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

PROTOCOL NO.: A3921039

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Confirm Dose Responsiveness Following 12 Weeks of the Administration of CP-690,550 (4 Doses) or Placebo in Subjects With Active Rheumatoid Arthritis Inadequately Controlled With Methotrexate Alone

Study Centers: A total of 19 centers in Japan took part in the study and randomized subjects.

Study Initiation and Final Completion Dates: 24 January 2008 to 26 September 2008

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To evaluate the dose-response relationship in tofacitinib (1, 3, 5, and 10 mg, twice daily:BID) doses including placebo for the treatment of signs and symptoms in subjects with active rheumatoid arthritis (RA) which had been inadequately controlled with methotrexate (MTX) ("active RA" hereafter) in a 12-week therapy.

Secondary Objectives:

- To evaluate the safety and the tolerability of all dose levels of tofacitinib (1, 3, 5, and 10 mg, BID) versus placebo in a 12-week add-on therapy with MTX in active RA subjects.

- To check the relationship between plasma concentrations of tofacitinib (1, 3, 5, and 10 mg, BID) and efficacy and safety outcomes in a 12-week add-on therapy with MTX in active RA subjects.

- To evaluate subjects' quality of life (QOL) and functional status in a 12-week add-on therapy with MTX in active RA subjects.

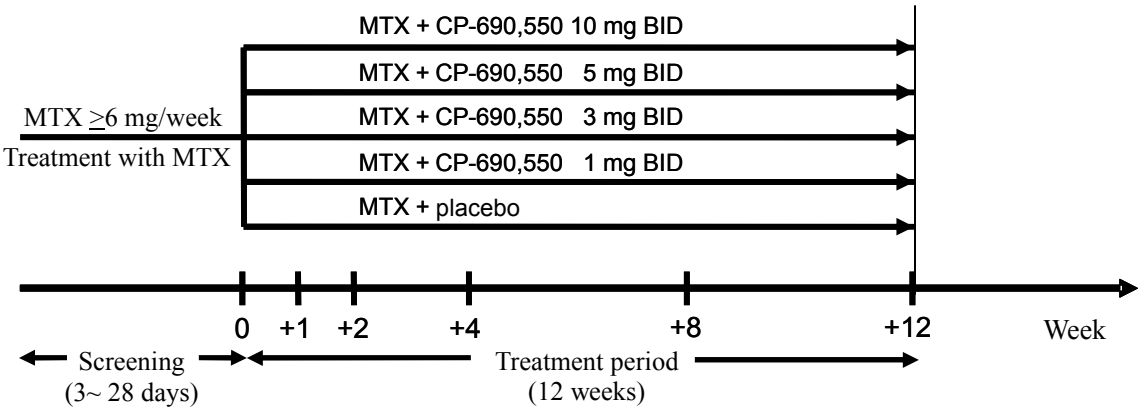
- To conduct Population Pharmacokinetic analyses in active RA subjects.

METHODS

Study Design: This was a Phase 2, multicenter, randomized, placebo-controlled, parallel group, double-blind study. It was planned to randomize 125 subjects with RA, who had had an inadequate response to MTX alone, in a 1:1:1:1:1 ratio to receive 1 of 4 dose regimens of tofacitinib (1 mg, 3 mg, 5 mg, and 10 mg BID) or placebo tablets.

For each subject, the study comprised screening period (at least 3 days but not longer than 28 days prior to first study drug administration) and treatment period (12 weeks). For the observation and test items scheduled for each visit, it was permitted to use data obtained during an acceptable time window of ±3 days. The study design is presented in Figure 1 and in Table 1.

Figure 1. Study Design



BID = twice daily, CP-690,550 = tofacitinib, MTX = methotrexate.

Table 1. Timetable of Study Procedures/Evaluations

Items		Screening[a]	Baseline	Visits During Treatment Phase[b]				End of Treatment[b]
		Day -28	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12/ Discontinuation
Informed consent		X						
Randomization			X					
Subject characteristics	Background investigation (e.g., complications, medical history, treatment conditions)[c]	X						
	Questions/examinations by physician (physical examination, joint palpation)[d]	X[d]	X	X	X	X	X	X[d]
	Measurement of height, abdominal circumference	X						
	Measurement of body weight	X	X	X	X	X	X	X
	RA diagnosis (ACR classification criteria 1987)	X						
	Eligibility confirmation (e.g., inclusion/exclusion criteria)	X	X					
Assessment	ACR assessments[e]	X	X	X	X	X	X	X
	DAS28-3 (CRP), DAS28-4 (ESR) assessments	X	X	X	X	X	X	X
	QOL1 (SF-36 v2 EQ-5D)		X					X
	QOL2 (MOS-sleep, FACIT fatigue)		X		X			X
	Vital signs (sitting blood pressure/pulse rate, axillary body temperature)	X	X	X	X	X	X	X
	Adverse event assessment		X	X	X	X	X	X
Lab tests/exploratory tests/physiological test	ESR (Westergren method)	X	X	X	X	X	X	X
	Serum rheumatoid factor	X						
	Tuberculosis test[f]	X						
	HIV test, hepatitis test (hepatitis B virus antigen, hepatitis C virus antibody)	X						
	Hematology[g]	X	X	X	X	X	X	X
	Biochemistry: standard (fasting)[h]	X	X			X	X	X
	Biochemistry: hepatic/renal function (fasting)[i]			X	X			
	Biochemistry: lipid special (fasting)[j]		X		X	X	X	X
	CRP	X	X	X	X	X	X	X
	Blood EBV DNA		X		X			X
	Pregnancy test (serum)[k]	X						X
	Urinalysis (general/pregnancy)[k]	X	X	X	X	X	X	X
	Pharmacogenomic sampling (DNA)[l]		X					
	Standard 12-lead electrocardiogram	X	X					X
	SpO_2	X	X	X	X	X	X	X
	Chest X-rays	X						X

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Items		Screening[a]	Baseline	Visits During Treatment Phase[b]				End of Treatment[b]
		Day -28	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12/ Discontinuation
Drug supplies	Study drug dispensing[m]		X			X	X	
	Study drug recovery, remaining drug check[m]			X	X	X	X	X
	Confirmation of concomitant medications	X	X	X	X	X	X	X
	Instructions on the use of drugs[m]	X	X	X	X	X	X	
Eligibility confirmation (for subjects who will enter into the continuous study)							X	X

ACR = American College of Rheumatology, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, Ca^{++} = calcium, Cl^{-} = chlorine, CRP = C-reactive protein, DAS = disease activity score, DNA = deoxyribonucleic acid, EBV = Epstein-Barr virus, EOT = end of treatment, EQ-5D = EuroQol- dimensions, ESR = erythrocyte sedimentation rate, FACIT = functional assessment of chronic illness therapy, FACS = fluorescence activated cell sorting, FSH = follicle-stimulating hormone, HAQ = Health Assessment Questionnaire, HCO_3^{-} = bicarbonate, HDL = high density lipoprotein, HIV = human immunodeficiency virus, IgG = immunoglobulin G, IgM = immunoglobulin M, IgA = immunoglobulin A, K^{+} = potassium, LDH = lactate dehydrogenase, LDL = low density lipoprotein, MOS = Medical Outcomes Study, Na^{+} = sodium, PK = pharmacokinetic, QOL = quality of life, RA = rheumatoid arthritis, RBC = red blood cell count, SF-36 = short form-36 health survey, SpO_2 = percutaneous arterial oxygen saturation, TB = tuberculosis, T-Chol = total cholesterol, TG = triglycerides, VAS = visual analog scale, WBC = white blood cell count.

a. The screening period consisted of 3-28 days prior to the Baseline, and during this period, the predetermined screening parameters were investigated.
b. The data observed for the observation/test parameters specified for all visits were accepted provided they were observed within a time window of ±3 days, relative to the day of treatment initiation. For example, if an observation/test had not been performed, the Investigator tried to prevent this from becoming a protocol violation by, for example, requesting that the subject come in for a visit within the allowable time window.
c. Subject characteristics (e.g., complications, past medical history, treatment status) were investigated at the time of the interview (subjects were questioned about their family history of cardiovascular disease to the extent possible, including familial characteristics). Subjects were questioned about their preferences regarding smoking and the average amount of alcohol they consumed in 1 week (e.g., presence or absence of alcohol dependency or drug abuse).
d. Questioning / examination by physician consisted of weight and examination of heart, lungs, abdomen, and lymph nodes. At screening and the EOT, they were monitored carefully.
e. The following assessments based on the ACR core set were performed at all visits whenever possible: Tender/Painful Joint Count (68); Swollen Joint Count (66); Patient's Assessment of Arthritis Pain (VAS); Patient's Global Assessment of Active Arthritis (VAS); Physician's Global Assessment of Active Arthritis (VAS); HAQ Functional Impairment Index.
f. Confirmation of tuberculosis infection by means of QuantiFERON-TB or tuberculin skin test were performed only if a tuberculin test had not been performed in the 3 months prior to obtaining informed consent (the assessment of tuberculin skin test was made within 48-72 hours).
g. WBC, differential WBC, RBC, hemoglobin, hematocrit, reticulocytes, platelet count.
h. Biochemistry tests (standard): protein, total bilirubin, albumin, ALP, BUN, creatinine, blood glucose, AST, ALT, Na^{+}, K^{+}, Cl^{-}, Ca^{++}, HCO_3^{-}, uric acid, LDH (all measured at fasting at least 9 hours except for the case of that day of informed consent at screening visit).
i. Biochemistry tests (hepatic/renal function): AST, ALT, total bilirubin, albumin, creatinine (all measured at fasting at least 9 hours).
j. Biochemistry tests (lipid): T-Chol, LDL, HDL, TG (all measured at fasting at least 9 hours) at Baseline, Week 2, 4, 8 and 12/early termination. Apolipoprotein A-I and A-II, apolipoprotein B (all measured at fasting at least 9 hours) at Baseline and Week 12/early termination.
k. Pregnancy tests were performed for women of child bearing potential (serum FSH [test] was optional). Urinalysis were performed using dipsticks and, if a clinically significant abnormality was observed or at the discretion of the Investigator, additional examination by means of, for example, microscopy was performed.

Table 1. Timetable of Study Procedures/Evaluations

Items	Screening[a]	Baseline	Visits During Treatment Phase[b]				End of Treatment[b]
	Day -28	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12/ Discontinuation

l. In principle, pharmacogenomic (DNA) sampling was performed with other blood sampling for the study at Baseline; (pharmacogenomic [DNA] sampling, a separate molecular profiling consent had to be obtained). If a molecular profiling informed consent was not obtained at Baseline by subject, additional 9 mL blood sampling for pharmacogenomics together with study blood sampling at available visit was performed after obtaining consent.

m. Subjects were instructed to start taking study medication after the evening meal on the treatment initiation day (Baseline). Similarly, on the days corresponding to (the visits at) Weeks 4 and 8, when study medication were dispensed, subjects were instructed to take the study medication they were given after returning home in the evening. Subjects were instructed to return to the Investigator all remaining study medication at the visits at Weeks 4 and 8, as well as on the last day of the study (including the visit following discontinuation).

Number of Subjects (Planned and Analyzed): The planned sample size was 125 subjects (25 subjects per group × 5 groups). A total of 140 subjects (28 subjects per treatment group) were enrolled and randomized. The number of subjects treated and analyzed was 28, 27, 27, 26, and 28 in the 1, 3, 5, 10 mg tofacitinib BID and placebo groups, respectively.

Diagnosis and Main Criteria for Inclusion: The subjects were males and females between the ages of 20 and 70 years old. The subjects had a diagnosis of RA based on the 1987 revised criteria of the American College of Rheumatology (ACR) and active disease at both screening and Baseline visits, defined as ≥6 joints tender or painful on motion and ≥6 joints swollen. Each subject also had to have either erythrocyte sedimentation rate (ESR) (Westergren method) greater than the upper limit of normal range (ULN) in the study site or C-reactive protein (CRP) >0.7 mg/dL in the central laboratory at screening. Subjects had received MTX for at least 4 months consecutively, and must have received doses of at least 6 mg/week for at least 6 weeks prior to Baseline. Furthermore, it must have been confirmed by the Principal Investigator and others that the subject had active RA at a level sufficient to satisfy the inclusion criteria for this study. Subjects who were receiving therapy with any disease-modifying anti-rheumatic drugs or biologic other than MTX were excluded from the study.

Study Treatment: Study drug was dispensed to the subject at the visits on the first day of dosing (Baseline) and Weeks 4 and 8. Three tablets of tofacitinib 1 mg or 5 mg, or placebo were administered orally BID (separated by 12 ±2 hours), total 6 tablets/day. Tofacitinib was supplied by the Sponsor as 1 mg and 5 mg tablets.

Efficacy and Safety Endpoints:

Primary Endpoint:

- ACR20 (American College of Rheumatology 20% improvement in disease activity) response rate at Week 12.

Secondary Endpoints:

- ACR20 response rates at timepoints other than Week 12.
- Over-time change in ACR50 (50% improvement in disease activity), ACR70 (70% improvement in disease activity), and ACR90 (90% improvement in disease activity) response rates at all the timepoints.
- Observation values and changes from Baseline of the 7 components of the ACR Core set. Tender/Painful Joint Count (68), Swollen Joint Count (66), Patient's Assessment of Arthritis Pain (VAS), Patient's Global Assessment of Active Arthritis (VAS), Physician's Global Assessment of Active Arthritis (VAS), Health Assessment Questionnaire - Disability Index (HAQ – DI), CRP.
- ACR-N and area under the ACR-N curve.
- Disease activity score (DAS) 28-3 (CRP), DAS28-4 (ESR).

- QOL assessments (short form-36 [SF-36], HAQ-DI, EuroQol- 5 dimensions [EQ-5D], Medical Outcomes Study [MOS]-Sleep Scale, Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue Scale).

Safety Endpoints:

- Incidence and severity of adverse events (AEs) and laboratory test abnormalities.
- Vital signs, electrocardiogram (ECG).

Statistical Methods: The full analysis set (FAS) was used for the primary analysis population. This population was based on all randomized subjects who had received at least 1 dose of study drug. For the secondary analysis population, the per protocol set (PPS) was used. PPS was a subset of FAS, counting only those subjects who did not have a protocol deviation judged to have the potential to affect efficacy. The safety analysis was performed for the subjects who received at least 1 dose of study drug.

Analysis of Primary Endpoint: The primary endpoint was ACR20 at Week 12. Last observation carried forward (LOCF) approach was used for missing components in ACR20 response rate.

Primary Analysis of Primary Endpoint: To evaluate the dose-response relationship in tofacitinib doses (including placebo), Cochran-Armitage test was used for ACR20 response rate at Week 12 at a significance level (one-sided) of 5%.

Secondary Analysis of Primary Endpoint: The differences of ACR20 response rate between each tofacitinib group and placebo group was tested using normal approximation at a significance level (one-sided) of 5%. The 90% confidence interval of the differences was calculated.

Analysis of Secondary Endpoints: The Cochran-Armitage test was used for ACR50, ACR70 and ACR90 response rate at Week 12 at a significance level (one-sided) of 5%. LOCF was used for missing components.

Safety Parameters: All the safety data were summarized descriptively by treated dose group through appropriate data tabulations and descriptive statistics.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2. A total of 165 subjects were screened and each subject was randomized to 1 of 5 treatment groups of 28 subjects. Of these subjects, 28, 27, 27, 26, and 28 took study medication in the 1, 3, 5, 10 mg tofacitinib BID and placebo groups, respectively.

The number of subjects who discontinued the study from the 1, 3, 5, 10 mg tofacitinib BID and placebo groups were 2, 4, 4, 5 and 5 subjects, respectively. Reasons for discontinuation are presented in Table 3.

Table 2. Subject Evaluation Groups

	Tofacitinib				
	1 mg BID	**3 mg BID**	**5 mg BID**	**10 mg BID**	**Placebo**
Number (%) of subjects					
Screened N=165					
Randomized to study treatment	28	28	28	28	28
Treated	28	27	27	26	28
Completed	26 (92.9)	23 (82.1)	23 (82.1)	21 (75.0)	23 (82.1)
Discontinued	2 (7.1)	4 (14.3)	4 (14.3)	5 (17.9)	5 (17.9)

BID = twice daily, N = number of subjects.

Table 3. Discontinuations From Study

	Tofacitinib				
	1 mg BID	**3 mg BID**	**5 mg BID**	**10 mg BID**	**Placebo**
Number (%) of subjects	28	27	27	26	28
Discontinuations					
Related to study drug	0	2 (7.4)	3 (11.1)	4 (15.4)	3 (10.7)
Adverse event	0	1 (3.7)	3 (11.1)	4 (15.4)	2 (7.1)
Lack of efficacy	0	1 (3.7)	0	0	1 (3.6)
Not related to study drug	2 (7.1)	2 (7.4)	1 (3.7)	1 (3.8)	2 (7.1)
Adverse event	0	1 (3.7)	1 (3.7)	0	0
Subject no longer willing to participate in study	0	0	0	0	1 (3.6)
Other[a]	2 (7.1)	1 (3.7)	0	1 (3.8)	1 (3.6)
Total	2 (7.1)	4 (14.8)	4 (14.8)	5 (19.2)	5 (17.9)

BID = twice daily.
a. Protocol violation or did not meet inclusion criteria.

Table 4 summarizes the number of subjects that were included in the efficacy and safety analyses. Four subjects were excluded from the FAS who were randomized but never received study drug. A further 6 subjects were excluded from the PPS. Among subjects randomized to treatment, 28, 27, 27, 26, and 28 subjects took study medication and were evaluated for efficacy measures (FAS) and safety measures for the 1, 3, 5, and 10 mg tofacitinib BID and placebo groups, respectively.

Table 4. Subjects Included in Efficacy and Safety Analyses

	Tofacitinib				
	1 mg BID	**3 mg BID**	**5 mg BID**	**10 mg BID**	**Placebo**
Number (%) of subjects					
Randomized to study treatment	28	28	28	28	28
Treated	28	27	27	26	28
Analyzed for efficacy:					
Full analysis set	28 (100)	27 (96.4)	27 (96.4)	26 (92.9)	28 (100)
Per protocol set	28 (100)	26 (92.9)	27 (96.4)	24 (85.7)	25 (89.3)
Analyzed for safety:					
Adverse events	28 (100)	27 (96.4)	27 (96.4)	26 (92.9)	28 (100)
Laboratory data	28 (100)	27 (96.4)	27 (96.4)	26 (92.9)	28 (100)

BID = twice daily.

Treatment groups were comparable with regard to demography and baseline characteristics (Table 5). Subjects ranged in age from 24 to 70 years with mean ages ranging from 50.0 to 53.3 years among treatment groups. The majority of the subjects were females.

Table 5. Demographic Characteristics

	Tofacitinib				
	1 mg BID	**3 mg BID**	**5 mg BID**	**10 mg BID**	**Placebo**
Number of subjects	28	27	27	26	28
Age (years):					
18-44	6	7	6	9	7
45-64	21	16	21	15	18
≥65	1	4	0	2	3
Mean	52.0	53.3	50.0	50.6	50.6
SD	9.4	12.1	9.8	10.0	12.4
Range	30-68	30-70	24-62	33-69	24-68
Sex					
Male	7	3	5	1	3
Female	21	24	22	25	25
Weight (kg):					
Mean	55.8	53.7	54.6	52.6	53.4
SD	10.4	9.7	10.4	10.8	8.4
Range	40.0-80.0	37.6-81.2	41.0-76.1	39.2-80.8	41.3-70.6
Body Mass Index(kg/m^2):					
Mean	22.1	21.3	21.5	21.4	21.8
SD	3.4	3.1	3.0	3.8	3.3
Range	16.6-30.1	15.5-27.2	17.0-28.0	16.7-30.2	17.0-33.1
Height (cm):					
Mean	158.8	158.4	158.9	156.6	156.6
SD	8.4	7.4	9.4	6.3	7.0
Range	144.5-175.0	146.2-179.9	143.5-181.0	141.0-166.4	143.5-171.3

BID = twice daily, SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoint:

American College of Rheumatology 20% Improvement in Disease Activity (ACR20) Response Rate at Week 12:

The significant dose-response relationship in tofacitinib doses including placebo was shown by using Cochran-Armitage trend test on ACR20 response rate at Week 12 on the FAS. The ACR20 response rates using LOCF for handling missing components, at Week 12 were 64.3%, 77.8%, 96.3%, 80.8% and 14.3% for 1, 3, 5, 10 mg BID and placebo respectively (Table 6). The response rate differences from placebo were at least 50% for all tofacitinib treatment groups (Table 7).

Table 6. Cochran-Armitage Trend Test on ACR20 Response Rate at Week 12 (FAS, LOCF)

		Response Rate		
Treatment	**N**	**n**	**(%)**	**p-Value**
1 mg BID	28	18	64.3	<0.0001
3 mg BID	27	21	77.8	–
5 mg BID	27	26	96.3	–
10 mg BID	26	21	80.8	–
Placebo	28	4	14.3	–

ACR20 = American College of Rheumatology 20% improvement in disease activity, BID = twice daily, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria.

Table 7. Normal Approximation to ACR20 Response Rate at Week 12 (FAS, LOCF)

					Difference From Placebo				
							90% CI		
	N	**n**	**Percent**	**SE**	**Difference (%)**	**SE**	**Lower**	**Upper**	**p-Value**
Week 12									
1 mg BID	28	18	64.29	9.06	50.00	11.21	31.55	68.45	<0.0001
3 mg BID	27	21	77.78	8.00	63.49	10.38	46.42	80.57	<0.0001
5 mg BID	27	26	96.30	3.63	82.01	7.55	69.60	94.42	<0.0001
10 mg BID	26	21	80.77	7.73	66.48	10.17	49.75	83.22	<0.0001
Placebo	28	4	14.29	6.61	–	–	–	–	–

ACR20 = American College of Rheumatology 20% improvement in disease activity, BID = twice daily, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria, SE = standard error.

Secondary Efficacy Endpoints:

American College of Rheumatology 20% Improvement in Disease Activity (ACR20) Response Rate at Weeks 1, 2, 4 and 8:

The ACR20 response rates are shown in Table 8. The response rates were significant ($p < 0.05$) for tofacitinib-treated groups (except for only 3 mg BID at Week 1) compared to placebo. The doses of 1, 3, 5, 10 mg BID showed both statistically and in clinically meaningful increases from placebo group.

Table 8. Normal Approximation to ACR20 Response Rate at Weeks 1, 2, 4 and 8 (FAS, LOCF)

					Difference From Placebo				
							90% CI		
	N	n	Percent	SE	Difference (%)	SE	Lower	Upper	p-Value
Week 1									
1 mg BID	28	8	28.57	8.54	25.00	9.23	9.82	40.18	0.0068
3 mg BID	27	4	14.81	6.84	11.24	7.68	-1.40	23.88	0.1434
5 mg BID	27	8	29.63	8.79	26.06	9.46	10.49	41.62	0.0059
10 mg BID	26	10	38.46	9.54	34.89	10.17	18.17	51.61	0.0006
Placebo	28	1	3.57	3.51	–	–	–	–	–
Week 2									
1 mg BID	28	9	32.14	8.83	21.43	10.59	4.01	38.84	0.0429
3 mg BID	27	11	40.74	9.46	30.03	11.12	11.74	48.31	0.0069
5 mg BID	27	17	62.96	9.29	52.25	10.98	34.19	70.31	<0.0001
10 mg BID	26	13	50.00	9.81	39.29	11.42	20.51	58.06	0.0006
Placebo	28	3	10.71	5.85	–	–	–	–	–
Week 4									
1 mg BID	28	14	50.00	9.45	39.29	11.11	21.01	57.56	0.0004
3 mg BID	27	15	55.56	9.56	44.84	11.21	26.40	63.28	<0.0001
5 mg BID	27	24	88.89	6.05	78.17	8.41	64.34	92.01	<0.0001
10 mg BID	26	20	76.92	8.26	66.21	10.12	49.56	82.86	<0.0001
Placebo	28	3	10.71	5.85	–	–	–	–	–
Week 8									
1 mg BID	28	19	67.86	8.83	46.43	11.75	27.10	65.75	<0.0001
3 mg BID	27	18	66.67	9.07	45.24	11.93	25.61	64.87	0.0002
5 mg BID	27	26	96.30	3.63	74.87	8.56	60.78	88.96	<0.0001
10 mg BID	26	21	80.77	7.73	59.34	10.95	41.33	77.35	<0.0001
Placebo	28	6	21.43	7.75	–	–	–	–	–

ACR20 = American College of Rheumatology 20% improvement in disease activity, BID = twice daily, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria, SE = standard error.

American College of Rheumatology 50% Improvement in Disease Activity (ACR50) Response Rate at Weeks 1, 2, 4, 8 and 12:

The ACR50 response rates using LOCF at Week 12 are shown in Table 9. The dose-response relationship in tofacitinib doses including placebo was shown with statistical significance ($p < 0.0001$) by Cochran-Armitage trend test. ACR50 response rates at each week are shown in Table 10. The difference was largest for 5 mg BID at Week 12 (67.20%). The 1 mg BID dose failed to achieve significant separation from placebo except Week 8. The 3 mg BID dose group was not statistically different from placebo until Week 2. The 5 mg and 10 mg BID doses showed both statistically ($p < 0.05$) and in clinically meaningful increases from placebo from Week 2.

Table 9. Cochran-Armitage Trend Test on ACR50 Response Rate at Week 12 (FAS, LOCF)

		Response Rate		
Treatment	N	n	(%)	p-Value
1 mg BID	28	9	32.1	<0.0001
3 mg BID	27	12	44.4	–
5 mg BID	27	22	81.5	–
10 mg BID	26	15	57.7	–
Placebo	28	4	14.3	–

ACR50 = American College of Rheumatology 50% improvement in disease activity, BID = twice daily, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria.

Table 10. Normal Approximation to ACR50 Response Rate at Weeks 1, 2, 4, 8 and 12 (FAS, LOCF)

					Difference From Placebo				
							90% CI		
	N	n	Percent	SE	Difference (%)	SE	Lower	Upper	p-Value
Week 1									
1 mg BID	28	2	7.14	4.87	7.14	4.87	-0.86	15.15	0.1422
3 mg BID	27	1	3.70	3.63	3.70	3.63	-2.27	9.68	0.3082
5 mg BID	27	0	0.00	–	0.00	–	–	–	1.0000
10 mg BID	26	2	7.69	5.23	7.69	5.23	-0.90	16.29	0.1410
Placebo	28	0	0.00	–	–	–	–	–	–
Week 2									
1 mg BID	28	2	7.14	4.87	7.14	4.87	-0.86	15.15	0.1422
3 mg BID	27	2	7.41	5.04	7.41	5.04	-0.88	15.70	0.1416
5 mg BID	27	7	25.93	8.43	25.93	8.43	12.05	39.80	0.0021
10 mg BID	26	7	26.92	8.70	26.92	8.70	12.61	41.23	0.0020
Placebo	28	0	0.00	–	–	–	–	–	–
Week 4									
1 mg BID	28	3	10.71	5.85	7.14	6.82	-4.07	18.36	0.2947
3 mg BID	27	6	22.22	8.00	18.65	8.74	4.28	33.02	0.0328
5 mg BID	27	8	29.63	8.79	26.06	9.46	10.49	41.62	0.0059
10 mg BID	26	9	34.62	9.33	31.04	9.97	14.65	47.44	0.0018
Placebo	28	1	3.57	3.51	–	–	–	–	–
Week 8									
1 mg BID	28	8	28.57	8.54	21.43	9.83	5.26	37.59	0.0292
3 mg BID	27	8	29.63	8.79	22.49	10.0	5.96	39.01	0.0252
5 mg BID	27	19	70.37	8.79	63.23	10.0	46.70	79.75	<0.0001
10 mg BID	26	13	50.00	9.81	42.86	10.9	24.85	60.87	<0.0001
Placebo	28	2	7.14	4.87	–	–	–	–	–
Week 12									
1 mg BID	28	9	32.14	8.83	17.86	11.0	-0.28	36.00	0.1054
3 mg BID	27	12	44.44	9.56	30.16	11.6	11.03	49.28	0.0095
5 mg BID	27	22	81.48	7.48	67.20	9.98	50.78	83.61	<0.0001
10 mg BID	26	15	57.69	9.69	43.41	11.7	24.11	62.70	0.0002
Placebo	28	4	14.29	6.61	–	–	–	–	–

ACR50 = American College of Rheumatology 50% improvement in disease activity, BID = twice daily, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria, SE = standard error.

American College of Rheumatology 70% Improvement in Disease Activity (ACR70) Response Rate at Weeks 1, 2, 4, 8 and 12:

The ACR70 response rates using LOCF at Week 12 are shown in Table 11. The dose-response relationship in tofacitinib doses including placebo was shown with statistical significance ($p < 0.0001$) by Cochran-Armitage trend test. ACR70 response rates at each week are shown in Table 12. The difference was largest for 10 mg BID at Week 12 (31.04%). The 1 and 3 mg BID doses failed to achieve significant separation from placebo. The 5 mg BID dose group was not statistically different from placebo until Week 2. The 5 mg and 10 mg BID doses showed both statistically ($p < 0.05$) and in clinically meaningful increases from placebo from Week 8.

Table 11. Cochran-Armitage Trend Test on ACR70 Response Rate at Week 12 (FAS, LOCF)

		Response Rate		
Treatment	**N**	**n**	**(%)**	**p-Value**
1 mg BID	28	2	7.1	<0.0001
3 mg BID	27	4	14.8	–
5 mg BID	27	9	33.3	–
10 mg BID	26	9	34.6	–
Placebo	28	1	3.6	–

ACR70 = American College of Rheumatology 70% improvement in disease activity, BID = twice daily, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria.

Table 12. Normal Approximation to ACR70 Response Rate at Weeks 1, 2, 4, 8 and 12 (FAS, LOCF)

					Difference From Placebo				
							90% CI		
	N	n	Percent	SE	Difference (%)	SE	Lower	Upper	p-Value
Week 1									
1 mg BID	28	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	27	0	0.00	–	0.00	–	–	–	1.0000
5 mg BID	27	0	0.00	–	0.00	–	–	–	1.0000
10 mg BID	26	1	3.85	3.77	3.85	3.77	-2.36	10.05	0.3078
Placebo	28	0	0.00	–	–	–	–	–	–
Week 2									
1 mg BID	28	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	27	1	3.70	3.63	3.70	3.63	-2.27	9.68	0.3082
5 mg BID	27	3	11.11	6.05	11.11	6.05	1.16	21.06	0.0662
10 mg BID	26	1	3.85	3.77	3.85	3.77	-2.36	10.05	0.3078
Placebo	28	0	0.00	–	–	–	–	–	–
Week 4									
1 mg BID	28	1	3.57	3.51	3.57	3.51	-2.20	9.34	0.3085
3 mg BID	27	2	7.41	5.04	7.41	5.04	-0.88	15.70	0.1416
5 mg BID	27	4	14.81	6.84	14.81	6.84	3.57	26.06	0.0302
10 mg BID	26	2	7.69	5.23	7.69	5.23	-0.90	16.29	0.1410
Placebo	28	0	0.00	–	–	–	–	–	–
Week 8									
1 mg BID	28	1	3.57	3.51	0.00	4.96	-8.16	8.16	1.0000
3 mg BID	27	2	7.41	5.04	3.84	6.14	-6.26	13.94	0.5321
5 mg BID	27	9	33.33	9.07	29.76	9.73	13.76	45.76	0.0022
10 mg BID	26	7	26.92	8.70	23.35	9.38	7.92	38.78	0.0128
Placebo	28	1	3.57	3.51	–	–	–	–	–
Week 12									
1 mg BID	28	2	7.14	4.87	3.57	6.00	-6.30	13.44	0.5516
3 mg BID	27	4	14.81	6.84	11.24	7.68	-1.40	23.88	0.1434
5 mg BID	27	9	33.33	9.07	29.76	9.73	13.76	45.76	0.0022
10 mg BID	26	9	34.62	9.33	31.04	9.97	14.65	47.44	0.0018
Placebo	28	1	3.57	3.51	–	–	–	–	–

ACR70 = American College of Rheumatology 70% improvement in disease activity, BID = twice daily, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria, SE = standard error.

American College of Rheumatology 70% Improvement in Disease Activity (ACR90) Response Rate at Weeks 1, 2, 4, 8 and 12:

The ACR90 response rates using LOCF at Week 12 are shown in Table 13. The dose-response relationship in tofacitinib doses including placebo was shown with statistical significance (p =0.0315) by Cochran-Armitage trend test. ACR90 response rates at each week are shown in Table 14. The difference was largest for 10 mg BID at Week 12 (11.54%).

Table 13. Cochran-Armitage Trend Test on ACR90 Response Rate at Week 12 (FAS, LOCF)

		Response Rate		
Treatment	N	n	(%)	p-Value
1 mg BID	28	0	0.0	0.0315
3 mg BID	27	3	11.1	–
5 mg BID	27	1	3.7	–
10 mg BID	26	3	11.5	–
Placebo	28	0	0.0	–

ACR90 = American College of Rheumatology 90% improvement in disease activity, BID = twice daily, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria.

Table 14. Normal Approximation to ACR90 Response Rate at Weeks 1, 2, 4, 8 and 12 (FAS, LOCF)

					Difference From Placebo				
							90% CI		
	N	n	Percent	SE	Difference (%)	SE	Lower	Upper	p-Value
Week 1									
1 mg BID	28	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	27	0	0.00	–	0.00	–	–	–	1.0000
5 mg BID	27	0	0.00	–	0.00	–	–	–	1.0000
10 mg BID	26	0	0.00	–	0.00	–	–	–	1.0000
Placebo	28	0	0.00	–	–	–	–	–	–
Week 2									
1 mg BID	28	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	27	0	0.00	–	0.00	–	–	–	1.0000
5 mg BID	27	0	0.00	–	0.00	–	–	–	1.0000
10 mg BID	26	1	3.85	3.77	3.85	3.77	-2.36	10.05	0.3078
Placebo	28	0	0.00	–	–	–	–	–	–
Week 4									
1 mg BID	28	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	27	0	0.00	–	0.00	–	–	–	1.0000
5 mg BID	27	1	3.70	3.63	3.70	3.63	-2.27	9.68	0.3082
10 mg BID	26	0	0.00	–	0.00	–	–	–	1.0000
Placebo	28	0	0.00	–	–	–	–	–	–
Week 8									
1 mg BID	28	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	27	1	3.70	3.63	3.70	3.63	-2.27	9.68	0.3082
5 mg BID	27	2	7.41	5.04	7.41	5.04	-0.88	15.70	0.1416
10 mg BID	26	1	3.85	3.77	3.85	3.77	-2.36	10.05	0.3078
Placebo	28	0	0.00	–	–	–	–	–	–
Week 12									
1 mg BID	28	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	27	3	11.11	6.05	11.11	6.05	1.16	21.06	0.0662
5 mg BID	27	1	3.70	3.63	3.70	3.63	-2.27	9.68	0.3082
10 mg BID	26	3	11.54	6.27	11.54	6.27	1.23	21.85	0.0655
Placebo	28	0	0.00	–	–	–	–	–	–

ACR90 = American College of Rheumatology 90% improvement in disease activity, BID = twice daily, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting prespecified criteria, SE = standard error.

Tender/Painful Joint Count (68):

The mean changes from Baseline in painful and tender joint counts are presented in Table 15. All BID doses separated from placebo with statistically significant decreases ($p < 0.10$) from Week 4.

Table 15. Mean Change From Baseline in Painful and Tender Joint Counts at Weeks 1, 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-4.45	1.304	-0.96	1.844	-4.01	2.08	0.6013
3 mg BID	26	-4.41	1.344	-0.93	1.873	-4.01	2.16	0.6215
5 mg BID	27	-4.01	1.330	-0.52	1.862	-3.60	2.55	0.7787
10 mg BID	26	-4.81	1.354	-1.33	1.880	-4.43	1.77	0.4810
Placebo	28	-3.49	1.304	–	–	–	–	–
Week 2								
1 mg BID	27	-4.67	1.323	0.15	1.885	-2.96	3.26	0.9378
3 mg BID	27	-6.63	1.328	-1.81	1.888	-4.93	1.30	0.3372
5 mg BID	27	-7.71	1.330	-2.90	1.890	-6.01	0.22	0.1262
10 mg BID	25	-7.42	1.375	-2.61	1.922	-5.78	0.56	0.1758
Placebo	26	-4.82	1.343	–	–	–	–	–
Week 4								
1 mg BID	27	-6.26	1.323	-3.71	1.898	-6.84	-0.58	0.0517
3 mg BID	26	-9.01	1.346	-6.45	1.914	-9.61	-3.30	0.0008
5 mg BID	27	-9.01	1.330	-6.45	1.903	-9.59	-3.31	0.0008
10 mg BID	24	-10.21	1.395	-7.65	1.949	-10.86	-4.43	0.0001
Placebo	25	-2.56	1.362	–	–	–	–	–
Week 8								
1 mg BID	26	-9.41	1.340	-5.23	1.924	-8.40	-2.06	0.0069
3 mg BID	25	-10.59	1.364	-6.41	1.941	-9.61	-3.21	0.0011
5 mg BID	26	-12.36	1.347	-8.17	1.930	-11.36	-4.99	<0.0001
10 mg BID	23	-12.39	1.416	-8.21	1.977	-11.47	-4.95	<0.0001
Placebo	24	-4.18	1.381	–	–	–	–	–
Week 12								
1 mg BID	26	-10.22	1.340	-4.96	1.924	-8.13	-1.78	0.0104
3 mg BID	24	-9.62	1.382	-4.36	1.954	-7.58	-1.13	0.0264
5 mg BID	24	-13.63	1.382	-8.36	1.955	-11.59	-5.14	<0.0001
10 mg BID	21	-12.87	1.459	-7.61	2.009	-10.92	-4.29	0.0002
Placebo	24	-5.27	1.381	–	–	–	–	–

BID = twice daily, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, SE = standard error.

Swollen Joint Count (66):

The mean changes from Baseline in swollen joint counts are presented in Table 16. From Week 2, all BID doses showed statistically significant decreases ($p < 0.10$) from placebo.

Table 16. Mean Change From Baseline in Swollen Joint Counts at Weeks 1, 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-3.60	1.007	-2.71	1.422	-5.05	-0.36	0.0578
3 mg BID	26	-2.44	1.038	-1.55	1.446	-3.93	0.84	0.2856
5 mg BID	27	-2.47	1.025	-1.58	1.437	-3.95	0.79	0.2734
10 mg BID	26	-5.15	1.044	-4.25	1.450	-6.64	-1.86	0.0036
Placebo	28	-0.90	1.006	–	–	–	–	–
Week 2								
1 mg BID	27	-5.29	1.022	-3.36	1.455	-5.76	-0.96	0.0214
3 mg BID	27	-5.21	1.024	-3.28	1.458	-5.69	-0.88	0.0249
5 mg BID	27	-5.77	1.025	-3.84	1.459	-6.25	-1.44	0.0088
10 mg BID	25	-6.86	1.061	-4.93	1.484	-7.37	-2.48	0.0010
Placebo	26	-1.93	1.037	–	–	–	–	–
Week 4								
1 mg BID	27	-5.70	1.022	-3.74	1.466	-6.16	-1.32	0.0112
3 mg BID	26	-6.42	1.039	-4.46	1.479	-6.90	-2.02	0.0027
5 mg BID	27	-7.77	1.025	-5.81	1.470	-8.23	-3.39	<0.0001
10 mg BID	24	-8.41	1.077	-6.45	1.506	-8.93	-3.96	<0.0001
Placebo	25	-1.96	1.053	–	–	–	–	–
Week 8								
1 mg BID	26	-7.50	1.036	-5.07	1.487	-7.52	-2.62	0.0007
3 mg BID	25	-8.49	1.053	-6.06	1.501	-8.54	-3.59	<0.0001
5 mg BID	26	-10.79	1.039	-8.36	1.491	-10.82	-5.90	<0.0001
10 mg BID	23	-9.94	1.094	-7.52	1.529	-10.04	-4.99	<0.0001
Placebo	24	-2.43	1.068	–	–	–	–	–
Week 12								
1 mg BID	26	-8.23	1.036	-5.84	1.487	-8.30	-3.39	<0.0001
3 mg BID	24	-9.31	1.068	-6.92	1.511	-9.42	-4.43	<0.0001
5 mg BID	24	-11.71	1.068	-9.33	1.512	-11.82	-6.84	<0.0001
10 mg BID	21	-11.30	1.129	-8.92	1.555	-11.48	-6.35	<0.0001
Placebo	24	-2.39	1.068	–	–	–	–	–

BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of subjects, SE = standard error.

Patient's Assessment of Pain Visual Analog Scale (VAS):

The mean changes from Baseline in pain VAS scores are presented in Table 17. The 3, 5 and 10 mg BID doses separated from placebo, with statistically significant decreases ($p < 0.10$) from Week 1. The 1 mg BID dose separated from placebo with statistically significant decreases ($p < 0.10$) from Week 4.

Table 17. Mean Change From Baseline Pain Visual Analog Score at Weeks 1, 2, 4, 8, 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-8.89	3.585	-4.42	5.071	-12.79	3.95	0.3837
3 mg BID	26	-13.50	3.691	-9.04	5.148	-17.53	-0.54	0.0804
5 mg BID	27	-13.59	3.652	-9.12	5.117	-17.57	-0.68	0.0758
10 mg BID	26	-16.19	3.723	-11.72	5.167	-20.25	-3.19	0.0241
Placebo	28	-4.47	3.586	–	–	–	–	–
Week 2								
1 mg BID	27	-9.83	3.629	-5.62	5.166	-14.14	2.91	0.2778
3 mg BID	27	-15.42	3.656	-11.21	5.188	-19.77	-2.65	0.0316
5 mg BID	27	-20.59	3.652	-16.37	5.180	-24.92	-7.82	0.0017
10 mg BID	25	-22.96	3.770	-18.74	5.264	-27.43	-10.05	0.0004
Placebo	26	-4.22	3.676	–	–	–	–	–
Week 4								
1 mg BID	27	-12.50	3.629	-10.99	5.197	-19.57	-2.42	0.0353
3 mg BID	26	-20.74	3.696	-19.23	5.248	-27.89	-10.57	0.0003
5 mg BID	27	-28.59	3.652	-27.08	5.211	-35.68	-18.48	<0.0001
10 mg BID	24	-24.50	3.815	-23.00	5.327	-31.79	-14.21	<0.0001
Placebo	25	-1.51	3.719	–	–	–	–	–
Week 8								
1 mg BID	26	-22.29	3.666	-20.07	5.253	-28.73	-11.40	0.0002
3 mg BID	25	-25.17	3.736	-22.95	5.306	-31.70	-14.19	<0.0001
5 mg BID	27	-31.18	3.652	-28.96	5.241	-37.61	-20.31	<0.0001
10 mg BID	23	-34.09	3.860	-31.87	5.388	-40.76	-22.97	<0.0001
Placebo	24	-2.22	3.761	–	–	–	–	–
Week 12								
1 mg BID	26	-22.75	3.666	-16.61	5.253	-25.28	-7.94	0.0017
3 mg BID	24	-27.56	3.777	-21.43	5.334	-30.23	-12.62	<0.0001
5 mg BID	24	-34.33	3.766	-28.19	5.321	-36.97	-19.41	<0.0001
10 mg BID	21	-36.82	3.956	-30.68	5.457	-39.69	-21.68	<0.0001
Placebo	24	-6.14	3.761	–	–	–	–	–

BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of subjects, SE = standard error.

Patient's Global Assessment of Arthritis Visual Analog Scale (VAS):

The mean changes from Baseline in the patient's global assessment of arthritis are presented in Table 18. The 3, 5 and 10 mg BID doses separated from placebo, with statistically significant decreases from Week 2. The 10 mg BID dose was already statistically significant ($p < 0.10$) at Week 1. The 1 mg BID dose separated from placebo with statistically significant decreases ($p < 0.10$) from Week 4. Changes in patient's global assessment, compared to placebo, were generally similar to changes in patient assessment of pain, except the case of 3 mg and 5 mg BID at Week 1.

Table 18. Mean Change From Baseline in Patient Global Assessment at Weeks 1, 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-11.43	3.581	-2.91	5.071	-11.28	5.46	0.5662
3 mg BID	26	-15.31	3.690	-6.78	5.153	-15.29	1.72	0.1890
5 mg BID	27	-15.11	3.648	-6.59	5.119	-15.03	1.86	0.1993
10 mg BID	26	-19.59	3.726	-11.07	5.161	-19.58	-2.55	0.0328
Placebo	28	-8.52	3.585	–	–	–	–	–
Week 2								
1 mg BID	27	-11.76	3.627	-6.38	5.171	-14.91	2.16	0.2185
3 mg BID	27	-15.84	3.652	-10.45	5.195	-19.02	-1.88	0.0451
5 mg BID	27	-23.88	3.648	-18.50	5.188	-27.06	-9.94	0.0004
10 mg BID	25	-24.97	3.773	-19.58	5.262	-28.27	-10.90	0.0002
Placebo	26	-5.38	3.681	–	–	–	–	–
Week 4								
1 mg BID	27	-13.24	3.627	-9.59	5.205	-18.18	-1.00	0.0665
3 mg BID	26	-24.14	3.696	-20.49	5.260	-29.17	-11.81	0.0001
5 mg BID	27	-28.74	3.648	-25.08	5.221	-33.70	-16.47	<0.0001
10 mg BID	24	-25.62	3.820	-21.97	5.328	-30.76	-13.18	<0.0001
Placebo	25	-3.66	3.728	–	–	–	–	–
Week 8								
1 mg BID	26	-22.85	3.666	-19.46	5.264	-28.14	-10.77	0.0003
3 mg BID	25	-27.26	3.738	-23.87	5.322	-32.65	-15.09	<0.0001
5 mg BID	27	-35.85	3.648	-32.45	5.253	-41.12	-23.78	<0.0001
10 mg BID	23	-33.59	3.868	-30.19	5.393	-39.09	-21.30	<0.0001
Placebo	24	-3.40	3.772	–	–	–	–	–
Week 12								
1 mg BID	26	-26.55	3.666	-17.73	5.264	-26.42	-9.05	0.0009
3 mg BID	24	-33.03	3.781	-24.22	5.352	-33.05	-15.39	<0.0001
5 mg BID	24	-38.92	3.767	-30.11	5.335	-38.91	-21.31	<0.0001
10 mg BID	21	-37.58	3.969	-28.77	5.466	-37.79	-19.75	<0.0001
Placebo	24	-8.81	3.772	–	–	–	–	–

BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of subjects, SE = standard error.

Physician's Global Assessment of Arthritis Visual Analog Scale (VAS):

The mean changes from Baseline in the physician's global assessment of arthritis are presented in Table 19. The 1 mg and 3 mg BID doses separated from placebo, with statistically significant decreases ($p < 0.10$) from Week 4. The 5 mg BID doses separated from placebo, with statistically significant decreases ($p < 0.10$) from Week 2. The 10 mg BID dose was already statistically significant ($p < 0.10$) at Week 1. Changes in physician's global assessment, compared to placebo, were generally similar to changes in patient's global assessment, except for the case of 3 mg BID at Week 2.

Table 19. Mean Change From Baseline in Physician Global Assessment at Weeks 1, 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-13.43	3.241	-4.01	4.579	-11.56	3.54	0.3819
3 mg BID	26	-14.01	3.322	-4.59	4.631	-12.23	3.05	0.3219
5 mg BID	27	-14.79	3.285	-5.37	4.602	-12.96	2.22	0.2439
10 mg BID	26	-23.76	3.348	-14.35	4.647	-22.01	-6.68	0.0022
Placebo	28	-9.42	3.225	–	–	–	–	–
Week 2								
1 mg BID	27	-19.50	3.287	-5.27	4.681	-12.99	2.45	0.2607
3 mg BID	27	-18.57	3.284	-4.35	4.670	-12.05	3.36	0.3527
5 mg BID	27	-25.45	3.285	-11.23	4.668	-18.93	-3.53	0.0167
10 mg BID	25	-31.13	3.398	-16.90	4.748	-24.73	-9.07	0.0004
Placebo	26	-14.23	3.319	–	–	–	–	–
Week 4								
1 mg BID	27	-22.24	3.287	-12.55	4.715	-20.33	-4.77	0.0082
3 mg BID	26	-27.68	3.326	-17.99	4.733	-25.79	-10.18	0.0002
5 mg BID	27	-35.38	3.285	-25.69	4.700	-33.44	-17.94	<0.0001
10 mg BID	24	-35.56	3.446	-25.87	4.814	-33.81	-17.93	<0.0001
Placebo	25	-9.69	3.366	–	–	–	–	–
Week 8								
1 mg BID	26	-33.64	3.326	-16.82	4.775	-24.70	-8.95	0.0005
3 mg BID	25	-34.01	3.369	-17.19	4.796	-25.10	-9.28	0.0004
5 mg BID	26	-42.46	3.325	-25.64	4.761	-33.49	-17.79	<0.0001
10 mg BID	23	-42.09	3.495	-25.27	4.880	-33.32	-17.23	<0.0001
Placebo	24	-16.82	3.412	–	–	–	–	–
Week 12								
1 mg BID	26	-36.98	3.326	-20.88	4.775	-28.75	-13.00	<0.0001
3 mg BID	24	-35.50	3.413	-19.39	4.826	-27.35	-11.43	<0.0001
5 mg BID	24	-45.87	3.410	-29.76	4.820	-37.71	-21.81	<0.0001
10 mg BID	21	-43.70	3.598	-27.59	4.956	-35.77	-19.42	<0.0001
Placebo	24	-16.11	3.412	–	–	–	–	–

BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of subjects, SE = standard error.

Health Assessment Questionnaire-Disability Index (HAQ-DI):

The HAQ-DI values decreased over time and with increased dose of tofacitinib, which was indicative of improved functional status. The changes from Baseline in HAQ-DI values are presented in Table 20. The 1 mg and 3 mg BID did not separate from placebo until Week 8. Decreases from Baseline were statistically significant ($p < 0.10$) compared to placebo in the 5 mg BID dose from Week 2, in the 10 mg BID from Week 1.

Table 20. Mean Change From Baseline in Health Assessment Questionnaire-Disability Index at Weeks 1, 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-0.09	0.070	-0.10	0.099	-0.26	0.07	0.3224
3 mg BID	26	-0.08	0.072	-0.09	0.101	-0.25	0.08	0.3784
5 mg BID	27	-0.12	0.071	-0.13	0.100	-0.29	0.04	0.1977
10 mg BID	26	-0.32	0.073	-0.32	0.101	-0.49	-0.16	0.0016
Placebo	28	0.01	0.070	–	–	–	–	–
Week 2								
1 mg BID	27	-0.13	0.071	-0.11	0.101	-0.28	0.05	0.2571
3 mg BID	27	-0.15	0.072	-0.14	0.101	-0.31	0.03	0.1694
5 mg BID	27	-0.29	0.071	-0.28	0.101	-0.44	-0.11	0.0070
10 mg BID	25	-0.38	0.074	-0.37	0.103	-0.54	-0.20	0.0004
Placebo	26	-0.02	0.072	–	–	–	–	–
Week 4								
1 mg BID	27	-0.23	0.071	-0.14	0.101	-0.30	0.03	0.1829
3 mg BID	26	-0.23	0.072	-0.14	0.102	-0.31	0.03	0.1819
5 mg BID	27	-0.38	0.071	-0.29	0.102	-0.45	-0.12	0.0052
10 mg BID	24	-0.42	0.074	-0.33	0.104	-0.50	-0.16	0.0016
Placebo	25	-0.09	0.072	–	–	–	–	–
Week 8								
1 mg BID	26	-0.36	0.071	-0.40	0.102	-0.57	-0.23	0.0001
3 mg BID	25	-0.29	0.073	-0.33	0.103	-0.50	-0.16	0.0016
5 mg BID	27	-0.45	0.071	-0.49	0.102	-0.66	-0.32	<0.0001
10 mg BID	23	-0.52	0.075	-0.56	0.105	-0.73	-0.38	<0.0001
Placebo	24	0.04	0.073	–	–	–	–	–
Week 12								
1 mg BID	26	-0.38	0.071	-0.34	0.102	-0.50	-0.17	0.0012
3 mg BID	24	-0.39	0.073	-0.34	0.103	-0.52	-0.17	0.0010
5 mg BID	24	-0.51	0.073	-0.46	0.103	-0.64	-0.29	<0.0001
10 mg BID	21	-0.54	0.076	-0.50	0.106	-0.67	-0.32	<0.0001
Placebo	24	-0.05	0.073	–	–	–	–	–

BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of subjects, SE = standard error.

C-Reactive Protein (CRP):

The mean changes from Baseline in serum CRP level are presented in Table 21. All tofacitinib BID doses showed statistically significant decreases ($p < 0.10$) from placebo, from Week 1 excluding the case of 10 mg BID group at Week 8.

Table 21. Mean Change From Baseline in C-Reactive Protein (mg/L) at Weeks 1, 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-8.92	2.506	-7.10	3.540	-12.95	-1.26	0.0459
3 mg BID	26	-11.87	2.580	-10.05	3.594	-15.98	-4.12	0.0055
5 mg BID	27	-15.50	2.557	-13.68	3.576	-19.58	-7.78	0.0002
10 mg BID	26	-18.21	2.597	-16.39	3.605	-22.34	-10.44	<0.0001
Placebo	28	-1.82	2.501	–	–	–	–	–
Week 2								
1 mg BID	27	-9.03	2.538	-6.63	3.611	-12.59	-0.67	0.0675
3 mg BID	27	-14.42	2.554	-12.01	3.623	-17.99	-6.04	0.0010
5 mg BID	27	-16.85	2.557	-14.45	3.620	-20.42	-8.48	<0.0001
10 mg BID	25	-19.53	2.632	-17.13	3.675	-23.19	-11.06	<0.0001
Placebo	26	-2.40	2.566	–	–	–	–	–
Week 4								
1 mg BID	27	-10.49	2.538	-7.47	3.634	-13.47	-1.47	0.0407
3 mg BID	26	-15.23	2.583	-12.21	3.666	-18.26	-6.16	0.0010
5 mg BID	27	-17.67	2.557	-14.65	3.642	-20.66	-8.63	<0.0001
10 mg BID	24	-18.97	2.665	-15.95	3.720	-22.09	-9.81	<0.0001
Placebo	25	-3.02	2.597	–	–	–	–	–
Week 8								
1 mg BID	26	-11.51	2.566	-6.11	3.675	-12.17	-0.04	0.0976
3 mg BID	25	-18.75	2.612	-13.34	3.707	-19.46	-7.22	0.0004
5 mg BID	27	-15.83	2.557	-10.43	3.665	-16.48	-4.38	0.0047
10 mg BID	23	-10.46	2.698	-5.05	3.766	-11.27	1.16	0.1807
Placebo	24	-5.41	2.629	–	–	–	–	–
Week 12								
1 mg BID	26	-13.29	2.566	-9.96	3.675	-16.03	-3.90	0.0071
3 mg BID	24	-14.04	2.641	-10.71	3.728	-16.87	-4.56	0.0043
5 mg BID	24	-15.87	2.642	-12.54	3.724	-18.69	-6.40	0.0009
10 mg BID	21	-13.64	2.769	-10.32	3.817	-16.62	-4.02	0.0072
Placebo	24	-3.33	2.629	–	–	–	–	–

BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of subjects, SE = standard error.

ACR-N:

The mean changes from Baseline in ACR-N are presented in Table 22. All BID doses separated from placebo, with statistically significant increases ($p < 0.10$) from Week 1. The area under the ACR-N curve from Baseline to Week 12 is summarized in Table 23.

Table 22. Mean ACR-N at Weeks 1, 2, 4, 8 and 12 (FAS, LOCF)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	4.80	6.428	15.88	9.091	0.88	30.88	0.0816
3 mg BID	27	6.06	6.546	17.15	9.175	2.01	32.28	0.0625
5 mg BID	27	10.60	6.546	21.69	9.175	6.55	36.82	0.0187
10 mg BID	26	10.73	6.671	21.82	9.264	6.53	37.10	0.0191
Placebo	28	-11.08	6.428	–	–	–	–	–
Week 2								
1 mg BID	28	8.74	6.428	17.57	9.091	2.57	32.57	0.0541
3 mg BID	27	17.43	6.546	26.26	9.175	11.13	41.40	0.0045
5 mg BID	27	30.61	6.546	39.45	9.175	24.31	54.58	<0.0001
10 mg BID	26	25.15	6.671	33.99	9.264	18.71	49.27	0.0003
Placebo	28	-8.84	6.428	–	–	–	–	–
Week 4								
1 mg BID	28	14.67	6.428	38.22	9.091	23.22	53.22	<0.0001
3 mg BID	27	23.83	6.546	47.37	9.175	32.24	62.51	<0.0001
5 mg BID	27	40.88	6.546	64.43	9.175	49.29	79.56	<0.0001
10 mg BID	26	37.08	6.671	60.63	9.264	45.35	75.91	<0.0001
Placebo	28	-23.54	6.428	–	–	–	–	–
Week 8								
1 mg BID	28	30.40	6.428	49.15	9.091	34.15	64.14	<0.0001
3 mg BID	27	31.64	6.546	50.38	9.175	35.25	65.52	<0.0001
5 mg BID	27	56.76	6.546	75.50	9.175	60.37	90.64	<0.0001
10 mg BID	26	45.62	6.671	64.36	9.264	49.08	79.64	<0.0001
Placebo	28	-18.74	6.428	–	–	–	–	–
Week 12								
1 mg BID	28	30.26	6.428	41.45	9.091	26.45	56.44	<0.0001
3 mg BID	27	34.64	6.546	45.83	9.175	30.70	60.97	<0.0001
5 mg BID	27	60.16	6.546	71.34	9.175	56.21	86.48	<0.0001
10 mg BID	26	52.08	6.671	63.27	9.264	47.99	78.55	<0.0001
Placebo	28	-11.19	6.428	–	–	–	–	–

ACR-N = American College of Rheumatology criteria-N curve, BID = twice daily, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects, SE = standard error.

Table 23. Area Under the ACR-N Curve From Baseline to Week 12 (FAS, LOCF)

	Tofacitinib 1 mg BID	Tofacitinib 3 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
N	28	27	27	26	28
Mean	1708.31	2096.79	3685.71	3124.40	-1346.24
Standard deviation	2458.38	2355.96	1721.44	2011.19	2995.11

ACR-N = American College of Rheumatology criteria-N curve, BID = twice daily; FAS = full analysis set, LOCF = last observation carried forward, N = number of subjects.

Disease Activity Score (DAS) Assessment:

The mean changes from Baseline in DAS28-3 (CRP) are presented in Table 24. All BID doses separated from placebo, with statistically significant decreases ($p<0.10$) from Week 1 excluding the case of 1 mg BID group at Week 2.

The mean changes from Baseline in DAS28-4 (ESR) are presented in Table 25. The changes from Baseline in the DAS28-4 (ESR) assessments were similar to the changes from Baseline in the DAS28-3 (CRP) assessment except the case of 1 mg and 3 mg BID doses at Week 1.

Table 24. Mean Change From Baseline in DAS28-3 (CRP) at Weeks 1, 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-0.71	0.166	-0.40	0.235	-0.78	-0.01	0.0931
3 mg BID	26	-0.85	0.171	-0.53	0.239	-0.93	-0.14	0.0270
5 mg BID	27	-0.90	0.169	-0.59	0.237	-0.98	-0.20	0.0140
10 mg BID	26	-1.21	0.172	-0.90	0.240	-1.29	-0.50	0.0002
Placebo	28	-0.32	0.166	–	–	–	–	–
Week 2								
1 mg BID	27	-0.79	0.168	-0.32	0.240	-0.72	0.07	0.1797
3 mg BID	27	-1.13	0.170	-0.66	0.241	-1.06	-0.26	0.0065
5 mg BID	27	-1.53	0.169	-1.06	0.240	-1.45	-0.66	<0.0001
10 mg BID	25	-1.69	0.175	-1.22	0.244	-1.62	-0.82	<0.0001
Placebo	26	-0.47	0.171	–	–	–	–	–
Week 4								
1 mg BID	27	-1.07	0.168	-0.75	0.242	-1.15	-0.35	0.0022
3 mg BID	26	-1.42	0.172	-1.10	0.244	-1.50	-0.70	<0.0001
5 mg BID	27	-1.78	0.169	-1.46	0.242	-1.86	-1.06	<0.0001
10 mg BID	24	-2.13	0.177	-1.81	0.248	-2.21	-1.40	<0.0001
Placebo	25	-0.32	0.173	–	–	–	–	–
Week 8								
1 mg BID	26	-1.59	0.170	-1.05	0.244	-1.46	-0.65	<0.0001
3 mg BID	25	-1.97	0.174	-1.44	0.247	-1.84	-1.03	<0.0001
5 mg BID	26	-2.23	0.171	-1.70	0.245	-2.10	-1.29	<0.0001
10 mg BID	23	-2.37	0.180	-1.83	0.251	-2.24	-1.42	<0.0001
Placebo	24	-0.54	0.175	–	–	–	–	–
Week 12								
1 mg BID	26	-1.81	0.170	-1.12	0.244	-1.52	-0.72	<0.0001
3 mg BID	24	-1.84	0.176	-1.15	0.248	-1.56	-0.74	<0.0001
5 mg BID	24	-2.43	0.175	-1.74	0.248	-2.15	-1.33	<0.0001
10 mg BID	21	-2.69	0.184	-2.00	0.254	-2.42	-1.58	<0.0001
Placebo	24	-0.69	0.175	–	–	–	–	–

BID = twice daily, CI = confidence interval, CRP = C-reactive protein, DAS = disease activity score, FAS = full analysis set, N = number of subjects, SE = standard error.

Table 25. Mean Change From Baseline in DAS28-4 (ESR) at Weeks 1, 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						90% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 1								
1 mg BID	28	-0.67	0.176	-0.25	0.249	-0.66	0.16	0.3240
3 mg BID	26	-0.78	0.181	-0.36	0.252	-0.78	0.05	0.1498
5 mg BID	27	-0.92	0.179	-0.50	0.251	-0.92	-0.09	0.0462
10 mg BID	26	-1.00	0.182	-0.58	0.253	-1.00	-0.17	0.0220
Placebo	28	-0.42	0.176	–	–	–	–	–
Week 2								
1 mg BID	27	-0.79	0.178	-0.29	0.254	-0.70	0.13	0.2615
3 mg BID	27	-1.01	0.179	-0.51	0.254	-0.93	-0.09	0.0467
5 mg BID	27	-1.53	0.179	-1.02	0.254	-1.44	-0.60	<0.0001
10 mg BID	25	-1.60	0.185	-1.10	0.258	-1.52	-0.67	<0.0001
Placebo	26	-0.51	0.180	–	–	–	–	–
Week 4								
1 mg BID	27	-1.08	0.178	-0.76	0.256	-1.18	-0.34	0.0033
3 mg BID	26	-1.48	0.181	-1.15	0.257	-1.58	-0.73	<0.0001
5 mg BID	27	-1.98	0.179	-1.66	0.256	-2.08	-1.24	<0.0001
10 mg BID	24	-2.15	0.187	-1.83	0.261	-2.26	-1.40	<0.0001
Placebo	25	-0.32	0.183	–	–	–	–	–
Week 8								
1 mg BID	26	-1.70	0.180	-1.16	0.259	-1.59	-0.74	<0.0001
3 mg BID	25	-1.99	0.183	-1.45	0.261	-1.88	-1.02	<0.0001
5 mg BID	26	-2.54	0.181	-2.00	0.259	-2.43	-1.57	<0.0001
10 mg BID	23	-2.69	0.190	-2.14	0.265	-2.58	-1.71	<0.0001
Placebo	24	-0.54	0.185	–	–	–	–	–
Week 12								
1 mg BID	26	-2.00	0.180	-1.31	0.259	-1.73	-0.88	<0.0001
3 mg BID	24	-2.05	0.185	-1.36	0.262	-1.79	-0.93	<0.0001
5 mg BID	24	-2.83	0.185	-2.14	0.262	-2.57	-1.70	<0.0001
10 mg BID	21	-2.96	0.195	-2.27	0.268	-2.71	-1.82	<0.0001
Placebo	24	-0.69	0.185	–	–	–	–	–

BID = twice daily, CI = confidence interval, DAS = disease activity score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of subjects, SE = standard error.

Short Form-36 (SF-36) Health Survey:

The SF-36 health survey domain scores (physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health) at Baseline and Week 12 are summarized in Table 26.

For all domains the active dose groups had higher scores than the placebo group. Statistically significant differences ($p < 0.10$) from placebo in change from Baseline at Week 12 were seen in 1, 5 and 10 mg BID doses for physical function; 5 mg and 10 mg BID doses for role physical; all BID doses for bodily pain and general health; 5 mg BID dose for vitality; 10 mg BID dose for social function; 1 mg BID dose for role-emotion and 1 mg and 5 mg BID doses for mental health.

Table 26. SF-36 Scores at Baseline and Week 12 (FAS, No Imputation)

	Tofacitinib 1 mg BID	Tofacitinib 3 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Baseline					
N	28	27	27	26	28
Physical functioning	37.87±9.10	37.94±9.37	38.87±10.41	40.93±9.47	38.69 ±9.80
Role physical	39.27±11.83	41.43±13.22	44.25±10.25	45.64±13.33	42.77 ±11.69
Bodily pain	37.27±7.89	36.89±7.53	38.59±8.44	40.58±7.00	36.81 ±9.61
General health	37.54±6.14	37.56±7.53	37.57±10.16	38.87±8.25	37.42 ±7.00
Vitality	45.07±11.58	46.31±10.49	46.19±11.13	46.69±9.86	46.96 ±9.58
Social functioning	46.72±13.5	42.71±13.21	45.54±10.47	46.78±11.82	45.16 ±12.74
Role-emotional	40.61±13.00	41.05±13.47	45.37±10.33	45.11±14.93	44.91 ±13.13
Mental health	43.07±10.15	44.27±9.12	43.65±10.11	46.97±10.98	45.08 ±11.81
Physical component	37.16±7.71	37.54±7.92	38.75±8.59	40.39±7.02	37.35 ±8.56
Mental component	46.06±12.16	45.81±11.86	47.38±9.60	48.48±11.72	48.36 ±12.08
Week 12					
N	26	24	24	21	24
Physical functioning	42.71±10.07	43.27±9.69	46.42±9.00	47.51±9.86	40.72 ±9.40
Role physical	44.61±10.39	46.96±10.60	50.73±7.19	50.32±9.37	44.81 ±10.21
Bodily pain	42.81±7.05	44.58±8.93	48.70±7.20	49.94±8.45	39.77 ±7.98
General health	42.08±7.07	43.14±8.63	45.03±7.76	45.19±8.06	37.78 ±8.03
Vitality	50.53±10.27	49.88±11.52	53.65±11.24	52.24±11.53	48.71 ±11.20
Social functioning	48.46±10.37	46.62±12.49	51.85±7.36	52.43±8.20	47.99 ±12.12
Role-emotional	47.51±8.64	46.16±12.08	47.78±10.12	48.47±9.83	44.70 ±12.15
Mental health	50.22±7.96	47.90±11.87	51.53±7.33	49.07±12.51	46.25 ±13.81
Physical component	41.21±9.42	43.87±7.75	47.27±6.61	48.39±7.18	39.77 ±6.59
Mental component	51.90±8.68	48.93±13.44	52.07±8.99	50.68±10.10	49.00 ±13.09

BID = twice daily, FAS = full analysis set, N = number of subjects, SD = standard deviation, SF-36 = short form-36.

EuroQol 5-Dimension (EQ-5D):

The EQ-5D utility score at Baseline and Week 12 is summarized in Table 27. Statistically significant differences ($p < 0.10$) from placebo in change from Baseline at Week 12 were seen in 3, 5 and 10 mg BID doses.

Table 27. EQ-5D Utility Score at Baseline and Week 12 (FAS, No Imputation)

	Tofacitinib 1 mg BID	Tofacitinib 3 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Baseline					
N	28	27	27	26	28
Mean	0.55	0.45	0.58	0.55	0.51
Standard deviation	0.26	0.29	0.24	0.32	0.33
Week 12					
N	26	24	24	21	24
Mean	0.65	0.70	0.79	0.78	0.59
Standard deviation	0.23	0.27	0.13	0.28	0.27

BID = twice daily; EQ-5D = EuroQol 5-Dimension, FAS = full analysis set, N = number of subjects.

Medical Outcomes Study (MOS) - Sleep Scale:

The MOS sleep domain scores at Baseline, Week 2 and Week 12 are summarized in Table 28. Statistically significant differences ($p < 0.10$) from placebo in change from Baseline at Week 12 were indicated in all BID doses for sleep problems summary, overall sleep problems and somnolence; 5 mg and 10 mg BID doses for awaken short of breath; 5 mg BID doses for sleep disturbance; 3 mg and 10 mg BID doses for snoring. Adequacy, optimal and quantity indicated no statistically significant differences from placebo in change from Baseline at Week 12.

Table 28. MOS-Sleep Domain at Baseline, Weeks 2 and 12 (FAS, No Imputation)

	Tofacitinib 1 mg Mean±SD	Tofacitinib 3 mg Mean±SD	Tofacitinib 5 mg Mean±SD	Tofacitinib 10 mg Mean±SD	Placebo Mean±SD
Baseline					
N	28	27	27	26	28
Sleep problems summary	27.38±11.42	27.41±14.36	29.38±17.54	30.51±18.78	23.93±12.57
Overall sleep problems	28.00±10.53	27.55±12.40	31.07±17.38	31.28±18.60	25.95±12.89
Adequacy	52.86±24.47	52.96±24.93	49.63±27.80	51.54±26.64	58.57±27.98
Awaken short of breath	3.57±9.51	4.44±10.13	8.15±22.37	10.00±14.14	3.57±7.80
Sleep disturbance	24.06±17.70	23.84±21.10	25.28±20.95	25.77±21.45	21.43±16.66
Optimal	0.61±0.50	0.30±0.47	0.41±0.50	0.42±0.50	0.39±0.50
Quantity	6.61±1.10	6.37±1.45	6.30±0.87	6.38±1.27	6.43±1.29
Snoring	25.00±27.01	32.59±34.26	31.85±31.99	23.08±29.77	31.43±29.53
Somnolence	29.05±19.13	28.64±17.81	34.57±25.22	32.05±22.86	31.90±19.49
Week 2					
N	27	27	27	25	26
Sleep problems summary	27.04±11.52	25.19±12.55	22.10±16.28	27.87±19.41	26.67±16.49
Overall sleep problems	27.61±10.05	25.62±12.35	22.78±15.29	27.47±18.67	27.74±15.79
Adequacy	53.33±23.86	54.81±22.42	64.07±27.49	51.20±29.48	55.38±25.33
Awaken short of breath	5.93±16.47	4.44±8.47	8.15±20.95	7.20±12.75	4.62±11.74
Sleep disturbance	22.31±14.11	19.68±19.19	17.92±14.88	21.40±21.39	21.44±18.22
Optimal	0.63±0.49	0.44±0.51	0.56±0.51	0.52±0.51	0.38±0.50
Quantity	6.70±0.82	6.52±1.16	6.70±1.14	6.84±1.25	6.50±1.24
Snoring	25.19±26.94	25.19±22.60	23.70±29.89	17.60±24.71	30.00±34.06
Somnolence	30.37±18.05	29.14±19.93	27.90±23.46	26.13±23.88	35.64±20.65
Week 12					
N	26	24	24	21	24
Sleep problems summary	24.49±10.83	24.17±14.22	23.89±11.78	25.56±14.47	28.75±14.24
Overall sleep problems	25.19±10.33	24.19±13.39	23.08±10.74	24.52±14.29	29.56±13.10
Adequacy	60.00±22.63	58.75±26.75	51.67±24.08	53.33±23.94	54.17±19.54
Awaken short of breath	6.92±13.79	9.17±14.42	5.00±10.63	3.81±8.05	10.00±20.43
Sleep disturbance	20.34±13.42	19.22±18.43	14.43±10.52	18.99±19.05	21.09±16.56
Optimal	0.54±0.51	0.38±0.49	0.38±0.49	0.48±0.51	0.46±0.51
Quantity	6.35±1.20	6.54±1.28	6.38±0.97	6.71±1.38	6.54±1.53
Snoring	24.62±22.13	21.67±22.78	29.17±32.83	13.33±20.33	33.33±31.02
Somnolence	30.26±18.59	25.28±20.99	25.28±16.33	24.13±23.24	40.28±19.51

FAS = full analysis set, MOS = Medical Outcomes Study, N = number of subjects, SD = standard deviation.

Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale:

Results for the FACIT-fatigue scale at Baseline, Week 2 and Week 12 are summarized in Table 29. Statistically significant differences from placebo in change from Baseline at Week 12 were found in all active dose groups.

Table 29. Functional Assessment of Chronic Illness Therapy -Fatigue at Baseline, Weeks 2 and 12 (FAS, No Imputation)

	Tofacitinib 1 mg BID	Tofacitinib 3 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Baseline					
N	28	27	27	26	28
Mean	34.25	33.37	34.48	36.85	37.07
Standard deviation	10.45	11.03	9.99	9.43	9.87
Week 2					
N	27	27	27	25	26
Mean	36.78	36.48	39.30	40.80	37.38
Standard deviation	8.64	9.72	10.56	6.87	10.31
Week 12					
N	26	24	24	21	24
Mean	39.35	37.96	42.79	40.76	36.46
Standard deviation	7.47	9.95	8.47	10.65	9.93

BID = twice daily, FAS – full analysis set, N = number of subjects.

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 either treatment groups are summarized in Table 30.

Table 30. 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:	Placebo			Tofacitinib 1 mg BID			Tofacitinib 3 mg BID			Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
System Organ Class and Preferred Term	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:															
Evaluable for adverse events	28	-	-	28	-	-	27	-	-	27	-	-	26	-	-
With adverse events	7 (25.0)	-	-	9 (32.1)	-	-	6 (22.2)	-	-	13 (48.1)	-	-	14 (53.8)	-	-
Gastrointestinal disorders	0	0	0	2 (7.1)	2	2	0	0	0	3 (11.1)	3	3	1 (3.8)	1	0
Stomach discomfort	0	0	0	0	0	0	0	0	0	3 (11.1)	3	3	0	0	0
Stomatitis	0	0	0	2 (7.1)	2	2	0	0	0	0	0	0	1 (3.8)	1	0
Infections and infestations	5 (17.9)	5	5	3 (10.7)	3	3	3 (11.1)	3	1	1 (3.7)	1	1	7 (26.9)	9	9
Gastroenteritis	1 (3.6)	1	1	0	0	0	2 (7.4)	2	1	0	0	0	1 (3.8)	1	1
Nasopharyngitis	4 (14.3)	4	4	3 (10.7)	3	3	1 (3.7)	1	0	1 (3.7)	1	1	4 (15.4)	6	6
Pharyngitis	0	0	0	0	0	0	0	0	0	0	0	0	2 (7.7)	2	2
Investigations	1 (3.6)	2	2	2 (7.1)	3	3	4 (14.8)	10	10	9 (33.3)	15	15	7 (26.9)	9	9
Alanine aminotransferase increased	1 (3.6)	1	1	1 (3.6)	1	1	2 (7.4)	2	2	6 (22.2)	6	6	2 (7.7)	2	2
Aspartate aminotransferase increased	1 (3.6)	1	1	1 (3.6)	1	1	2 (7.4)	2	2	4 (14.8)	4	4	1 (3.8)	1	1
Blood cholesterol increased	0	0	0	0	0	0	3 (11.1)	3	3	1 (3.7)	1	1	1 (3.8)	1	1
Blood triglycerides increased	0	0	0	1 (3.6)	1	1	1 (3.7)	1	1	1 (3.7)	1	1	2 (7.7)	2	2
Low density lipoprotein increased	0	0	0	0	0	0	2 (7.4)	2	2	1 (3.7)	1	1	2 (7.7)	2	2
White blood cell count decreased	0	0	0	0	0	0	0	0	0	2 (7.4)	2	2	1 (3.8)	1	1
Nervous system disorders	1 (3.6)	1	1	2 (7.1)	2	1	0	0	0	2 (7.4)	2	2	0	0	0
Headache	1 (3.6)	1	1	2 (7.1)	2	1	0	0	0	2 (7.4)	2	2	0	0	0
Skin and subcutaneous tissue disorders	2 (7.1)	2	2	1 (3.6)	1	0	0	0	0	0	0	0	2 (7.7)	2	1
Erythema	2 (7.1)	2	2	1 (3.6)	1	0	0	0	0	0	0	0	0	0	0
Rash	0	0	0	0	0	0	0	0	0	0	0	0	2 (7.7)	2	1

Table 30. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) in >5 % of Subjects

Except for 'n1' 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, treatment-related.
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 11.1) coding dictionary applied.
BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities.

Treatment-emergent SAEs (all causalities and treatment-related) by SOC and preferred term in either treatment group are summarized in Table 31.

Table 31. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects with Adverse Events by:	Placebo			Tofacitinib 1 mg BID			Tofacitinib 3 mg BID			Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
System Organ Class and Preferred Term	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:															
Evaluable for adverse events	28	-	-	28	-	-	27	-	-	27	-	-	26	-	-
With adverse events	0	-	-	1 (3.6)	-	-	1 (3.7)	-	-	1 (3.7)	-	-	2 (7.7)	-	-
Cardiac disorders	0	0	0	0	0	0	0	0	0	0	0	0	1 (3.8)	1	1
Cardiac failure	0	0	0	0	0	0	0	0	0	0	0	0	1 (3.8)	1	1
Injury, poisoning and procedural complications	0	0	0	0	0	0	0	0	0	1 (3.7)	1	0	0	0	0
Femur fracture	0	0	0	0	0	0	0	0	0	1 (3.7)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (3.6)	1	0	1 (3.7)	1	0	0	0	0	0	0	0
Foot deformity	0	0	0	1 (3.6)	1	0	0	0	0	0	0	0	0	0	0
Osteoarthritis	0	0	0	0	0	0	1 (3.7)	1	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	0	0	0	0	0	0	1 (3.8)	1	1
Dyspnoea	0	0	0	0	0	0	0	0	0	0	0	0	1 (3.8)	1	1

Except for 'n1' 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, treatment-related.
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 11.1) coding dictionary applied.
BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities.

No deaths occurred during the study. Five subjects reported serious adverse events (SAEs) that were foot deformity in 1 mg BID, osteoarthritis in 3 mg BID, femur fracture in 5 mg BID, cardiac failure in 10 mg BID and dyspnea in 10 mg BID. Two subjects reported SAEs (cardiac failure and dyspnea) considered to be related to the study drug. These 2 treatment-related SAEs resolved after the subjects were permanently withdrawn from the study. The treatment-emergent AEs leading to permanent discontinuation are summarized in Table 32.

Table 32. Treatment-Emergent Adverse Events Leading to Permanent Discontinuation

Serial Number	MedDRA Preferred Term	Start Day[a]/ Stop Day[a]	Severity	Outcome	Relationship to Treatment
Tofacitinib 3 mg BID					
1	Alanine aminotransferase increased	57/ [>80]	Mild	Still present	Related
	Aspartate aminotransferase increased	57/ [>80]	Mild	Still present	Related
2	Osteoarthritis	57/ 107	Severe	Resolved	Disease under study
Tofacitinib 5 mg BID					
3	Femur fracture	57/ [>57]	Severe	Still present	Disease under study
4	White blood cell count decreased	57/ [>57]	Mild	Still present	Related
5	Alanine aminotransferase increased	57/ [>83]	Moderate	Still present	Related
	Aspartate aminotransferase increased	57/ [>83]	Moderate	Still present	Related
6	Alanine aminotransferase increased	29/ [>59]	Moderate	Still present	Related
	Aspartate aminotransferase increased	29/ 111	Moderate	Resolved	Related
Tofacitinib 10 mg BID					
7	Alanine aminotransferase increased	23/ 58	Mild	Resolved	Related
	Aspartate aminotransferase increased	23/ 58	Mild	Resolved	Related
8	Peritonsillitis	31/ 57	Moderate	Resolved	Related
9	Cardiac failure	61/ 111	Moderate	Resolved	Related
	Pneumonia	71/ 111	Mild	Resolved	Related
10	Dyspnoea	25/ 36	Severe	Resolved	Related
Placebo					
11	Gastroenteritis	7/ 13	Mild	Resolved	Related
	Upper respiratory tract infection	7/ 13	Mild	Resolved	Related
12	Purpura	48/ 66	Mild	Resolved	Related

[] Values in brackets are imputed from incomplete dates and times.
BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (version 11.1), n = number of subjects.
a. Day relative to start of study treatment. First day of study treatment = Day 1

Tofacitinib treatment groups except 1 and 3 mg BID had increases in mean Epstein-Barr Virus deoxyribonucleic acid levels greater than placebo. However, none were statistically significant at Week 12. There was no potentially life threatening anemia in all dose groups including placebo and severe anemia was uncommon in all dose groups. At Week 12, there were no statistically significant differences in hemoglobin from placebo in the tofacitinib treatment groups except for 3 mg BID dose group. The decreases in neutrophil counts were observed in the tofacitinib treatment groups compared to the placebo treatment group at all

timepoints except for Week 4 in the 1 mg BID treatment group. The mean decreasing change from Baseline in neutrophil count was statistically significantly heavier in all tofacitinib treatment groups compared to the placebo at Week 12. Dose dependent increases in serum lipid levels were observed in the tofacitinib treatment groups. The mean changes from Baseline in serum creatinine were statistically significantly greater in all tofacitinib treatment groups compared to the placebo at Week 12. Aspartate aminotransferase levels at >3 times ULN were observed in 1 subject in the 10 mg BID treatment groups and alanine aminotransferase levels at >3 times ULN were observed in 2 and 1 subjects in the 5 mg BID, and 10 mg BID treatment groups, respectively.

Mean changes from Baseline in diastolic or systolic blood pressure were generally small, and no notable trends were observed in the tofacitinib treatment groups.

Mean changes from Baseline in ECG were generally small and no notable trends were observed in the tofacitinib treatment groups.

No subject in any treatment group experienced immunoglobulin G level ≥50% decrease below Baseline value.

CONCLUSIONS:

The present study was conducted to evaluate the efficacy and safety of 1, 3, 5, and 10 mg tofacitinib BID treatment when used in a 12-week add-on therapy with MTX, for the treatment of signs and symptoms in subjects with active RA which had been inadequately controlled with MTX.

The significant dose-response relationship in tofacitinib doses including placebo was shown by using Cochran-Armitage trend test on ACR20 response rate at Week 12. The dose-response relationships were also shown on ACR50 and ACR70 response rate at Week 12. The ACR20 response rates were statistically significant for tofacitinib -treated groups except for 3 mg BID at Week 1 compared to placebo. Although there was lack of statistical separation of 1 mg BID from placebo in ACR50 and ACR70 response rates and a lack of separation of 3 mg BID in ACR70 response rate from placebo, efficacy was demonstrated by improvement in each of the ACR assessments, and by changes from Baseline in the DAS28-3 (CRP) and DAS28-4 (ESR).

Clinically significant reductions in signs and symptoms were observed with tofacitinib in all 4 dose groups.

Subjects in the tofacitinib treatment groups showed higher numbers of AEs compared to placebo. The most commonly observed all causality AEs were alanine aminotransferase increased, nasopharyngitis, aspartate aminotransferase increased, blood cholesterol increased, blood triglycerides increased and low density lipoprotein increased in the tofacitinib treatment groups. Most of the AEs were mild or moderate in severity. Of the total, 12 subjects (2 in 3 mg BID, 4 in 5 mg BID, 4 in 10 mg BID and 2 in placebo) permanently discontinued study medication as a result of all causality AEs. Two treatment-related SAEs (cardiac failure and dyspnea) were reported, and were resolved after the subjects were

permanently withdrawn from the study. There was no potentially life threatening anemia in all dose groups and severe anemia was uncommon in all dose groups. Decreases in neutrophil count and dose dependent increases in serum lipids were reported in the tofacitinib treatment groups. These result suggested that tofacitinib at doses of 1 mg BID, 3 mg BID, 5 mg BID, 10 mg BID, was safe and tolerated when compared to placebo over a treatment period of 12 weeks.

A range of doses appears suitable to evaluate further in Phase 3 studies.