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

PROTOCOL NO.: A3921043

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Safety and Efficacy of CP-690,550 in Subjects With Moderate to Severe Crohn's Disease

Study Center(s): A total of 48 centers took part in the study and randomized subjects; 3 in Belgium, 2 in Czech Republic, 3 in France, 6 in Hungary, 2 in Italy, 1 in the Netherlands, 1 in Poland, 2 in Slovakia, 4 in South Africa, 2 in Spain, 1 in the United Kingdom, and 21 in the United States.

Study Initiation and Final Completion Dates: 09 January 2008 to 29 October 2009

Phase of Development: Phase 2

Study Objective(s):

Primary Objective:

- The primary objective was to demonstrate efficacy of tofacitinib in inducing a clinical response in subjects with moderate-to-severe Crohn's disease.

Secondary Objectives:

- To evaluate the safety and tolerability of oral tofacitinib in subjects with active Crohn's disease.
- To further evaluate the efficacy of tofacitinib in inducing clinical remission and to characterize the time to response and remission in subjects with active Crohn's disease.
- To characterize the pharmacokinetics (PK) of tofacitinib in subjects with active Crohn's disease.
- To evaluate the effect of treatment of tofacitinib on Quality of Life in subjects with active Crohn's disease.
- To demonstrate the change from Baseline in the following biomarkers: C-reactive protein (CRP) and fecal calprotectin.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Subjects were screened within 3 weeks of the baseline visit. From the screening visit (Visit 1) throughout the study, all subjects completed a daily diary of their symptoms. Data from the last week prior to randomization were used to assess their baseline symptoms and calculate baseline Crohn's Disease Activity Index (CDAI) score. At the Baseline Visit, subjects with moderate-to-severe Crohn's disease were equally randomized into 1 of the 4 treatment arms of tofacitinib: 15 mg twice daily (BID), 5 mg BID, 1 mg BID, or placebo BID. Subjects were prospectively stratified according to the disease activity at Baseline (CDAI score <330 points vs a score ≥330 points). The double-blind treatment period lasted 4 weeks. All subjects were followed for 4 weeks after completion of study treatment or early withdrawal from the study.

This study included an additional research component involving collection of biological samples for deidentified genetic analysis. Subjects participated in this trial even if they chose not to participate in the pharmacogenomics component.

The schedule of study activities is presented in Table 1.

Table 1 Schedule of Activities

Protocol Activity	Screen	Baseline	Week Visit		End of Treatment	Follow-Up
	Week -3	Day 1	Week 1	Week 2	Week 4	Week 8
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Study Day	**-21 to -7 Days**	**1**	**+/- 2 Days**	**+/- 2 Days**	**+/- 2 Days**	**+/- 1 Week**
Informed consent	x					
Medical history	x					
Complete physical examination including weight	x	x			x	x
Targeted physical examination including weight			x	x		
Vital signs including temperature	x	x	x	x	x	x
Laboratory						
Hematology	x	x	x	x	x	x
Blood chemistry	x	x	x	x	x	x
Urinalysis	x	x	x	x	x	x
Stool culture	x					
Lipid profile (fasting)		x			x	
HBsAg, HCV Ab	x					
FSH	x[a]					
β-HCG (blood)	x[b]					
Serum immunoglobulin (Ig)G, IgM, IgA		x			x	
Urine pregnancy test		x[c]		x[c]	x[c]	x[c]
Mantoux PPD or QuantiFERON	x[d]					
Chest radiograph	x[d]					
Gastrointestinal colonoscopy	x[e]					
Electrocardiogram	x			x	x	
Pharmacokinetic sampling		x[f]	x[g]	x[g]	x[f]	
Pharmacogenomic sampling		x[h]				
Randomization		x				
Study medication dispensing		x				
Study drug accountability					x	
Assessments						
Diary	x	x	x	x	x	x
CDAI		x	x	x	x	x
Fistula drainage assessment		x		x	x	x

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Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Study Day	**-21 to -7 Days**	**1**	**+/- 2 Days**	**+/- 2 Days**	**+/- 2 Days**	**+/- 1 Week**
IBDQ		x			x	x
PGIC					x	
Adverse events		x	x	x	x	x
Concomitant medication	x	x	x	x	x	x
Biomarker analysis						
C-reactive protein		x	x	x	x	x
Fecal calprotectin		x	x	x	x	x

CDAI = Crohn's Disease Activity Index; FSH = follicle-stimulating hormone; h=hours; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV Ab = hepatitis C virus antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; PGIC = Patient Global Impression of Change; PPD = purified protein derivative.

a. FSH was done in postmenopausal females only.
b. β-HCG was done in females of childbearing potential only.
c. Urine pregnancy test was done in females of childbearing potential only
d. If not performed within 3 months prior to screening; if PPD skin test performed – needed reading by healthcare professional (nurse or doctor) within 48-72 hours
e. For subjects with colonic and terminal ileal disease, if gastrointestinal visualization (radiology, scintigraphy, or endoscopy) not performed within 24 months prior to screening. Gastrointestinal colonoscopy should have been done no later than 9 days prior to Baseline to allow minimum of 2 days washout period of bowel preparation agents prior to diary data collection.
f. Study medication dose taken in the clinic and blood samples taken prior to dosing, and at 0.25 hours, 0.5 hours, 1 hours, and 2-3 hours postdose (or if not possible, as close to 2 hours postdose as feasible).
g. Two blood samples collected at clinic at least 1 hour apart. Date and time of last 6 study drug doses was to be documented.
h. For deidentified pharmacogenomic (deoxyribonucleic acid [DNA]) sampling, a separate molecular profiling consent must have been obtained.

Number of Subjects (Planned and Analyzed): A total of 136 subjects were planned to be randomized to double-blind treatment to provide 120 evaluable subjects for the analyses. The study enrolled 139 subjects: 6 in Belgium, 12 in Czech Republic, 10 in France, 4 in Poland, 26 in Hungary, 6 in Italy, 1 in Netherland, 2 in Slovakia, 10 in South Africa, 4 in Spain, 1 in United Kingdom and 57 in the United States. A total of 139 subjects were randomized and treated (34 placebo; 36 tofacitinib 1 mg BID; 34 tofacitinib 5 mg BID; and 35 tofacitinib 15 mg BID subjects).

Diagnosis and Main Criteria for Inclusion: Subjects included male and females, at least 18 years of age, with clinical evidence of Crohn's disease for at least 3 months duration and moderate-to-severe disease at Baseline (CDAI score of 220 to 450, inclusive); visualization of the gastrointestinal (GI) tract within 24 months prior to screening to confirm diagnosis; receiving stable doses of medications used for Crohn's disease for specified periods of time. Subjects who received immunosuppressants, interferon, anti-tumor necrosis factor alpha and with evidence of hematopoietic disorders and active or latent tuberculosis were excluded.

Study Treatment: Subjects were equally randomized to 1 of the 4 treatment groups: tofacitinib 1 mg BID, tofacitinib 5 mg BID, tofacitinib 15 mg BID, or placebo BID. Subjects received their study medications as outpatients. Tofacitinib tablets and matching placebo for oral administration were dispensed in bottles. Tofacitinib may have been administered with or without food.

Efficacy Endpoints:

Primary Endpoints:

- Clinical response (Week 4) defined by a decrease in the CDAI score of at least 70 points from Baseline.

Secondary Endpoints:

- Clinical response (Week 1 and 2) defined by a decrease in the CDAI score of at least 70 points from Baseline.
- Percentage of subjects achieving clinical remission (Week 4) defined as a reduction of CDAI score below 150.
- Clinical response (Week 4) defined by a decrease in the CDAI score of at least 100 points from Baseline.
- Time to remission.
- Time to response.

Safety Evaluations: Safety evaluations included adverse events (AEs), clinical monitoring, vital signs (temperature, pulse rate, and blood pressure), 12-lead electrocardiograms (ECGs), physical examinations, and safety laboratory tests.

Statistical Methods:

Full Analysis Set (FAS)

The FAS included all randomized subjects, who had either withdrawn as a treatment failure or had completed at least one week of dosing and had at least one valid CDAI score during the active double-blind phase of the study.

Per Protocol Analysis Set (PPAS)

The PPAS was the subset of subjects from the Full Analysis Set who had no major protocol violations. Protocol deviations were assessed by the project team prior to unblinding the study.

Safety Analysis Set (SAS)

The SAS consisted of all randomized subjects who had received at least one dose of study medication.

The primary efficacy endpoint was the proportion of clinical responders at Week 4 defined by a decrease in the CDAI score of at least 70 points from Baseline (Response 70). Response 70 was analyzed using a nonlinear 3-parameter Emax model. A term was included in the model for baseline CDAI score. Center effects were not fitted in the model. The response function was the log odds (logit) of the proportion of subjects responding. Estimates of the treatment differences in response function and associated 80% confidence interval (CI) for each active dose against placebo were calculated. These results were back-transformed to give point estimates of the difference in proportions and associated 80% CIs using the δ-method. No adjustments for multiple comparisons were made. Dichotomous variables (eg, Response 100 and clinical remission) were analyzed using a logistic regression model with treatment as a factor and baseline CDAI score as a covariate in the model. Center effects were not fitted in the model. The response function was the log odds (logit) of the proportion of subjects responding. Estimates of the treatment differences in response function and associated 80% CI for each active dose against placebo were calculated. These results were back-transformed to give point estimates of the difference in proportions and associated 80% CI using the δ-method. No adjustments for multiple comparisons were made. Further model fitting similar to the methods proposed for the primary endpoint was explored if the data indicated a response associated with a monotonic increase in dose. For time to response variables, Kaplan-Meier time-to-event curves were used to compare treatments.

Safety parameters (AEs, vital signs, ECG, and safety laboratory tests data) were explored through the use of standard presentations of descriptive statistics.

RESULTS

Subject Disposition and Demography: A summary of subject evaluation groups is provided in Table 2. A total of 236 subjects were screened for participation in this study. A total of 139 subjects were randomized and treated (34 placebo; 36 tofacitinib 1 mg BID;

34 tofacitinib 5 mg BID; and 35 tofacitinib 15 mg BID subjects). A total of 126 of 139 (90.6%) subjects completed the study. More subjects in tofacitinib treatment groups than in the placebo treatment group completed the study (26 of 34 placebo, 34 of 36 tofacitinib 1 mg BID, 33 of 34 tofacitinib 5 mg BID, and 33 of 35 tofacitinib 15 mg BID subjects).

Of the 139 subjects, there were 69 male and 70 female subjects enrolled in this study. The mean age of subjects was 35.7 years for placebo, 36.6 years for tofacitinib 1 mg BID subjects, 38.7 years for tofacitinib 5 mg BID subjects, and 38.1 years for tofacitinib 15 mg BID subjects. Most subjects were between 18 and 44 years of age (99 of 139 subjects; 71.2%). Most subjects were white (125 of 139 subjects; 89.9%). Mean body mass index (BMI) was similar among groups and ranged from 24.3 to 26.6 kg/m^2. Most subjects were from Europe (72 subjects) and the United States (57 subjects), with fewer subjects from South Africa (10 subjects).

Table 2. Subject Evaluation Groups

No. of Subjects	Placebo	Tofacitinib 1 mg BID	Tofacitinib 5 mg BID	Tofacitinib 15 mg BID
Screened: 236				
Randomized: 139				
Assigned to Treatment	34	36	34	35
Treated	34	36	34	35
Completed	26	34	33	33
Discontinued	8	2	1	2
Related to study drug	3	1	1	1
Adverse event	1	1	1	0
Lack of efficacy	2	0	0	1
Not related to study drug	5	1	0	1
Adverse events	2	0	0	0
Lost to follow-up	1	0	0	0
Other[a]	0	0	0	1
No longer willing to participate	2	1	0	0

BID = twice daily; No. = number.
a. Protocol violation – subject took prohibited medication.

A summary of subject demography is provided in Table 3.

Table 3. Demographic Characteristics

Number of Subjects	Placebo (N=34)	Tofacitinib 1 mg BID (N=36)	Tofacitinib 5 mg BID (N=34)	Tofacitinib 15 mg BID (N=35)
Gender				
Male	12	25	14	18
Female	22	11	20	17
Age (years)				
18-44	24	28	21	26
45-64	10	8	13	9
Mean	35.7	36.6	38.7	38.1
SD	12.7	12.2	10.2	11.7
Range	18-60	20-62	22-60	18-61
Race				
White	32	34	28	31
Black	2	0	5	2
Asian	0	0	0	1
Other[a]	0	2	1	1
Weight (kg)				
Mean	74.8	74.5	70.4	70.1
SD	17.8	15.4	20.6	15.7
Range	47.0-112.0	51.3-111.8	37.0-107.9	42.6-110.9
Body Mass Index (kg/m^2)				
Mean	26.6	24.8	25.0	24.3
SD	7.2	5.1	6.5	5.2
Range	17.9-46.6	16.9-36.9	14.8-39.8	17.3-36.2
N	34	36	33	35
Smoking Status				
N	34	36	34	35
Never smoked	17	19	18	23
Smoker	10	8	11	8
Ex-smoker	7	9	5	4
Geographic Region				
United States	13 (38.2)	15 (41.7)	16 (47.1)	13 (37.1)
Europe	18 (52.9)	19 (52.8)	16 (47.1)	19 (54.3)
South Africa	3 (8.8)	2 (5.6)	2 (5.9)	3 (8.6)

BID = twice daily; N = number of subjects; SD = standard deviation.
a. Hispanic (2 subjects), North African, and mixed race.

Efficacy Results:

Primary Efficacy Endpoint:

The primary efficacy endpoint was the proportion of clinical responders at Week 4 defined by a decrease in the CDAI score of at least 70 points from Baseline (Response 70). The numbers (%) of subjects with clinical Response 70 at Week 4 (FAS) were 14 of 32 (43.8%) placebo, 13 of 35 (37.1%) tofacitinib 1 mg BID, 18 of 30 (60.0%) tofacitinib 5 mg BID, and 16 of 33 (48.5%) tofacitinib 15 mg BID subjects. The model predicted response rates for clinical Response 70 (FAS) were 40.8% for placebo, 44.6% for tofacitinib 1 mg BID, 50.1% for tofacitinib 5 mg BID, and 53.1% for tofacitinib 15 mg BID. None of the differences from placebo met the predefined proof-of-concept (POC) criteria although the result for tofacitinib 15 mg BID was borderline, with a mean difference from placebo of 12.3% with an

80% CI of -2.2 to 26.7%. The proportion of clinical responders at Week 4 is presented in Table 4.

Table 4. Clinical Response 70 at Week 4 – Full Analysis Set

		Raw Data			Fitted Emax Model			
Subset	**Dose**	**N**	**n**	**Observed Response Rate (%)**	**Estimated Response Rate (%)**	**80% CI (%)**	**Difference From Placebo (%) and 80% CI**	**p-Value (2-Sided)**
All subjects	Tofacitinib 1 mg BID	35	13	37.1	44.6	37.5, 51.7	3.8 (-3.7, 11.4)	0.517
	Tofacitinib 5 mg BID	30	18	60.0	50.1	43.0, 57.3	9.3 (-2.9, 21.5)	0.327
	Tofacitinib 15 mg BID	33	16	48.5	53.1	43.6, 62.5	12.3 (-2.2, 26.7)	0.277
	Placebo	32	14	43.8	40.8	31.1, 50.5		
CDAI<330	Tofacitinib 1 mg BID	26	9	34.6	42.0	34.1, 50.0	3.7 (-3.7, 11.1)	0.516
	Tofacitinib 5 mg BID	19	10	52.6	47.5	39.4, 55.6	9.2 (-2.8, 21.3)	0.326
	Tofacitinib 15 mg BID	23	11	47.8	50.5	40.2, 60.8	12.2 (-2.2, 26.5)	0.277
	Placebo	22	10	45.5	38.3	28.2, 48.4		
CDAI≥330	Tofacitinib 1 mg BID	9	4	44.4	49.8	38.6, 61.1	3.9 (-3.9, 11.60	0.520
	Tofacitinib 5 mg BID	11	8	72.7	55.4	44.4, 66.3	9.4 (-3.0, 21.8)	0.330
	Tofacitinib 15 mg BID	10	5	50.0	58.3	45.9, 70.6	12.3 (-2.2, 26.8)	0.278
	Placebo	10	4	40.0	46.0	32.8, 59.1		

N is the denominator for calculating response rate. The FAS population excludes subjects with data missing or falling outside the visit window for Week 4.
Estimates and difference from placebo in response rates were calculated using sample proportions of subjects with each CDAI category to weight to E0 estimates in the analysis.
Response 70 = a decrease from Baseline (Week 0) in CDAI score of at least 70 points.
BID = twice daily; CI = confidence interval; CDAI = Crohn's Disease Activity Index; E0 = relevant to the levels of CDAI score; FAS= full analysis set; N = number of subjects; n = number of subjects meeting prespecified criteria.

Secondary Efficacy Endpoints:

Clinical response (Week 1 and 2):

The numbers (%) of subjects with clinical Response 70 at Week 1 (FAS) were 12 of 34 (35.3%) placebo, 9 of 36 (25.0%) tofacitinib 1 mg BID, 11 of 32 (34.4%) tofacitinib 5 mg BID, and 9 of 35 (25.7%) tofacitinib 15 mg BID subjects. The numbers (%) of subjects with clinical Response 70 at Week 2 (FAS) were 10 of 31 (32.3%) placebo, 15 of 36 (41.7%) tofacitinib 1 mg BID, 13 of 31 (41.9%) tofacitinib 5 mg BID, and 16 of 35 (45.7%) tofacitinib 15 mg BID subjects. Clinical Response 70 at Week 1 and Week 2 is summarized in Table 5.

Table 5. Clinical Response 70 at Weeks 1 and 2 – Full Analysis Set

Baseline Category	Visit	Placebo (N=34)			Tofacitinib 1 mg BID (N=36)			Tofacitinib 5 mg BID (N=34)			Tofacitinib 15 mg BID (N=35)		
		n	N	(%)	n	N	(%)	n	N	(%)	n	N	(%)
Week 1													
All Subjects		12	34	(35.3)	9	36	(25.0)	11	32	(34.4)	9	35	(25.7)
CDAI													
<330		7	22	(31.8)	6	26	(23.1)	5	20	(25.0)	3	24	(12.5)
≥330		5	12	(41.7)	3	10	(30.0)	6	12	(50.0)	6	11	(54.5)
CRP													
<7.5 mg/L		5	12	(41.7)	4	17	(23.5)	4	15	(26.7)	2	10	(20.0)
≥7.5 mg/L		7	19	(36.8)	5	14	(35.7)	6	13	(46.2)	7	21	(33.3)
Immunosuppressant[a]													
Prior		0	7	(0)	3	8	(37.5)	4	9	(44.4)	3	15	(20.0)
No prior		12	27	(44.4)	6	28	(21.4)	7	23	(30.4)	6	19	(31.6)
Week 2													
All Subjects		10	31	(32.3)	15	36	(41.7)	13	31	(41.9)	16	35	(45.7)
CDAI													
<330		5	20	(25.0)	10	26	(38.5)	7	19	(36.8)	9	24	(37.5)
≥330		5	11	(45.5)	5	10	(50.0)	6	12	(50.0)	7	11	(63.6)
CRP													
<7.5 mg/L		3	10	(30.0)	5	17	(29.4)	5	14	(35.7)	4	10	(40.0)
≥7.5 mg/L		7	18	(38.9)	9	14	(64.3)	5	12	(41.7)	11	21	(52.4)
Immunosuppressant[a]													
Prior		1	6	(16.7)	3	8	(37.5)	3	8	(37.5)	6	15	(40.0)
No prior		9	25	(36.0)	12	28	(42.9)	10	23	(43.5)	9	19	(47.4)

BID = twice daily; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; N/n = number of subjects, n = number of subjects meeting prespecified criteria.
a. Immunosuppressant use within the past 3 months.

Clinical response (Week 4):

The numbers (%) of subjects with clinical Response 100 at Week 4 (FAS) were 9 of 32 (28.1%) placebo, 11 of 35 (31.4%) tofacitinib 1 mg BID, 14 of 30 (46.7%) tofacitinib 5 mg BID, and 13 of 33 (39.4%) tofacitinib 15 mg BID subjects. A nonlinear 3-parameter Emax model was fitted and the model predicted response rates for clinical Response 100 (FAS) were 27.4% for placebo, 34.4% for tofacitinib 1 mg BID, 40.6% for tofacitinib 5 mg BID, and 42.8% for tofacitinib 15 mg BID. For tofacitinib 15 mg BID, the

difference from placebo was 15.4% with 80% CI of 1.6 to 29.2%. For Response 100 the model results showed differences from placebo of 13.2% for tofacitinib 5 mg BID and 15.4% for tofacitinib 15 mg BID with 80% lower confidence limits above 0%. The clinical Response 100 at Week 4 is summarized in Table 6.

Table 6 Clinical Response 100 at Week 4 – Full Analysis Set

			Raw Data			Fitted Emax Model		
Subset	Dose	N	n	Observed Response Rate (%)	Estimated Response Rate (%)	80% CI (%)	Difference from Placebo (%) and 80% CI	p-Value (2-Sided)
All subjects	Tofacitinib 1 mg BID	35	11	31.4	34.4	25.9, 42.8	7.0 (-4.4, 18.4)	0.431
	Tofacitinib 5 mg BID	30	14	46.7	40.6	33.5, 47.6	13.2 (0.6, 25.7)	0.178
	Tofacitinib 15 mg BID	33	13	39.4	42.8	33.5, 52.1	15.4 (1.6, 29.2)	0.153
	Placebo	32	9	28.1	27.4	17.6, 37.2		
CDAI<330	Tofacitinib 1 mg BID	26	7	26.9	29.4	20.9, 37.9	6.3 (-4.0, 16.7)	0.430
	Tofacitinib 5 mg BID	19	7	36.8	35.2	27.5, 42.9	12.1 (0.7, 23.60	0.176
	Tofacitinib 15 mg BID	23	8	34.8	37.3	27.6, 47.1	14.2 (1.5, 27.0)	0.153
	Placebo	22	6	27.3	23.1	13.8, 32.4		
CDAI≥330	Tofacitinib 1 mg BID	9	4	44.4	45.4	32.9, 58.0	8.0 (-5.2, 21.1)	0.436
	Tofacitinib 5 mg BID	11	7	63.6	52.1	40.9, 63.2	14.6 90.4, 28.8)	0.189
	Tofacitinib 15 mg BID	10	5	50.0	54.3	41.8, 66.9	16.9 (1.6, 32.1)	0.157
	Placebo	10	3	30.0	37.5	23.7, 51.3		

N is the denominator for calculating response rate. The FAS population excludes subjects with data missing or falling outside the visit window for Week 4.
Estimates and difference from placebo in response rates were calculated using sample proportions of subjects with each CDAI category to weight to E0 estimates in the analysis.
Response 100 = a decrease from Baseline (Week 0) in CDAI score of at least 100 points.
BID = twice daily; CI = confidence interval; CDAI = Crohn's Disease Activity Index; E0 = relevant to the levels of CDAI score; FAS = full analysis set; N = number of subjects, n = number of subjects meeting prespecified criteria.

Clinical remission (Week 4): The numbers (%) of subjects with clinical remission at Week 4 (FAS) were 7 of 32 (21.9%) placebo, 11 of 35 (31.4%) tofacitinib 1 mg BID, 8 of 30 (26.7%) tofacitinib 5 mg BID, and 5 of 33 (15.2%) tofacitinib 15 mg BID subjects. The clinical remission at Week 4 is summarized in Table 7.

Table 7 Clinical Remission at Week 4 – Full Analysis Set

Baseline Category	Placebo (N=34)			Tofacitinib 1 mg BID (N=36)			Tofacitinib 5 mg BID (N=34)			Tofacitinib 15 mg BID (N=35)		
	n	N	(%)	n	N	(%)	n	N	(%)	n	N	(%)
All Subjects	7	32	(21.9)	11	35	(31.4)	8	30	(26.7)	5	33	(15.2)
CDAI												
<330	6	22	(27.3)	8	26	(30.8)	6	19	(31.6)	4	23	(17.4)
≥330	1	10	(10.0)	3	9	(33.3)	2	11	(18.2)	1	10	(10.0)
CRP												
<7.5 mg/L	4	12	(33.3)	6	17	(35.3)	5	13	(38.5)	2	10	(20.0)
≥7.5 mg/L	2	17	(11.8)	4	13	(30.8)	2	13	(15.4)	3	20	(15.0)
Immunosuppressant[a]												
Prior	0	6	(0)	2	8	(25.0)	3	9	(33.3)	3	15	(20.0)
No prior	7	26	(26.9)	9	27	(33.3)	5	21	(23.8)	2	17	(11.8)

BID = twice daily; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; N = number of subjects, n = number of subjects meeting prespecified criteria.
a. Immunosuppressant use within the past 3 months.

C-Reactive Protein (CRP): A summary of change from Baseline in CRP (mg/L) by visit for the FAS is provided in Table 8. Decreases from Baseline in mean CRP levels were observed for all tofacitinib treatment groups as early as Week 1, with some further decreases over time up to Week 4 in the 15 mg BID group. The changes at Week 4 occurred in a dose-related manner.

Table 8. Baseline and Change from Baseline in C-Reactive Protein (mg/L), by Visit – Full Analysis Set

Visit		Placebo	Tofacitinib 1 mg BID	Tofacitinib 5 mg BID	Tofacitinib 15 mg BID
Baseline	N	31	31	28	31
	Geometric Mean (mg/L)	8.24	6.61	8.44	10.40
	Mean (SD) Log	2.11 (1.40)	1.89 (1.54)	2.13 (1.27)	2.34 (1.69)
Week 1	N	30	31	27	31
	Geometric Mean (ratio)	1.04	0.78	0.59	0.51
	Mean Difference (SD) Log	0.04 (0.64)	-0.24 (0.77)	-0.52 (1.02)	-0.67 (1.20)
Week 2	N	29	31	27	31
	Geometric Mean (ratio)	0.91	0.64	0.63	0.44
	Mean Difference (SD) Log	-0.09 (1.02)	-0.44 (0.84)	-0.47 (1.13)	-0.81 (1.47)
Week 4	N	26	30	28	30
	Geometric Mean (ratio)	0.93	0.81	0.66	0.39
	Mean Difference (SD) Log	-0.07 (0.87)	-0.21 (0.84)	-0.42 (1.02)	-0.93 (1.60)[a]
Week 8	N	26	28	26	29
	Geometric Mean (ratio)	0.56	0.75	0.94	1.13
	Mean Difference (SD) Log	-0.59 (1.31)	-0.28 (1.12)	-0.07 (1.35)	0.12 (1.30)

Arithmetic means are log transformed.
There was a restandardization in the CRP assay during the study due to a bias found in a reagent for certain lot numbers. Samples analyzed with the affected reagents were excluded from the analyses.
BID = twice daily; CRP = C-reactive protein; N = number of subjects; SD = standard deviation; vs = versus.
a. Statistically significant; p = 0.008 for tofacitinib 15 mg BID vs placebo.

Fecal Calprotectin: A summary of baseline and change from Baseline in fecal calprotectin (mg/kg) by visit for the FAS is provided in Table 9.

Table 9. Baseline and Change from Baseline in Log-Transformed Fecal Calprotectin, by Visit – Full Analysis Set

Visit		Placebo	Tofacitinib 1 mg BID	Tofacitinib 5 mg BID	Tofacitinib 15 mg BID
Baseline	N	31	32	32	33
	Geometric Mean (mg/kg)	521.7	396.5	289.8	420.3
	Mean (SD) Log	6.26 (1.57)	5.98 (1.56)	5.67 (1.14)	6.04 (1.51)
Week 1	N	28	30	30	31
	Geometric Mean (ratio)	0.96	1.11	1.06	0.80
	Mean Difference (SD) Log	-0.04 (1.13)	0.10 (1.21)	0.06 (1.12)	-0.23 (0.74)
Week 2	N	28	31	31	31
	Geometric Mean (ratio)	1.16	1.00	0.82	0.76
	Mean Difference (SD) Log	0.15 (0.75)	-0.00 (1.29)	-0.20 (1.12)	-0.27 (1.39)
Week 4	N	25	30	32	31
	Geometric Mean (ratio)	1.09	1.33	1.24	0.50
	Mean Difference (SD) Log	0.08 (1.13)	0.28 (1.69)	0.21 (1.24)	-0.70 (1.11)[a]
Week 8	N	21	28	25	28
	Geometric Mean (ratio)	0.90	1.06	1.72	1.16
	Mean Difference (SD) Log	-0.11 (1.54)	0.06 (1.65)	0.54 (1.40)	0.15 (1.30)

BID = twice daily; N = number of subjects; SD = standard deviation; vs = versus.
a. Statistically significant; p = 0.015 for tofacitinib 15 mg BID vs placebo.

Time to remission: Kaplan-Meier estimates for time to first clinical remission (FAS) are provided in Table 10.

Table 10. Time to First Clinical Remission (Full Analysis Set)

	Placebo (N=34)	Tofacitinib 1 mg BID (N=36)	Tofacitinib 5 mg BID (N=33)	Tofacitinib 15 mg BID (N=35)
Kaplan-Meier estimate of time to first remission (days): Time (95% CI)				
25% Responded	29.0 (15.0, NA)	29.0 (15.0, NA)	30.0 (21.0, 31.0)	NA (15.0, NA)
50% Responded	NA (29.0, NA)	NA (30.0, NA)	30.0 (30.0, NA)	NA (NA, NA)
75% Responded	NA (NA, NA)	NA (NA, NA)	NA (30.0, NA)	NA (NA, NA)

BID = twice daily; CI = confidence interval; N = number of subjects; NA = not applicable.

Time to response: Kaplan-Meier estimates for time to first clinical response 70 and 100 (FAS) are provided in Table 11.

Table 11. Time to First Clinical Response 70 and 100 (Full Analysis Set)

Baseline Category	Placebo (N=34)	Tofacitinib 1 mg BID (N=36)	Tofacitinib 5 mg BID (N=33)	Tofacitinib 15 mg BID (N=35)
Kaplan-Meir estimate of time to first response (days): Time (95% CI)				
Clinical response by 70				
25% Responded	8.00 (8.00, 15.0)	11.0 (8.00, 16.0)	8.00 (8.00, 15.0)	9.00 (8.00, 16.0)
50% Responded	29.0 (11.0, 29.0)	30.0 (15.0, NA)	21.0 (13.0, 30.0)	29.0 (15.0, NA)
75% Responded	NA (29.0, NA)	NA (30.0, NA)	31.0 (29.0, 32.0)	NA (NA, NA)
Clinical response by 100				
25% Responded	16.0 (11.0, 29.0)	15.0 (8.00, 29.0)	16.0 (14.0, 29.0)	15.0 (8.00, 29.0)
50% Responded	NA (28.0, NA)	30.0 (29.0, NA)	30.0 (21.0, NA)	NA (16.0, NA)
75% Responded	NA (NA, NA)	NA (NA, NA)	31.0 (30.0, NA)	NA (NA, NA)

BID = twice daily; CI = confidence interval; N = number of subjects; NA = not applicable.

Safety Results:

Treatment-emergent nonserious AEs (all causalities and treatment-related) by system organ class (SOC) and preferred term that occurred in >5% of subjects in all treatment groups are summarized in Table 12.

Table 12. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) in >5 % of Subjects

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.1) Preferred Term	Placebo			Tofacitinib 1 mg BID			Tofacitinib 5 mg BID			Tofacitinib 15 mg BID		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	2	n (%)	n1	n2
Number (%) of subjects:												
Evaluable for adverse events	34	-	-	36	-	-	34	-	-	35	-	-
With adverse events	16 (47.1)	-	-	17 (47.2)	-	-	11 (32.4)	-	-	17 (48.6)	-	-
Blood and lymphatic system disorders	2 (5.9)	5	0	0	0	0	0	0	0	0	0	0
Lymphadenopathy	2 (5.9)	5	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	7 (20.6)	11	7	12 (33.3)	17	9	9 (26.5)	10	5	11 (31.4)	19	13
Abdominal pain	3 (8.8)	3	1	3 (8.3)	3	0	0	0	0	3 (8.6)	3	3
Crohn’s disease	1 (2.9)	1	1	1 (2.8)	1	0	2 (5.9)	2	1	2 (5.7)	2	1
Diarrhoea	0	0	0	2 (5.6)	2	1	1 (2.9)	1	1	3 (8.6)	4	1
Dyspepsia	0	0	0	0	0	0	0	0	0	2 (5.7)	2	2
Flatulence	1 (2.9)	1	1	2 (5.6)	2	2	1 (2.9)	1	0	0	0	0
Haematochezia	1 (2.9)	1	0	2 (5.6)	2	0	0	0	0	0	0	0
Mouth ulceration	0	0	0	0	0	0	2 (5.9)	2	1	1 (2.9)	1	0
Nausea	2 (5.9)	2	1	4 (11.1)	5	5	3 (8.8)	3	1	3 (8.6)	4	4
Vomiting	3 (8.8)	3	3	2 (5.6)	2	1	1 (2.9)	1	1	3 (8.6)	3	2
General disorders and administration site conditions	7 (20.6)	7	4	7 (19.4)	7	4	3 (8.8)	3	1	5 (14.3)	6	1
Asthenia	3 (8.8)	3	1	3 (8.3)	3	3	1 (2.9)	1	0	1 (2.9)	1	1
Fatigue	3 (8.8)	3	2	4 (11.1)	4	1	0	0	0	1 (2.9)	1	0
Pyrexia	1 (2.9)	1	1	0	0	0	2 (5.9)	2	1	3 (8.6)	4	0
Infections and infestations	1 (2.9)	1	0	5 (13.9)	7	2	2 (5.9)	2	0	2 (5.7)	2	0
Nasopharyngitis	1 (2.9)	1	0	3 (8.3)	5	1	1 (2.9)	1	0	1 (2.9)	1	0
Urinary tract infection	0	0	0	2 (5.6)	2	1	1 (2.9)	1	0	1 (2.9)	1	0
Investigations	3 (8.8)	3	1	2 (5.6)	2	2	0	0	0	0	0	0
Weight decreased	3 (8.8)	3	1	2 (5.6)	2	2	0	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	2 (5.6)	2	1	1 (2.9)	1	0	0	0	0
Decreased appetite	0	0	0	2 (5.6)	2	1	1 (2.9)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (2.9)	1	0	0	0	0	2 (5.9)	2	0	2 (5.7)	2	1
Arthralgia	1 (2.9)	1	0	0	0	0	2 (5.9)	2	0	0	0	0
Pain in extremity	0	0	0	0	0	0	0	0	0	2 (5.7)	2	1

Table 12. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) in >5 % of Subjects

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.1) Preferred Term	Placebo			Tofacitinib 1 mg BID			Tofacitinib 5 mg BID			Tofacitinib 15 mg BID		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	2	n (%)	n1	n2
Nervous system disorders	3 (8.8)	3	1	2 (5.6)	2	1	2 (5.9)	2	0	3 (8.6)	3	1
Dizziness	2 (5.9)	2	1	0	0	0	0	0	0	0	0	0
Headache	1 (2.9)	1	0	2 (5.6)	2	1	2 (5.9)	2	0	3 (8.6)	3	1
Psychiatric disorders	2 (5.9)	2	1	2 (5.6)	2	1	0	0	0	2 (5.7)	2	2
Insomnia	2 (5.9)	2	1	2 (5.6)	2	1	0	0	0	2 (5.7)	2	2
Vascular disorders	0	0	0	0	0	0	0	0	0	2 (5.7)	2	2
Hot flush	0	0	0	0	0	0	0	0	0	2 (5.7)	2	2

Except for 'n1' and 'n2' subjects are only counted once per treatment for each row.
n: The 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.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events calculated using the corresponding gender count as denominator.
MedDRA (version 12.1) coding dictionary applied.
BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; v = version.

The most commonly reported treatment-emergent AEs were from the gastrointestinal disorders and general disorders and administrative site conditions SOCs. The most commonly reported treatment-emergent AEs were nausea and vomiting and abdominal pain and asthenia. The most commonly reported treatment-emergent AEs by treatment group were vomiting for placebo, nausea and asthenia for tofacitinib 1 mg BID, diarrhea and pyrexia for tofacitinib 5 mg BID, and abdominal pain and nausea for tofacitinib 15 mg BID.

Treatment-emergent serious adverse event (SAEs - all causalities and treatment-related) by SOC and preferred term in either treatment group are summarized in Table 13.

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects with Adverse Events by: System Organ Class and	Placebo			Tofacitinib 1 mg BID			Tofacitinib 5 mg BID			Tofacitinib 15 mg BID		
MedDRA (v12.1) Preferred Term	**n (%)**	**n1**	**n2**	**n (%)**	**n1**	**n2**	**n (%)**	**n1**	**n2**	**n (%)**	**n1**	**n2**
Number (%) of subjects:												
Evaluable for adverse events	34	-	-	36	-	-	34	-	-	35	-	-
With adverse events	5 (14.7)	-	-	4 (11.1)	-	-	4 (11.8)	-	-	1 (2.9)	-	-
Cardiac disorders	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Atrial fibrillation	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	2 (5.9)	2	0	3 (8.3)	3	1	3 (8.8)	5	3	1 (2.9)	1	0
Abdominal pain	0	0	0	0	0	0	1 (2.9)	1	1	0	0	0
Crohn's disease	0	0	0	2 (5.6)	2	1	1 (2.9)	1	0	1 (2.9)	1	0
Diarrhoea	1 (2.9)	1	0	0	0	0	2 (5.9)	2	1	0	0	0
Intestinal obstruction	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Small intestinal obstruction	0	0	0	1 (2.8)	1	0	0	0	0	0	0	0
Subileus	0	0	0	0	0	0	1 (2.9)	1	1	0	0	0
General disorders and administration site conditions	0	0	0	0	0	0	1 (2.9)	2	2	0	0	0
Chills	0	0	0	0	0	0	1 (2.9)	1	1	0	0	0
Pyrexia	0	0	0	0	0	0	1 (2.9)	1	1	0	0	0
Hepatobiliary disorders	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Cholelithiasis	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Infections and infestations	3 (8.8)	4	0	0	0	0	1 (2.9)	1	0	0	0	0
Anal abscess	2 (5.9)	2	0	0	0	0	0	0	0	0	0	0
Pneumonia	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Sepsis	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Vulval abscess	0	0	0	0	0	0	1 (2.9)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (2.8)	1	0	0	0	0	0	0	0
Back pain	0	0	0	1 (2.8)	1	0	0	0	0	0	0	0
Psychiatric disorders	0	0	0	0	0	0	0	0	0	1 (2.9)	1	0
Factitious disorder	0	0	0	0	0	0	0	0	0	1 (2.9)	1	0
Renal and urinary disorders	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Renal failure	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Respiratory failure	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Rash	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.1) Preferred Term	Placebo			Tofacitinib 1 mg BID			Tofacitinib 5 mg BID			Tofacitinib 15 mg BID		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Vascular disorders	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0
Hypertension	1 (2.9)	1	0	0	0	0	0	0	0	0	0	0

Except for 'n1'and 'n2' subjects are only counted once per treatment for each row.
n: The 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.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events calculated using the corresponding gender count as denominator.
MedDRA (version 12.1) coding dictionary applied.
BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; v = version.

A fatal SAE occurred in one subject who received placebo BID for 15 days during the study. The subject underwent bowel surgery but his condition deteriorated and he died 3 days later. Ventricular fibrillation due to sepsis was considered the cause of death and unrelated to the study treatment.

A summary of permanent discontinuations due to AEs is provided in Table 14. A total of 6 subjects permanently discontinued the study due to an AE (3 of 34 [8.8%] placebo, 1 of 36 [2.8%] tofacitinib 1 mg BID, 1 of 34 [2.9%] tofacitinib 5 mg BID, and 1 of 35 [2.9%] tofacitinib 15 mg BID subjects).

Table 14. Summary of Permanent Discontinuations Due to Adverse Events

Serial Number	Gender/Age	System Organ Class	MedDRA Preferred Term	Study Start Day/Study Stop Day	Severity/Outcome	Causality
Placebo						
1	F/39	Gastrointestinal disorders	Crohn's disease	13/35	Moderate/resolved	Study drug
			Vomiting	12/18	Moderate/resolved	Study drug
2	M/41	Gastrointestinal disorders	Intestinal obstruction[a]	16/21	Severe/resolved	Disease under study
3	F/45	Infections and infestations	Anal abscess[a]	24/78	Severe/resolved	Disease under study
Tofacitinib 1 mg BID						
4	M/28	Investigations	Weight decreased	1/>8	Moderate/unknown	Study drug
Tofacitinib 5 mg BID						
5	F/26	Gastrointestinal disorders	Subileus[a]	10/18	Severe/resolved	Study drug
Tofacitinib 15 mg BID						
6	F/38	Gastrointestinal disorders	Crohn's disease[a]	17/28	Severe/resolved	Disease under study

Study start day and stop date relative to the start of study treatment. First day of study treatment = Day 1.
BID = twice daily; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.
a. This event was a serious adverse event.

CONCLUSIONS:

- The percentages of subjects with clinical Response 70 at Week 4 (FAS) were 37.1% for tofacitinib 1 mg BID, 60.0% for tofacitinib 5 mg BID, 48.5% for tofacitinib 15 mg BID, and 43.8% for placebo subjects. The placebo response was higher than expected. From the dose-response modeling of the data, no tofacitinib BID dose achieved the predefined POC criteria at Week 4 for Response 70 (FAS), although results for the 15 mg treatment group were borderline. This was confirmed by the sensitivity analysis using last observation carried forward where tofacitinib 15 mg met the POC criteria.

- For Response 100 the model results showed differences from placebo of 13.2% for tofacitinib 5 mg BID and 15.4% for tofacitinib 15 mg BID with 80% lower confidence limits above 0%.

- There were no treatment-related effects seen for clinical remission at Week 4.

- There were dose-related decreases in CRP from Baseline to Week 4 in all treatment groups and the differences from placebo were significant in the highest dose group (tofacitinib 15 mg BID). There was also a decrease in fecal calprotectin from Baseline to Week 4 in the highest dose group (tofacitinib 15 mg BID). Overall, results of the clinical biomarkers suggest biological activity of tofacitinib in Crohn's disease.

- Tofacitinib, administered at doses of 1 mg BID, 5 mg BID, and 15 mg BID for 4 weeks, was safe and generally well tolerated in subjects with active Crohn's disease, with treatment-related AEs in 28.8% of subjects, AEs in 17.6% of subjects, and study discontinuations due to AEs in 4.3% of subjects.

- One subject had a fatal SAE during the study (subject received placebo BID for 15 days). The day after the last dose of study medication, the subject was hospitalized with intestinal obstruction and pneumonia, and subsequently developed sepsis, respiratory failure, and renal failure. The subject underwent bowel surgery, but his general condition deteriorated. Three days following the hospital admission, the subject died; the cause of death was ventricular fibrillation due to sepsis. This was the only death in the study; the death was considered unrelated to study treatment.