction studies.

- Per protocol analysis set (PPAS): The PPAS was defined as a subset of FAS who had no major protocol violations. The subjects excluded from the PPAS were determined and documented before the study was unblinded.

- Safety analysis set: The safety analysis set consisted of all randomized subjects who received at least 1 dose of study medication.

Efficacy Analyses:

The primary endpoint was remission at Week 52, defined by a Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0. The 2 key secondary efficacy endpoints were mucosal healing at Week 52 and sustained corticosteroid-free remission among subjects in remission at baseline.

Both centrally-read and locally-read endoscopic subscores were used for the derivation of all efficacy endpoints. The primary analyses were based on the efficacy endpoints derived from the centrally-read endoscopic subscores.

In order to control the family-wise Type I error rate at 0.05 level, a sequentially rejective Bonferroni-based iterative multiple test procedure was used for the comparisons between each of the 2 active doses and placebo in the primary endpoint and the 2 key secondary efficacy endpoints.

Analysis of Primary Efficacy Endpoint

The primary endpoint of remission at Week 52 was analyzed in the FAS population using a stratified Cochran-Mantel-Haenszel (CMH) Chi-square test unless cell frequencies were too small (wherein a Fisher's exact test was to be used). The primary analysis was stratified by treatment received in the induction study and status of remission (remission or not) at Study A3921096 baseline. The non-responder imputation (NRI) method was used to handle missing values in summaries and analyses. The difference in the proportion of responders and associated 95% confidence intervals (CIs) were presented for active versus placebo groups using the normal approximation for the difference in binomial proportions. In addition, the primary endpoint analysis was also conducted using the mFAS and PPAS.

Analysis of Key Secondary Efficacy Endpoints

The 2 key secondary endpoints of the study were mucosal healing at Week 52 and sustained corticosteroid-free remission among subjects in remission at baseline of Study A3921096. Both of these binary endpoints were analyzed and summarized using the same methods (if applicable) as those for the primary endpoint. Note, the analysis for sustained corticosteroid free remission among subjects in remission at baseline was only to be stratified by treatment received in the induction study as, by definition of the endpoint, the status of remission (remission or not) at baseline stratification was not applicable.

Analysis of Other Secondary Efficacy Endpoints

For all other secondary endpoints, the summary presentations and analyses were performed on the FAS population. All binary secondary endpoints derived from the Mayo score were descriptively summarized by treatment group using frequency counts and percentages at each visit. Week 24 and Week 52 data and the endpoints derived by the data of both visits were analyzed using the stratified CMH test. For endpoints of remission among subjects with remission at baseline or mucosal healing in subjects with mucosal healing at baseline, the analysis was stratified by treatment received in the induction study only. For all other endpoints the stratification also included status of remission (remission or not) at baseline. For all of these binary secondary endpoints, the NRI method was used to handle missing values in both the summary presentations and analyses.

Descriptive summaries of the continuous Mayo scores were presented by treatment group and each visit for both the observed values and change from baseline. The changes from baseline for Mayo scores at Week 24 and Week 52 were analyzed using a linear mixed-effects model. Treatment assignment in the induction study was included as a baseline stratification factor in the model. The status of remission at baseline was not included as a fixed effect in the analyses for Mayo scores since it was likely to be highly correlated with the baseline value. Missing data were assumed missing at random.

Additional analyses were conducted based on mFAS.

Safety Analysis:

Safety evaluations were summarized and analyzed using the safety analysis set. Missing data for safety endpoints were not imputed and were left as missing. All the safety data were summarized through appropriate data tabulations and descriptive statistics.

RESULTS

Subject Disposition and Demography:

Subject disposition by treatment group is summarized in Table 1. Overall, 593 subjects were randomized to study treatment (FAS). This included 198 subjects randomized to the tofacitinib 5 mg BID group, 197 subjects to the tofacitinib 10 mg BID group, and 198 subjects randomized to the placebo group. Of the 593 randomized subjects, 592 subjects received at least 1 dose of study drug (safety analysis set). Of the 592 subjects included in the safety analysis set, 290 (49.0%) completed the study and 302 (51.0%) discontinued the

study (including 43.9% of subjects in the tofacitinib 5 mg BID group, 35.7% of subjects in the tofacitinib 10 mg BID group, and 73.2% in the placebo group).

Table 1. Subject Disposition by Treatment Group – FAS

	Tofacitinib 5 mg BID n (%)	Tofacitinib 10 mg BID n (%)	Placebo n (%)	Total n (%)
Randomized[a]	198 (100.0)	197 (100.0)	198 (100.0)	593 (100.0)
Treated[b,c]	198	196	198	592
Analyzed for efficacy				
FAS	198 (100.0)	197 (100.0)	198 (100.0)	593 (100.0)
PPAS	183 (92.4)	186 (94.4)	188 (94.9)	557 (93.9)
mFAS	176 (88.9)	173 (87.8)	174 (87.9)	523 (88.2)
Analyzed for safety				
Safety analysis set	198 (100.0)	196 (99.5)	198 (100.0)	592 (99.8)
mFAS	176 (88.9)	173 (87.8)	174 (87.9)	523 (88.2)
AEs	198 (100.0)	196 (99.5)	198 (100.0)	592 (99.8)
Laboratory data[d]	198 (100.0)	195 (99.0)	198 (100.0)	591 (99.7)
Completed[c]	111 (56.1)	126 (64.3)	53 (26.8)	290 (49.0)
Discontinued[c]	87 (43.9)	70 (35.7)[e]	145 (73.2)	302 (51.0)
Primary reason for discontinuation[c]				
Subject died	0	0	0	0
Related to study drug	74 (37.4)	61 (31.1)	134 (67.7)	269 (45.4)
AE	4 (2.0)	8 (4.1)	2 (1.0)	14 (2.4)
Insufficient clinical response[f]	70 (35.4)	53 (27.0)	132 (66.7)	255 (43.1)
Not related to study drug	13 (6.6)	9 (4.6)	11 (5.6)	33 (5.6)
AE	1 (0.5)	1 (0.5)	5 (2.5)	7 (1.2)
No longer willing to participate in study	6 (3.0)	3 (1.5)	5 (2.5)	14 (2.4)
Protocol violation	0	1 (0.5)	0	1 (0.2)
Lost to follow-up	3 (1.5)	2 (1.0)	1 (0.5)	6 (1.0)
Discontinued due to pregnancy	1 (0.5)	1 (0.5)	0	2 (0.3)
Other	2 (1.0)	1 (0.5)	0	3 (0.5)

AE = adverse event; BID = twice a day; FAS = full analysis set; mFAS = modified full analysis set; n = number of subjects meeting prespecified criteria; PPAS = per protocol analysis set; UC = ulcerative collitis.

a. One subject was misrandomized to tofacitinib 5 mg BID (did not achieve clinical response) and was de-randomized after receiving 2 days of study drug. This subject had no reported AEs and was not included in the analysis sets.

b. One subject was randomized to tofacitinib 10 mg BID but withdrew consent and did not receive any doses of study drug.

c. The percentages for completed, discontinued, and primary reason for discontinuation were based on the number of subjects treated (ie, the safety analysis set).

d. Laboratory data consisted of all randomized subjects that have lab data collected at both baseline and 1 of the post-baseline visits. One of the subjects with only baseline labs was not counted.

e. Percentage for discontinued in the tofacitinib 10 mg BID group was based on the safety analysis set (the number of subjects treated).

f. AEs of worsening of UC leading to discontinuation were designated as insufficient clinical response.

A summary of demographic and other baseline characteristics for the FAS is presented in Table 2. Overall, demographic characteristics were similar across treatment groups. For all subjects included in the FAS, there were more male (329/593, 55.5%) than female subjects (264/593, 44.5%). Overall, the mean age of subjects was 42.7 years, (range: 18 to 80 years); the mean weight of subjects was 74.8 kg (range: 31.3 to 154.9 kg), and the mean body mass index was 25.5 kg/m^2 (range: 11.8 to 55.6 kg/m^2).

Table 2. Demographic and Baseline Characteristics by Treatment Group – FAS

	Tofacitinib 5 mg BID (N = 198)	Tofacitinib 10 mg BID (N = 197)	Placebo (N = 198)	Total (N = 593)
Age (years)[a]				
Mean (SD)	41.9 (13.7)	42.9 (14.4)	43.4 (14.0)	42.7 (14.0)
Median	41.0	40.0	42.0	41.0
Range	18-79	18-79	19-80	18-80
<18, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18 to 44, n (%)	114 (57.6)	110 (55.8)	111 (56.1)	335 (56.5)
45 to 64, n (%)	71 (35.9)	70 (35.5)	69 (34.8)	210 (35.4)
≥65, n (%)	13 (6.6)	17 (8.6)	18 (9.1)	48 (8.1)
Gender, n (%)				
Male	103 (52.0)	110 (55.8)	116 (58.6)	329 (55.5)
Female	95 (48.0)	87 (44.2)	82 (41.4)	264 (44.5)
Race, n (%)[b,c]				
White	164 (82.8)	153 (77.7)	155 (78.3)	472 (79.6)
Black	2 (1.0)	0 (0.0)	3 (1.5)	5 (0.8)
Asian	23 (11.6)	25 (12.7)	26 (13.1)	74 (12.5)
Other	5 (2.5)	9 (4.6)	9 (4.5)	23 (3.9)
Unspecified	4 (2.0)	10 (5.1)	5 (2.5)	19 (3.2)
Ethnicity, n (%)[b]				
Hispanic/Latino	5 (2.5)	7 (3.6)	7 (3.5)	19 (3.2)
Not Hispanic/Latino	189 (95.5)	180 (91.4)	186 (93.9)	555 (93.6)
Unspecified	4 (2.0)	10 (5.1)	5 (2.5)	19 (3.2)
Geographic region, n (%)				
N1	198	197	198	593
Europe	113 (57.1)	121 (61.4)	112 (56.6)	346 (58.3)
North America	39 (19.7)	44 (22.3)	45 (22.7)	128 (21.6)
Other[d]	46 (23.2)	32 (16.2)	41 (20.7)	119 (20.1)
Weight (kg)[a]				
Mean (SD)	73.4 (17.8)	74.6 (15.1)	76.2 (16.7)	74.8 (16.6)
Median	71.3	73.2	74.3	73.0
Range	31.3-154.9	39.4-137.1	44.5-134.0	31.3-154.9
BMI (kg/m^2)[e]				
Mean (SD)	25.1 (5.1)	25.5 (4.8)	25.8 (4.9)	25.5 (4.9)
Median	24.5	24.9	24.9	24.7
Range	11.8-49.1	17.0-55.6	17.4-43.5	11.8-55.6

BID = twice a day; BMI = body mass index; FAS = full analysis set; N = number of subjects randomized; n = number of subjects meeting prespecified criteria; N1 = number of subjects in the specified category with non-missing values; SD = standard deviation.

a. Weight was from Week 8 of induction study, while height and age were from screening of induction study.
b. Race/Ethnicity was not collected for French subjects.
c. Racial designation was collected for those subjects whose race was marked as Asian, other, or unspecified.
d. Geographic regions other than Europe and North America included Asia-Pacific, South America, and Africa.
e. BMI was defined as weight/(height × 0.01)^2, with weight in kg, and height in cm.

A summary of selected Study A3921096 baseline clinical characteristics for the FAS is presented in Table 3.

Table 3. Baseline Clinical Characteristics From A3921096 Study – FAS

	Tofacitinib 5 mg BID (N = 198)	Tofacitinib 10 mg BID (N = 197)	Placebo (N = 198)	Total (N = 593)
Treatment assignment in induction study, n (%)				
Placebo	22 (11.1)	24 (12.2)	24 (12.1)	70 (11.8)
Tofacitinib 10 mg and 15 mg	176 (88.9)	173 (87.8)	174 (87.9)	523 (88.2)
Tofacitinib 10 mg	170 (85.9)	167 (84.8)	167 (84.3)	504 (85.0)
Remission at baseline, n (%)				
Yes	65 (32.8)	55 (27.9)	59 (29.8)	179 (30.2)
No	133 (67.2)	142 (72.1)	139 (70.2)	414 (69.8)
Mucosal healing at baseline, n (%)				
Yes	105 (53.0)	89 (45.2)	101 (51.0)	295 (49.7)
No	93 (47.0)	108 (54.8)	97 (49.0)	298 (50.3)
Mayo score, n (%)				
<3	71 (35.9)	64 (32.5)	74 (37.4)	209 (35.2)
≥3	127 (64.1)	133 (67.5)	124 (62.6)	384 (64.8)
Mayo score				
Mean (SD)	3.3 (1.8)	3.4 (1.8)	3.3 (1.8)	3.3 (1.8)
Median	3.0	3.0	3.0	3.0
Range	(0.0-10.0)	(0.0-7.0)	(0.0-8.0)	(0.0-10.0)
Partial Mayo score, n (%)				
<2	89 (44.9)	88 (44.7)	85 (42.9)	262 (44.2)
≥2	109 (55.1)	109 (55.3)	113 (57.1)	331 (55.8)
Partial Mayo score				
Mean (SD)	1.8 (1.3)	1.8 (1.3)	1.8 (1.4)	1.8 (1.3)
Median	2.0	2.0	2.0	2.0
Range	(0.0-7.0)	(0.0-6.0)	(0.0-7.0)	(0.0-7.0)
hsCRP[a]				
Mean (SD)	2.2 (3.8)	4.0 (9.3)	3.3 (6.1)	NA
Median	0.69	0.89	1.00	NA
Min	0.1	0.1	0.1	NA
Max	33.7	74.3	45.0	NA
Baseline CRP (mg/L), n (%)				
≤3	157 (79.3)	147 (74.6)	141 (71.2)	445 (75.0)
>3	41 (20.7)	50 (25.4)	57 (28.8)	148 (25.0)
≤6	181 (91.4)	168 (85.3)	166 (83.8)	515 (86.8)
>6	17 (8.6)	29 (14.7)	32 (16.2)	78 (13.2)

BID = twice a day; CRP = C-reactive protein; FAS = full analysis set; hsCRP = high sensitivity C-reactive protein; N = number of randomized subjects in the total population; n = number of subjects meeting prespecified criteria; NA = not available; SD = standard deviation.
a. Values are for the safety analysis set.

Demographic and baseline clinical characteristics of the mFAS population were consistent with those of the FAS population at baseline. In addition, within the mFAS, these characteristics were similar across treatment groups.

Efficacy Results

Primary Efficacy Endpoint:

Analysis of remission at Week 52 is presented in Table 4 (FAS, NRI), including both centrally-read and locally-read endoscopy. The proportion of subjects in remission at Week 52 (FAS, NRI) was statistically significantly ($p < 0.0001$) greater in both the tofacitinib 5 mg BID group (34.3%) and the tofacitinib 10 mg BID group (40.6%) compared with the placebo group (11.1%). Results based on locally-read endoscopic findings for remission were consistent with centrally-read findings, with a significant difference ($p < 0.0001$) observed for both tofacitinib treatment groups (39.4% in the tofacitinib 5 mg BID group and 47.7% in the tofacitinib 10 mg BID group) compared with placebo (13.1%). These results were supported by various sensitivity analyses, including those based on the mFAS population.

Table 4. Proportion of Subjects in Remission at Week 52 –FAS (NRI)

	Placebo (N = 198)		Tofacitinib 5 mg BID (N = 198)				Tofacitinib 10 mg BID (N = 197)			
					Difference From Placebo				Difference From Placebo	
	N1	n (%)	N1	n (%)	Diff (95% CI)[a]	p-value[b]	N1	n (%)	Diff (95% CI)[a]	p-value[b]
Remission										
Centrally-read	198	22 (11.1)	198	68 (34.3)	23.2 (15.3, 31.2)	<0.0001	197	80 (40.6)	29.5 (21.4, 37.6)	<0.0001
Locally-read	198	26 (13.1)	198	78 (39.4)	26.3 (18.0, 34.5)	<0.0001	197	94 (47.7)	34.6 (26.2, 43.0)	<0.0001

BID = twice a day; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Diff = difference; FAS = full analysis set; N = number of subjects in the analysis set; N1 = number of subjects in each group at Week 52, and used as the denominator in the percentage calculation; n = number of subjects meeting specific criteria; NRI = non-responder imputation.

a. 95% CI was based on the normal approximation for the difference in binomial proportions.

b. P-value was based on CMH Chi-squared test stratified by induction study treatment assignment (tofacitinib, placebo) and remission at baseline (yes, no).

Key Secondary Endpoints:

***Mucosal Healing at Week 52*:** Analysis of mucosal healing at Week 52 is presented in Table 5 (FAS, NRI), including both centrally-read and locally-read endoscopy. The proportion of subjects with mucosal healing at Week 52 (FAS, NRI) was statistically significantly ($p < 0.0001$) greater in both the tofacitinib 5 mg BID group (37.4%) and the tofacitinib 10 mg BID group (45.7%) compared with the placebo group (13.1%). Results based on locally-read endoscopic findings for mucosal healing were consistent with centrally-read findings, with a significant difference ($p < 0.0001$) observed for both tofacitinib treatment groups (44.9% in the tofacitinib 5 mg BID group and 53.8% in the tofacitinib 10 mg BID group) compared with placebo (15.7%). These results were supported by various sensitivity analyses, including those based on the mFAS population.

Table 5. Proportion of Subjects With Mucosal Healing at Week 52 – FAS (NRI)

	Placebo (N = 198)		Tofacitinib 5 mg BID (N = 198)				Tofacitinib 10 mg BID (N = 197)			
					Difference From Placebo				Difference From Placebo	
	N1	n (%)	N1	n (%)	Diff (95% CI)[a]	p-value[b]	N1	n (%)	Diff (95% CI)[a]	p-value[b]
Mucosal Healing										
Centrally-read	198	26 (13.1)	198	74 (37.4)	24.2 (16.0, 32.5)	<0.0001	197	90 (45.7)	32.6 (24.2, 41.0)	<0.0001
Locally-read	198	31 (15.7)	198	89 (44.9)	29.3 (20.7, 37.9)	<0.0001	197	106 (53.8)	38.2 (29.5, 46.8)	<0.0001

BID = twice a day; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Diff = difference; FAS = full analysis set; N = number of subjects in the analysis set; N1 = number of subjects in each group at Week 52, and used as the denominator in the percentage calculation; n = number of subjects meeting specific criteria; NRI = non-responder imputation.

a. 95% CI was based on the normal approximation for the difference in binomial proportions.

b. P-value was based on CMH Chi-squared test stratified by induction study treatment assignment (tofacitinib, placebo) and remission at baseline (yes, no).

***Sustained Corticosteroid-Free Remission Among Subjects in Remission at Baseline*:**
Analysis of sustained corticosteroid-free remission among subjects in remission at baseline is presented in Table 6 (FAS, NRI), including both centrally-read and locally-read endoscopy. The proportion of subjects in sustained corticosteroid-free remission among subjects in remission at baseline (FAS, NRI) was statistically significantly ($p < 0.0001$) greater in both the tofacitinib 5 mg BID group (35.4%) and the tofacitinib 10 mg BID group (47.3%) compared with the placebo group (5.1%). Results based on locally-read endoscopic findings for sustained corticosteroid-free remission among subjects in remission at baseline were consistent with centrally-read findings, with a significant difference ($p < 0.0001$) observed for both tofacitinib treatment groups (47.7% in the tofacitinib 5 mg BID group and 58.2% in the tofacitinib 10 mg BID group) compared with placebo (11.9%). These results were supported by various sensitivity analyses, including those based on the mFAS population.

Table 6. Proportion of Subjects in Sustained Corticosteroid-Free Remission Among Subjects in Remission at Baseline - FAS (NRI)

	Placebo (N = 198)		Tofacitinib 5 mg BID (N = 198)				Tofacitinib 10 mg BID (N = 197)			
					Difference From Placebo				Difference From Placebo	
	N1	n (%)	N1	n (%)	%Diff (95% CI)[a]	p-value[b]	N1	n (%)	Diff (95% CI)[a]	p-value[b]
Centrally-read	59	3 (5.1)	65	23 (35.4)	30.3 (17.4, 43.2)	<0.0001	55	26 (47.3)	42.2 (27.9, 56.5)	<0.0001
Locally-read	59	7 (11.9)	65	31 (47.7)	35.8 (21.1, 50.5)	<0.0001	55	32 (58.2)	46.3 (30.9, 61.7)	<0.0001

BID = twice a day; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Diff = difference; FAS = full analysis set; N = number of subjects in the analysis set; N1 = number of subjects in each group in remission at baseline regardless of corticosteroid use at baseline, and used as the denominator in the percentage calculation; n = number of subjects in sustained corticosteroid-free remission, defined as being in remission and corticosteroid-free at both Week 24 and Week 52; NRI = non-responder imputation.

a. 95% CI was based on the normal approximation for the difference in binomial proportions.

b. P-value was based on CMH Chi-squared test stratified by induction study treatment assignment in the induction study (tofacitinib, placebo).

Other Secondary Endpoints:

Binary Efficacy Endpoints:

The analyses of other secondary binary efficacy endpoints based on centrally-read and locally-read endoscopy are presented for FAS in Table 7 and Table 8, respectively.

***Remission at Week 24 and Sustained Remission*:** A statistically significantly ($p < 0.0001$) greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group were in remission based on centrally-read endoscopic subscores at Week 24 (33.8% and 35.5%, respectively) and sustained remission at both Week 24 and Week 52 (22.2% and 25.4%, respectively) than those in the placebo group (Week 24: 11.1%; sustained: 5.1%). The significant difference between tofacitinib treatment groups and placebo was also observed based on locally-read endoscopic subscores ($p < 0.0001$). For remission at Week 24 and for sustained remission, results for the mFAS were consistent with those of the FAS for both the tofacitinib 5 mg BID and 10 mg BID treatment groups compared with placebo based on centrally-read and locally-read endoscopy.

***Remission at Week 24 and Week 52 and Sustained Remission Among Subjects With Remission at Baseline*:** A statistically significantly ($p < 0.0001$) greater proportion of subjects with remission at baseline in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group were in remission based on centrally-read endoscopic subscores at Week 24 (55.4% and 63.6%, respectively), Week 52 (46.2% and 56.4%, respectively), and sustained remission at both Week 24 and Week 52 (36.9% and 47.3%, respectively) than those in the placebo group (Week 24: 15.3%; Week 52: 10.2%; sustained: 5.1%). Statistically significant difference between treatment groups was also observed based on locally-read endoscopic subscores ($p < 0.0001$). For remission at Week 24 and Week 52 and sustained remission among subjects with remission at baseline, results for the mFAS were consistent with those of the FAS for both the tofacitinib 5 mg BID and 10 mg BID treatment groups compared with placebo based on centrally-read and locally-read endoscopic subscores.

***Mucosal Healing at Week 24 and Sustained Mucosal Healing*:** A statistically significantly ($p < 0.0001$) greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group demonstrated mucosal healing based on centrally-read endoscopic subscores at Week 24 (43.9% and 46.2%, respectively) and sustained mucosal healing at both Week 24 and Week 52 (27.8% and 33.0%, respectively) than those in the placebo group (Week 24: 17.2%; sustained: 6.6%). The significant difference between tofacitinib treatment groups and placebo was also observed based on locally-read endoscopic subscores ($p < 0.0001$). For mucosal healing at Week 24 and for sustained mucosal healing, results for the mFAS were consistent with those of the FAS for both the tofacitinib 5 mg BID and 10 mg BID treatment groups compared with placebo based on centrally-read and locally-read endoscopy.

***Mucosal Healing at Week 24 and Week 52 and Sustained Mucosal Healing Among Subjects With Mucosal Healing at Baseline*:** A statistically significantly ($p < 0.0001$) greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group with mucosal healing at baseline based on centrally-read endoscopic subscores demonstrated mucosal healing at Week 24 (52.4% and 66.3%, respectively), at Week 52 (41.9% and 55.1%, respectively), and sustained mucosal healing (33.3% and 49.4%), than those in the placebo group (Week 24: 21.8%; Week 52: 11.9%; sustained: 8.9%). The significant difference between tofacitinib treatment groups and placebo was also observed based on locally-read endoscopic subscores ($p < 0.0001$). For mucosal healing at Week 24 and Week 52 and sustained mucosal healing among subjects with mucosal healing at baseline, results for the mFAS were consistent with those of the FAS for both the tofacitinib 5 mg BID and 10 mg BID treatment groups compared with placebo based on centrally-read and locally-read endoscopy.

***Corticosteroid-Free Remission at Week 24 and Week 52 Among Subjects in Remission at Baseline*:** A statistically significantly ($p < 0.0001$) greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group were in corticosteroid-free remission based on centrally-read endoscopic subscores at Week 24 (53.8% and 63.6%, respectively) and at Week 52 (44.6% and 56.4%, respectively) than those in the placebo group (Week 24: 15.3%; Week 52: 10.2%). The significant difference between tofacitinib treatment groups and placebo was also observed based on locally-read endoscopic subscores ($p < 0.0001$). For corticosteroid-free remission among subjects in remission at baseline at Week 24 and Week 52, results for the mFAS were consistent with those of the FAS for both the tofacitinib 5 mg BID and 10 mg BID treatment groups compared with placebo based on centrally-read and locally-read endoscopy.

***Clinical Remission at Week 24 and Week 52 and Sustained Clinical Remission*:** A statistically significantly ($p < 0.0001$) greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group were in clinical remission based on centrally-read endoscopic subscores at Week 24 (34.3% and 35.5%, respectively) and Week 52 (34.3% and 41.1%, respectively) and sustained clinical remission (22.2% and 25.9%, respectively), than those in the placebo group (Week 24: 11.1%; Week 52: 11.1%; sustained: 5.1%). The significant difference between tofacitinib treatment groups and placebo was also observed based on locally-read endoscopic subscores ($p < 0.0001$). For clinical remission at Week 24 and Week 52 and for sustained clinical remission, results for the mFAS were consistent with those of the FAS for both the tofacitinib 5 mg BID and 10 mg BID treatment groups compared with placebo based on centrally-read and locally-read endoscopy.

***Clinical Response at Week 24 and Week 52 and Sustained Clinical Response*:** A statistically significantly ($p < 0.0001$) greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group demonstrated clinical response based on centrally-read endoscopic subscores at Week 24 (63.6% and 70.6%, respectively) and at Week 52 (51.5% and 61.9%, respectively) and sustained clinical response (49.0% and 59.4%, respectively) than those in the placebo group (Week 24: 33.3%; Week 52: 20.2%; sustained: 19.2%). The significant difference between tofacitinib treatment groups and placebo was also observed based on locally-read endoscopic subscores ($p < 0.0001$). For clinical response at Week 24 and Week 52 and for sustained clinical response, results for the mFAS were consistent with those of the FAS for both the tofacitinib 5 mg BID and 10 mg BID treatment groups compared with placebo based on centrally-read and locally-read endoscopy.

***Deep Remission at Week 24 and Week 52 and Sustained Deep Remission*:** A statistically significantly greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group were in deep remission based on centrally-read endoscopic subscores at Week 24 (14.1%, [$p = 0.0006$] and 10.7% [$p = 0.0092$], respectively) and at Week 52 (14.6% [$p = 0.0004$] and 15.2% [$p < 0.0001$], respectively) and sustained deep remission (6.1% [$p = 0.0029$] and 3.6%, [$p = 0.0350$], respectively) than those in the placebo group (Week 24: 4.0%; Week 52: 4.0%; sustained: 0.5%). Statistically significant difference between the tofacitinib 5 mg and 10 mg BID groups and placebo was also observed based on locally-read endoscopic subscores (Week 24: $p = 0.0002$ and $p < 0.0001$, respectively; Week 52: both $p < 0.0001$; sustained: $p = 0.0005$ and $p < 0.0001$, respectively).

***Symptomatic Remission at Week 24 and Week 52 and Sustained Symptomatic Remission*:** A statistically significantly ($p < 0.0001$) greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group were in symptomatic remission based on centrally-read endoscopic subscores at Week 24 (23.7% and 21.8%, respectively) and Week 52 (22.7% and 26.9%, respectively), and sustained symptomatic remission (13.6% and 15.7%, respectively) than those in the placebo group (Week 24: 6.6%; Week 52: 7.1%; sustained: 2.5%). Statistically significant difference between the tofacitinib 5 mg and 10 mg BID groups and placebo was also observed based on locally-read endoscopic subscores (Week 24, Week 52, and sustained: all $p < 0.0001$).

***Endoscopic Remission at Week 24 and Week 52 and Sustained Endoscopic Remission*:** A statistically significantly greater proportion of subjects in the FAS in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group were in endoscopic remission based on centrally-read endoscopic subscores at Week 24 (16.2% [$p < 0.0001$] and 12.2% [$p = 0.0021$], respectively) and Week 52 (14.6% [$p = 0.0004$] and 16.8% [$p < 0.0001$], respectively) and sustained endoscopic remission (6.1% [$p = 0.0029$] and 5.1% [$p = 0.0064$], respectively) than those in the placebo group (Week 24: 4.0%; Week 52: 4.0%; sustained: 0.5%). Statistically significant difference between tofacitinib 5 mg and 10 mg BID groups and placebo was also observed based on locally-read endoscopic subscores (Week 24: $p = 0.0001$ and $p < 0.0001$, respectively; Week 52: both $p < 0.0001$; sustained: $p = 0.0005$ and $p < 0.0001$, respectively).

***Corticosteroid-Free Remission at Week 24 and Week 52 and Sustained Corticosteroid-Free Remission Among Subjects Receiving Corticosteroids at Baseline*:** A statistically significantly greater proportion of subjects in the FAS receiving corticosteroids at baseline in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group were in corticosteroid-free remission based on centrally-read endoscopic subscores at Week 24 (23.8% [p = 0.0074] and 24.1% [p = 0.0103], respectively) and Week 52 (27.7% [p = 0.0018] and 27.6% [p = 0.0029], respectively) and sustained (12.9% [p = 0.0419] and 16.1% [p = 0.0121], respectively) than those in the placebo group (Week 24: 10.9%; Week 52: 10.9%; sustained: 5.0%). Statistically significant difference between tofacitinib 5 mg and 10 mg BID groups and placebo was also observed based on locally-read endoscopic subscores (Week 24: p = 0.0016 and p = 0.0062, respectively; Week 52: p = 0.0010 and p = 0.0026, respectively; sustained: p = 0.0294 and p = 0.0485, respectively).

Table 7. Summary of Binary Efficacy Endpoints – FAS (NRI, Centrally-Read)

	Placebo		Tofacitinib 5 mg BID				Tofacitinib 10 mg BID			
					Difference From Placebo				Difference From Placebo	
	N	n (%)	N	n (%)	%Diff (95% CI)	p-value[a]	N	n (%)	%Diff (95% CI)	p-value[a]
Remission										
Baseline	198	59 (29.8)	198	65 (32.8)			197	55 (27.9)		
Week 24	198	22 (11.1)	198	67 (33.8)	22.7 (14.8, 30.6)	<0.0001	197	70 (35.5)	24.4 (16.4, 32.4)	<0.0001
Week 52	198	22 (11.1)	198	68 (34.3)	23.2 (15.3, 31.2)	<0.0001	197	80 (40.6)	29.5 (21.4, 37.6)	<0.0001
Sustained (Weeks 24 and 52)	198	10 (5.1)	198	44 (22.2)	17.2 (10.6, 23.7)	<0.0001	197	50 (25.4)	20.3 (13.5, 27.1)	<0.0001
Remission among subjects in remission at baseline[b]										
Baseline	59	59 (100)	65	65 (100)			55	55 (100)		
Week 24	59	9 (15.3)	65	36 (55.4)	40.1 (25.0, 55.3)	<0.0001	55	35 (63.6)	48.4 (32.7, 64.1)	<0.0001
Week 52	59	6 (10.2)	65	30 (46.2)	36.0 (21.6, 50.3)	<0.0001	55	31 (56.4)	46.2 (31.0, 61.4)	<0.0001
Sustained (Weeks 24 and 52)	59	3 (5.1)	65	24 (36.9)	31.8 (18.8, 44.8)	<0.0001	55	26 (47.3)	42.2 (27.9, 56.5)	<0.0001
Mucosal healing										
Baseline	198	101 (51.0)	198	105 (53.0)			197	89 (45.2)		
Week 24	198	34 (17.2)	198	87 (43.9)	26.8 (18.1, 35.5)	<0.0001	197	91 (46.2)	29.0 (20.3, 37.7)	<0.0001
Week 52	198	26 (13.1)	198	74 (37.4)	24.2 (16.0, 32.5)	<0.0001	197	90 (45.7)	32.6 (24.2, 41.0)	<0.0001
Sustained (Weeks 24 and 52)	198	13 (6.6)	198	55 (27.8)	21.2 (14.1, 28.3)	<0.0001	197	65 (33.0)	26.4 (19.0, 33.8)	<0.0001
Mucosal healing among subjects with mucosal healing at baseline[b]										
Baseline	101	101 (100)	105	105 (100)			89	89 (100)		
Week 24	101	22 (21.8)	105	55 (52.4)	30.6 (18.1, 43.1)	<0.0001	89	59 (66.3)	44.5 (31.8, 57.2)	<0.0001
Week 52	101	12 (11.9)	105	44 (41.9)	30.0 (18.7, 41.4)	<0.0001	89	49 (55.1)	43.2 (31.1, 55.3)	<0.0001
Sustained (Weeks 24 and 52)	101	9 (8.9)	105	35 (33.3)	24.4 (13.8, 35.0)	<0.0001	89	44 (49.4)	40.5 (28.7, 52.3)	<0.0001
Corticosteroid-free remission among subjects in remission at baseline[b]										
Week 24	59	9 (15.3)	65	35 (53.8)	38.6 (23.4, 53.8)	<0.0001	55	35 (63.6)	48.4 (32.7, 64.1)	<0.0001
Week 52	59	6 (10.2)	65	29 (44.6)	34.4 (20.1, 48.8)	<0.0001	55	31 (56.4)	46.2 (31.0, 61.4)	<0.0001
Sustained (Weeks 24 and 52)	59	3 (5.1)	65	23 (35.4)	30.3 (17.4, 43.2)	<0.0001	55	26 (47.3)	42.2 (27.9, 56.5)	<0.0001
Clinical remission										
Baseline	198	60 (30.3)	198	65 (32.8)			197	56 (28.4)		
Week 24	198	22 (11.1)	198	68 (34.3)	23.2 (15.3, 31.2)	<0.0001	197	70 (35.5)	24.4 (16.4, 32.4)	<0.0001
Week 52	198	22 (11.1)	198	68 (34.3)	23.2 (15.3, 31.2)	<0.0001	197	81 (41.1)	30.0 (21.9, 38.2)	<0.0001
Sustained (Weeks 24 and 52)	198	10 (5.1)	198	44 (22.2)	17.2 (10.6, 23.7)	<0.0001	197	51 (25.9)	20.8 (14.0, 27.7)	<0.0001

Table 7. Summary of Binary Efficacy Endpoints – FAS (NRI, Centrally-Read)

	Placebo		Tofacitinib 5 mg BID				Tofacitinib 10 mg BID			
					Difference From Placebo				Difference From Placebo	
	N	n (%)	N	n (%)	%Diff (95% CI)	p-value[a]	N	n (%)	%Diff (95% CI)	p-value[a]
Clinical response										
Baseline	198	195 (98.5)	198	193 (97.5)			197	195 (99.0)		
Week 24	198	66 (33.3)	198	126 (63.6)	30.3 (20.9, 39.7)	<0.0001	197	139 (70.6)	37.2 (28.1, 46.4)	<0.0001
Week 52	198	40 (20.2)	198	102 (51.5)	31.3 (22.4, 40.2)	<0.0001	197	122 (61.9)	41.7 (32.9, 50.5)	<0.0001
Sustained (Weeks 24 and 52)	198	38 (19.2)	198	97 (49.0)	29.8 (20.9, 38.7)	<0.0001	197	117 (59.4)	40.2 (31.4, 49.0)	<0.0001
Deep remission										
Baseline	198	23 (11.6)	198	18 (9.1)			197	16 (8.1)		
Week 24	198	8 (4.0)	198	28 (14.1)	10.1 (4.5, 15.7)	0.0006	197	21 (10.7)	6.6 (1.5, 11.7)	0.0092
Week 52	198	8 (4.0)	198	29 (14.6)	10.6 (5.0, 16.2)	0.0004	197	30 (15.2)	11.2 (5.5, 16.9)	<0.0001
Sustained (Weeks 24 and 52)	198	1 (0.5)	198	12 (6.1)	5.6 (2.1, 9.0)	0.0029	197	7 (3.6)	3.0 (0.3, 5.8)	0.0350
Symptomatic remission										
Baseline	198	38 (19.2)	198	43 (21.7)			197	35 (17.8)		
Week 24	198	13 (6.6)	198	47 (23.7)	17.2 (10.3, 24.0)	<0.0001	197	43 (21.8)	15.3 (8.5, 22.0)	<0.0001
Week 52	198	14 (7.1)	198	45 (22.7)	15.7 (8.8, 22.5)	<0.0001	197	53 (26.9)	19.8 (12.7, 27.0)	<0.0001
Sustained (Weeks 24 and 52)	198	5 (2.5)	198	27 (13.6)	11.1 (5.9, 16.4)	<0.0001	197	31 (15.7)	13.2 (7.7, 18.7)	<0.0001
Endoscopic remission										
Baseline	198	26 (13.1)	198	22 (11.1)			197	20 (10.2)		
Week 24	198	8 (4.0)	198	32 (16.2)	12.1 (6.3, 17.9)	<0.0001	197	24 (12.2)	8.1 (2.8, 13.5)	0.0021
Week 52	198	8 (4.0)	198	29 (14.6)	10.6 (5.0, 16.2)	0.0004	197	33 (16.8)	12.7 (6.8, 18.6)	<0.0001
Sustained (Weeks 24 and 52)	198	1 (0.5)	198	12 (6.1)	5.6 (2.1, 9.0)	0.0029	197	10 (5.1)	4.6 (1.4, 7.8)	0.0064
Corticosteroid-free remission among subjects receiving corticosteroids at baseline										
Week 24	101	11 (10.9)	101	24 (23.8)	12.9 (2.6, 23.2)	0.0074	87	21 (24.1)	13.2 (2.4, 24.1)	0.0103
Week 52	101	11 (10.9)	101	28 (27.7)	16.8 (6.2, 27.5)	0.0018	87	24 (27.6)	16.7 (5.5, 27.9)	0.0029
Sustained (Weeks 24 and 52)	101	5 (5.0)	101	13 (12.9)	7.9 (0.1, 15.7)	0.0419	87	14 (16.1)	11.1 (2.3, 19.9)	0.0121

95% CI was based on the normal approximation for the difference in binomial proportions.
BID = twice a day; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Diff = difference; FAS = full analysis set; N = number of subjects in the analysis set; n = number of subjects meeting endpoint criteria; NRI = non-responder imputation.
a. P-value was based on CMH Chi-squared test stratified by treatment assignment in the induction study (tofacitinib, placebo) and remission at baseline (yes, no), unless specified otherwise.
b. P-value was based on CMH Chi-squared test stratified by treatment assignment in the induction study (tofacitinib, placebo).

Table 8. Summary of Binary Efficacy Endpoints – FAS (NRI, Locally-Read)

	Placebo		Tofacitinib 5 mg BID				Tofacitinib 10 mg BID			
					Difference From Placebo				Difference From Placebo	
	N	n (%)	N	n (%)	%Diff (95% CI)	p-value[a]	N	n (%)	%Diff (95% CI)	p-value[a]
Remission										
Baseline	198	80 (40.4)	198	75 (37.9)			197	74 (37.6)		
Week 24	198	35 (17.7)	198	87 (43.9)	26.3 (17.5, 35.0)	<0.0001	197	91 (46.2)	28.5 (19.8, 37.3)	<0.0001
Week 52	198	26 (13.1)	198	78 (39.4)	26.3 (18.0, 34.5)	<0.0001	197	94 (47.7)	34.6 (26.2, 43.0)	<0.0001
Sustained (Weeks 24 and 52)	198	19 (9.6)	198	62 (31.3)	21.7 (14.1, 29.4)	<0.0001	197	73 (37.1)	27.5 (19.6, 35.4)	<0.0001
Remission among subjects in remission at baseline[b]										
Baseline	59	56 (94.9)	65	57 (87.7)			55	50 (90.9)		
Week 24	59	15 (25.4)	65	44 (67.7)	42.3 (26.4, 58.2)	<0.0001	55	39 (70.9)	45.5 (29.1, 61.8)	<0.0001
Week 52	59	7 (11.9)	65	33 (50.8)	38.9 (24.2, 53.6)	<0.0001	55	36 (65.5)	53.6 (38.6, 68.6)	<0.0001
Sustained (Weeks 24 and 52)	59	7 (11.9)	65	32 (49.2)	37.4 (22.7, 52.1)	<0.0001	55	32 (58.2)	46.3 (30.9, 61.7)	<0.0001
Mucosal healing										
Baseline	198	129 (65.2)	198	137 (69.2)			197	117 (59.4)		
Week 24	198	52 (26.3)	198	114 (57.6)	31.3 (22.1, 40.5)	<0.0001	197	117 (59.4)	33.1 (23.9, 42.3)	<0.0001
Week 52	198	31 (15.7)	198	89 (44.9)	29.3 (20.7, 37.9)	<0.0001	197	106 (53.8)	38.2 (29.5, 46.8)	<0.0001
Sustained (Weeks 24 and 52)	198	25 (12.6)	198	82 (41.4)	28.8 (20.5, 37.1)	<0.0001	197	98 (49.7)	37.1 (28.7, 45.5)	<0.0001
Mucosal healing among subjects with mucosal healing at baseline[b]										
Baseline	101	95 (94.1)	105	96 (91.4)			89	83 (93.3)		
Week 24	101	33 (32.7)	105	71 (67.6)	34.9 (22.1, 47.7)	<0.0001	89	62 (69.7)	37.0 (23.8, 50.2)	<0.0001
Week 52	101	14 (13.9)	105	48 (45.7)	31.9 (20.2, 43.5)	<0.0001	89	56 (62.9)	49.1 (37.0, 61.1)	<0.0001
Sustained (Weeks 24 and 52)	101	13 (12.9)	105	48 (45.7)	32.8 (21.3, 44.4)	<0.0001	89	53 (59.6)	46.7 (34.6, 58.8)	<0.0001
Corticosteroid-free remission among subjects in remission at baseline[b]										
Week 24	59	15 (25.4)	65	42 (64.6)	39.2 (23.1, 55.3)	<0.0001	55	39 (70.9)	45.5 (29.1, 61.8)	<0.0001
Week 52	59	7 (11.9)	65	32 (49.2)	37.4 (22.7, 52.1)	<0.0001	55	36 (65.5)	53.6 (38.6, 68.6)	<0.0001
Sustained (Weeks 24 and 52)	59	7 (11.9)	65	31 (47.7)	35.8 (21.1, 50.5)	<0.0001	55	32 (58.2)	46.3 (30.9, 61.7)	<0.0001
Clinical response										
Baseline	198	194 (98.0)	198	194 (98.0)			197	188 (95.4)		
Week 24	198	70 (35.4)	198	129 (65.2)	29.8 (20.4, 39.2)	<0.0001	197	140 (71.1)	35.7 (26.5, 44.9)	<0.0001
Week 52	198	41 (20.7)	198	101 (51.0)	30.3 (21.3, 39.3)	<0.0001	197	121 (61.4)	40.7 (31.9, 49.5)	<0.0001
Sustained (Weeks 24 and 52)	198	39 (19.7)	198	97 (49.0)	29.3 (20.4, 38.2)	<0.0001	197	118 (59.9)	40.2 (31.4, 49.0)	<0.0001

Table 8. Summary of Binary Efficacy Endpoints – FAS (NRI, Locally-Read)

	Placebo		Tofacitinib 5 mg BID				Tofacitinib 10 mg BID			
					Difference From Placebo				Difference From Placebo	
	N	n (%)	N	n (%)	%Diff (95% CI)	p-value[a]	N	n (%)	%Diff (95% CI)	p-value[a]
Clinical remission										
Baseline	198	81 (40.9)	198	75 (37.9)			197	75 (38.1)		
Week 24	198	35 (17.7)	198	88 (44.4)	26.8 (18.0, 35.5)	<0.0001	197	92 (46.7)	29.0 (20.3, 37.8)	<0.0001
Week 52	198	26 (13.1)	198	79 (39.9)	26.8 (18.5, 35.1)	<0.0001	197	95 (48.2)	35.1 (26.7, 43.5)	<0.0001
Sustained (Weeks 24 and 52)	198	19 (9.6)	198	62 (31.3)	21.7 (14.1, 29.4)	<0.0001	197	75 (38.1)	28.5 (20.6, 36.4)	<0.0001
Deep Remission										
Baseline	198	34 (17.2)	198	28 (14.1)			197	27 (13.7)		
Week 24	198	19 (9.6)	198	47 (23.7)	14.1 (6.9, 21.3)	0.0002	197	52 (26.4)	16.8 (9.4, 24.2)	<0.0001
Week 52	198	10 (5.1)	198	43 (21.7)	16.7 (10.2, 23.2)	<0.0001	197	57 (28.9)	23.9 (16.9, 30.9)	<0.0001
Sustained (Weeks 24 and 52)	198	7 (3.5)	198	27 (13.6)	10.1 (4.7, 15.5)	0.0005	197	32 (16.2)	12.7 (7.0, 18.5)	<0.0001
Symptomatic Remission										
Baseline	198	50 (25.3)	198	50 (25.3)			197	47 (23.9)		
Week 24	198	23 (11.6)	198	60 (30.3)	18.7 (10.9, 26.5)	<0.0001	197	55 (27.9)	16.3 (8.6, 24.0)	<0.0001
Week 52	198	18 (9.1)	198	55 (27.8)	18.7 (11.3, 26.1)	<0.0001	197	61 (31.0)	21.9 (14.3, 29.5)	<0.0001
Sustained (Weeks 24 and 52)	198	10 (5.1)	198	39 (19.7)	14.6 (8.3, 21.0)	<0.0001	197	44 (22.3)	17.3 (10.7, 23.9)	<0.0001
Endoscopic Remission										
Baseline	198	38 (19.2)	198	31 (15.7)			197	30 (15.2)		
Week 24	198	21 (10.6)	198	51 (25.8)	15.2 (7.7, 22.6)	0.0001	197	59 (29.9)	19.3 (11.6, 27.0)	<0.0001
Week 52	198	11 (5.6)	198	44 (22.2)	16.7 (10.1, 23.3)	<0.0001	197	58 (29.4)	23.9 (16.8, 31.0)	<0.0001
Sustained (Weeks 24 and 52)	198	7 (3.5)	198	27 (13.6)	10.1 (4.7, 15.5)	0.0005	197	38 (19.3)	15.8 (9.7, 21.8)	<0.0001
Corticosteroid-free remission among subjects receiving steroids at baseline										
Week 24	101	16 (15.8)	101	34 (33.7)	17.8 (6.2, 29.5)	0.0016	87	27 (31.0)	15.2 (3.1, 27.2)	0.0062
Week 52	101	14 (13.9)	101	33 (32.7)	18.8 (7.5, 30.2)	0.0010	87	27 (31.0)	17.2 (5.3, 29.0)	0.0026
Sustained (Weeks 24 and 52)	101	12 (11.9)	101	23 (22.8)	10.9 (0.6, 21.2)	0.0294	87	18 (20.7)	8.8 (-1.8, 19.4)	0.0485

95% CI was based on the normal approximation for the difference in binomial proportions.
BID = twice a day; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Diff = difference; FAS = full analysis set; N = number of subjects in the analysis set; n = number of subjects meeting endpoint criteria; NRI = non-responder imputation.
a. P-value was based on CMH Chi-squared test stratified by treatment assignment in the induction study (tofacitinib, placebo) and remission at baseline (yes, no), unless specified otherwise.
b. P-value was based on CMH Chi-squared test stratified by treatment assignment in the induction study (tofacitinib, placebo).

Change in Mayo Score Over Time:

The mean Mayo score at baseline was similar across treatment groups (3.3, 3.4, and 3.3, in the tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo groups, respectively).

The analysis of change from baseline for Mayo score using the linear mixed-effects model (FAS, observed cases) is presented in Table 9. At Week 24, both the tofacitinib 5 mg BID and tofacitinib 10 mg BID groups demonstrated significant treatment effects in change from baseline in Mayo score compared with placebo, with adjusted mean differences from placebo of -2.6 (95% CI: -3.2, -1.9; p <0.0001), and -2.8 (95% CI: -3.5, -2.2; p <0.0001), respectively. Similarly, at Week 52, both the tofacitinib 5 mg BID and 10 mg BID groups demonstrated significant treatment effects in change from baseline in Mayo score compared with placebo, with adjusted mean differences from placebo of -2.6 (95% CI: -3.4, -1.7; p <0.0001), and -3.3 (95% CI: -4.1, -2.5; p <0.0001), respectively.

Table 9. Analysis of Change From Baseline for Mayo Score Using the Linear Mixed-Effects Model – FAS (Observed Cases)

	Placebo		Tofacitinib 5 mg BID				Tofacitinib 10 mg BID			
					Difference From Placebo				Difference From Placebo	
	N	Adjusted Mean (SE)	N	Adjusted Mean	Diff (95% CI)	p-value	N	Adjusted Mean	Diff (95% CI)	p-value
Mayo Score										
Week 24	181	2.9 (0.3)	179	0.3 (0.3)	-2.6 (-3.2, -1.9)	<0.0001	186	0.0 (0.3)	-2.8 (-3.5, -2.2)	<0.0001
Week 52	68	2.9 (0.4)	129	0.4 (0.3)	-2.6 (-3.4, -1.7)	<0.0001	137	-0.4 (0.3)	-3.3 (-4.1, -2.5)	<0.0001

Adjusted Means and p-value were derived from the analysis of linear mixed effect model: change from baseline = treatment + baseline partial mayo score + induction treatment + week + treatment*week with subject as a random effect.
For Mayo score, data on early termination subjects from Week 4, 8, or 16 windowed visits were treated as Week 24 windowed visit data, and data on early termination subjects from Week 32 or 40 windowed visits were treated as Week 52 windowed visit data.
BID = twice a day; CI = confidence interval; Diff = difference; FAS = full analysis set; N = number of subjects with non-missing data; SE = standard error.

Safety Results:

All-Causality Treatment-Emergent Non-Serious Adverse Events

The incidence (>5% of subjects) of all-causality non-serious treatment-emergent adverse events (TEAEs) was similar for subjects treated in tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo groups (Table 10). Colitis ulcerative was the most frequent non-serious AE by preferred term (PT) occurring in tofacitinib 5 mg BID (17.68%), tofacitinib 10 mg BID (14.80%), and placebo groups (32.32%).

Table 10. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in >5% of Subjects

	Tofacitinib 5 mg BID n (%)	Tofacitinib 10 mg BID n (%)	Placebo n (%)
Number (%) of subjects			
Evaluable for AEs	198	196	198
With AEs	87 (43.94)	107 (54.59)	108 (54.55)
Number (%) of subjects with AEs by: SOCs and MedDRA PTs			
Gastrointestinal Disorders	39 (19.70)	36 (18.37)	72 (36.36)
Abdominal pain	5 (2.53)	7 (3.57)	11 (5.56)
Colitis ulcerative	35 (17.68)	29 (14.80)	64 (32.32)
General Disorders and Administration Site Conditions	8 (4.04)	4 (2.04)	11 (5.56)
Fatigue	8 (4.04)	4 (2.04)	11 (5.56)
Infections and Infestations	32 (16.16)	46 (23.47)	18 (9.09)
Herpes zoster	2 (1.01)	10 (5.10)	1 (0.51)
Nasopharyngitis	19 (9.60)	27 (13.78)	11 (5.56)
Upper respiratory tract infection	13 (6.57)	12 (6.12)	7 (3.54)
Investigations	6 (3.03)	13 (6.63)	4 (2.02)
Blood creatine phosphokinase increased	6 (3.03)	13 (6.63)	4 (2.02)
Metabolism and Nutrition Disorders	4 (2.02)	11 (5.61)	2 (1.01)
Hypercholesterolaemia	4 (2.02)	11 (5.61)	2 (1.01)
Musculoskeletal and Connective Tissue Disorders	17 (8.59)	17 (8.67)	19 (9.60)
Arthralgia	17 (8.59)	17 (8.67)	19 (9.60)
Nervous System Disorders	17 (8.59)	6 (3.06)	12 (6.06)
Headache	17 (8.59)	6 (3.06)	12 (6.06)
Skin and Subcutaneous Tissue Disorders	6 (3.03)	11 (5.61)	8 (4.04)
Rash	6 (3.03)	11 (5.61)	8 (4.04)

Subjects are only counted once per treatment for each row.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
Includes events from study database, even those that occur after last dose of study drug.
MedDRA (v19.0) coding dictionary applied.
AE = adverse events; BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects meeting prespecified criteria; PT = preferred term; SOC = system organ class.

All-Causality Treatment-Emergent Serious Adverse Events

The incidence of all-causality serious TEAEs were reported in 5.05% and 5.61% of subjects in the tofacitinib 5 mg BID group and 10 mg BID group, respectively, compared with 6.57% for subjects treated with placebo Table 11. The most frequent serious adverse event (SAE) was colitis ulcerative (tofacitinib 5 mg BID: 2 subjects [1.01%]; tofacitinib 10 mg BID: 1 subject [0.51%]; placebo: 8 subjects [4.04%]). For all PTs, SAEs occurred in <2% of subjects in either tofacitinib treatment group.

Table 11. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Tofacitinib 5 mg BID n (%)	Tofacitinib 10 mg BID n (%)	Placebo n (%)
Number (%) of Subjects			
Evaluable for AEs	198	196	198
With AEs	10 (5.05)	11 (5.61)	13 (6.57)
Number (%) of Subjects with AEs by: SOCs and MedDRA PTs			
Cardiac Disorders	1 (0.51)	0	0
Myocardial infarction	1 (0.51)	0	0
Gastrointestinal Disorders	3 (1.52)	3 (1.53)	9 (4.55)
Abdominal pain	0	1 (0.51)	0
Colitis ulcerative	2 (1.01)	1 (0.51)	8 (4.04)
Diarrhoea	0	1 (0.51)	0
Gastrointestinal haemorrhage	1 (0.51)	0	0
Pancreatitis	0	0	1 (0.51)
General Disorders and Administration Site Conditions	1 (0.51)	0	1 (0.51)
Chest pain	1 (0.51)	0	0
Malaise	0	0	1 (0.51)
Hepatobiliary Disorders	0	1 (0.51)	0
Cholecystitis acute	0	1 (0.51)	0
Infections and Infestations	2 (1.01)	1 (0.51)	2 (1.01)
Bacterial diarrhoea	0	1 (0.51)	0
Diverticulitis	0	0	1 (0.51)
Peritonsillar abscess	1 (0.51)	0	0
Subcutaneous abscess	0	0	1 (0.51)
Urinary tract infection	1 (0.51)	0	0
Injury, Poisoning and Procedural Complications	2 (1.01)	1 (0.51)	0
Lower limb fracture	1 (0.51)	0	0
Lumbar vertebral fracture	1 (0.51)	0	0
Spinal compression fracture	0	1 (0.51)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.51)	1 (0.51)	0
Osteoarthritis	0	1 (0.51)	0
Spondylolisthesis	1 (0.51)	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	1 (0.51)	1 (0.51)

Table 11. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Tofacitinib 5 mg BID n (%)	Tofacitinib 10 mg BID n (%)	Placebo n (%)
Bowen's disease	0	1 (0.51)	0
Invasive ductal breast carcinoma	0	0	1 (0.51)
Squamous cell carcinoma of skin	0	1 (0.51)	0
Nervous System Disorders	0	3 (1.53)	0
Generalised tonic-clonic seizure	0	1 (0.51)	0
Haemorrhagic stroke	0	1 (0.51)	0
Sciatica	0	1 (0.51)	0
Seizure	0	1 (0.51)	0
Pregnancy, Puerperium and Perinatal Conditions	1 (1.05)	0	0
Abortion spontaneous	1 (1.05)	0	0
Skin And Subcutaneous Tissue Disorders	0	2 (1.02)	0
Dermatitis acneiform	0	1 (0.51)	0
Rash maculo-papular	0	1 (0.51)	0
Vascular Disorders	0	0	1 (0.51)
Embolism venous	0	0	1 (0.51)

Subjects are only counted once per treatment for each row.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
Includes events from study database, even those that occur after last dose of study drug.
MedDRA (v19.0) coding dictionary applied.
AE = adverse events; BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects meeting prespecified criteria; PT = preferred term; SOC = system organ class.

Withdrawals of Subjects from the Study

Discontinuations from the study are listed in Table 12. A greater proportion of subjects in the placebo group discontinued from the study compared with the tofacitinib 5 mg and 10 mg BID groups.

Table 12. Discontinuations from Study

	Tofacitinib 5 mg BID n (%)	Tofacitinib 10 mg BID n (%)	Placebo n (%)
Number (%) of subjects	198	196	198
Completed	111 (56.1)	126 (64.3)	53 (26.8)
Discontinuations	87 (43.9)	70 (35.7)	145 (73.2)
Related to study drug	74 (37.4)	61 (31.1)	134 (67.7)
AE	4 (2.0)	8 (4.1)	2 (1.0)
Insufficient clinical response	70 (35.4)	53 (27.0)	132 (66.7)
Not related to study drug	13 (6.6)	9 (4.6)	11 (5.6)
AE	1 (0.5)	1 (0.5)	5 (2.5)
Lost to follow-up	3 (1.5)	2 (1.0)	1 (0.5)
No longer willing to participate in study	6 (3.0)	3 (1.5)	5 (2.5)
Other	2 (1.0)	1 (0.5)	0
Protocol violation	0	1 (0.5)	0
Withdrawn due to pregnancy	1 (0.5)	1 (0.5)	0

AE = adverse event; BID = twice daily; n = number of subjects meeting prespecified criteria.

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

CONCLUSIONS:

- This Phase 3 study demonstrated efficacy of tofacitinib 5 mg BID and 10 mg BID as maintenance therapy for UC, with statistically significantly greater treatment effects for both treatment groups versus placebo for remission at Week 52 (primary endpoint), mucosal healing at Week 52, and sustained corticosteroid-free remission among subjects in remission at baseline (key secondary endpoints).

- The efficacy of tofacitinib 5 mg BID and 10 mg BID was supported by all other secondary efficacy endpoints, various analysis populations, sensitivity analyses, and locally-read endoscopic findings.

- The observed treatment effect was higher in the tofacitinib 10 mg BID group than the tofacitinib 5 mg BID group in the overall population for primary and key secondary endpoints.

- Tofacitinib 5 mg BID and 10 mg BID also demonstrated significantly higher proportions of subjects with clinical remission and clinical response compared with placebo.

- For all efficacy endpoints, the efficacy results based on the mFAS were consistent with the results based on the FAS.

- In this 52-week maintenance study, both the tofacitinib 5 mg BID and 10 mg BID doses appeared to be well tolerated. Most frequent TEAEs were colitis ulcerative (higher incidence in the placebo group) and nasopharyngitis (higher incidence in the tofacitinib groups).

- SAEs occurred at similar frequencies across treatment groups, and there were no deaths reported during this study.