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

PROTOCOL NO.: A3921046

PROTOCOL TITLE: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 in Patients With Active Rheumatoid Arthritis on Background DMARDs

Study Centers: A total of 144 centers took part in the study and randomized subjects; 5 in Australia, 20 in China, 4 in Chile, 3 in Columbia, 1 in Croatia, 1 in Denmark, 3 in Finland, 6 in Germany, 4 in Malaysia, 5 in Mexico, 5 in Poland, 3 in Russian Federation, 4 in Spain, 6 in Slovakia, 2 in Sweden, 3 in Thailand, 34 in United States, 3 in United Kingdom and 2 in Venezuela.

Study Initiation and Final Completion Dates: 18 May 2009 to 17 Jan 2011

Phase of Development: Phase 3

Study Objectives:

Primary Objectives:

- To compare the efficacy of tofacitinib in doses of 5 mg twice daily (BID) and 10 mg BID versus (vs) placebo for the treatment of signs and symptoms of Rheumatoid Arthritis (RA) in subjects with active RA who have had an inadequate response to a disease modifying antirheumatic drug (DMARD) (traditional or biologic), as measured by the American College of Rheumatology (ACR) definition for improvement in RA; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures (ACR20) response rates at Month 6.

- To compare physical function status of subjects after administration of tofacitinib in doses of 5 mg BID or 10 mg BID vs placebo using the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Month 6 compared to Baseline in subjects with active RA on background traditional DMARDs.

- To compare the incidence of major clinical response, defined as maintaining an ACR definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures (ACR70) response sustained for 6 months, after administration of tofacitinib in doses of 5 mg BID or 10 mg BID vs placebo in subjects with active RA on background traditional DMARDs.

- To evaluate the safety and tolerability of tofacitinib in doses of 5 mg BID and 10 mg BID vs placebo in subjects with active RA on background traditional DMARDs.

Secondary Objectives:

- To compare the efficacy of tofacitinib in doses of 5 mg BID and 10 mg BID vs placebo for the treatment of signs and symptoms of RA in subjects with active RA on background traditional DMARDs, as measured by ACR20 response rates at Months 1 and 3, the ACR definition for improvement in RA calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR core set measures (ACR50), ACR70, and DAS 28 response rates at Months 1, 3, and 6.

- To compare the durability of ACR20, ACR50, and ACR70 and DAS28 response rates from Month 6 through Month 12.

- To compare the incidence of DAS28 remission and low disease activity state at each visit.

- To compare effects on all health outcomes measures in the study at each visit, as appropriate for the specific outcome, compared to Baseline.

METHODS

Study Design: This was a Phase 3 randomized, 1-year, double-blind, placebo-controlled, parallel group study. Subjects were randomized in a 4:4:1:1 ratio to 1 of the 4 parallel treatment sequences presented in Table 1.

Table 1. Randomization Treatment Sequence

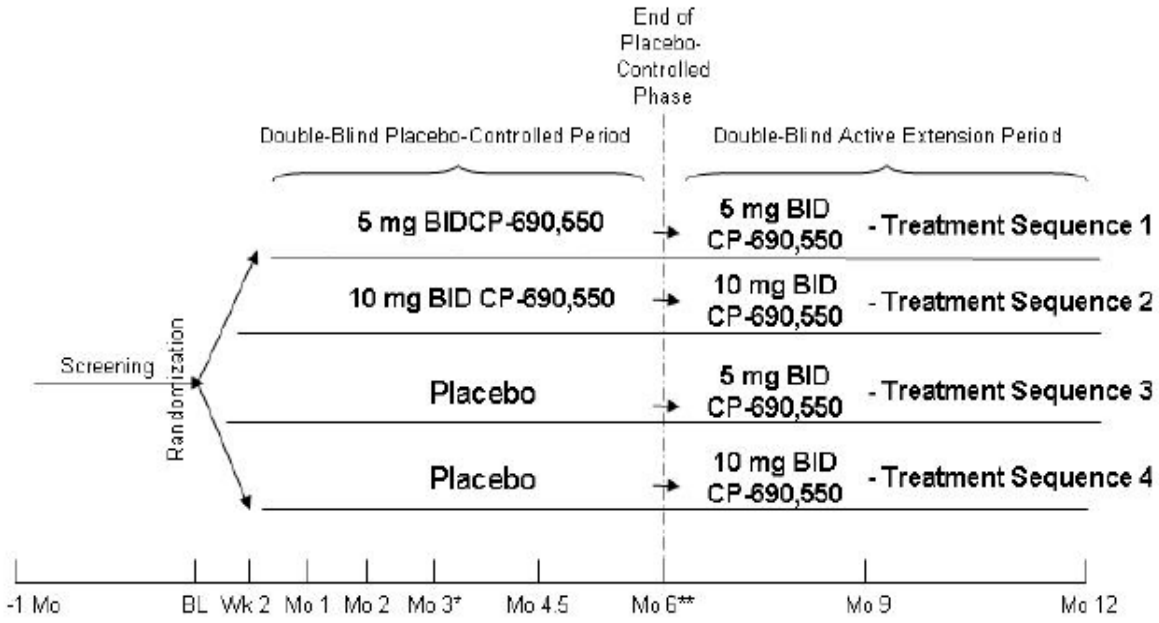
Treatment Sequence	Double-Blind Placebo-Controlled Period[a]	Double-Blind Active-Extension Period[b]
Sequence 1	Tofacitinib 5 mg BID	Tofacitinib 5 mg BID
Sequence 2	Tofacitinib 10 mg BID	Tofacitinib 10 mg BID
Sequence 3	Placebo	Tofacitinib 5 mg BID
Sequence 4	Placebo	Tofacitinib 10 mg BID

BID = twice daily.
a. Duration of 3 to 6 months; response was assessed at Month 3, and non-responsive subjects were advanced to the double-blind active-extension period.
b. All subjects had entered this period by Month 6.

At the Month 3 visit, the tender/painful joint counts and swollen joint counts were compared to Baseline values. If there was not a 20% improvement in both the tender/painful and swollen joint counts, the subject was considered a non-responder. If a subject was randomized to active treatment (Treatment Sequence 1 or Treatment Sequence 2), that subject remained on the same treatment, at the same dose for the remainder of the study. If the subject was randomized to Treatment Sequence 3 or Treatment Sequence 4, the subject was advanced to his/her second predetermined treatment in a blinded fashion for the remainder of the study by the drug allocation system. At the end of Month 6, all subjects

were automatically advanced to their second predetermined treatment in a blinded fashion for the remainder of the study (Figure 1 and Table 2).

Figure 1. Study Design



*At Month 3, nonresponders were blindly advanced to the active extension period of their respective treatment sequence.
** At Month 6, all subjects not previously advanced were blindly advanced to their active extension period of their respective treatment sequence.
BID = twice daily, BL = baseline, Mo = month.

Table 2 Schedule of Activities

Schedule of Events		Screening[a]	Visits								
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
			Baseline Day 0	Wk 2	Mo 1	Mo 2	Mo 3	Mo 4.5	Mo 6	Mo 9	Mo 12 or End of Study
Informed Consent		X									
RA diagnosis, medical history[b]		X									
Concomitant medications		X	X	X	X	X	X	X	X	X	X
Complete physical examination		X	X								X
Targeted physical examination[c]				X	X	X	X	X	X	X	
Vital signs, temperature		X	X	X	X	X	X	X	X	X	X
QuantiFERON-Gold or PPD		X									
Radiograph of chest		X									
12-lead electrocardiogram											X
Blood/Urine	Rheumatoid factor		X								X
	Antibodies to cyclic citrullinated peptide		X								X
	Hematology[d], urinalysis, safety chemistry panel[e]	X	X	X	X	X	X	X	X	X	X
	Lipid profile (fasting)[f]		X		X		X		X	X	X
	Safety laboratories[g]		As appropriate for standard of care								
	Urine pregnancy test (HCG)[h]	X	X	X	X	X	X	X	X	X	X
	Stool examination for parasites (Brazil only)	X									
	HIV, HBsAg, HCV Ab	X									
	Molecular profiling[i]		X	X	X		X		X		X
	C-Reactive protein	X	X	X	X	X	X	X	X	X	X
	Erythrocyte sedimentation rate[j]	X	X				X		X		X
ACR/DAS	Tender/painful joint count, swollen joint count	X	X	X	X	X	X	X	X	X	X
	Patient Assessment of Arthritis Pain		X	X	X	X	X	X	X	X	X
	Patient Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X
	Physician Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X
	Health Assessment Questionnaire – Disability Index		X	X	X	X	X	X	X	X	X
SF-36 (Version 2, Acute)			X		X		X		X	X	X
MOS-Sleep and FACIT- Fatigue Scale			X		X		X		X		X
EuroQoL EQ-5D			X				X		X		X
RA Healthcare Resource Utilization Questionnaire			X				X		X		X

Table 2 Schedule of Activities

Schedule of Events	Screening[a]	Visits								
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
		Baseline Day 0	Wk 2	Mo 1	Mo 2	Mo 3	Mo 4.5	Mo 6	Mo 9	Mo 12 or End of Study
Work Limitations Questionnaire		X				X		X		X
Randomization		X								
2 Week IVRS diary instructions[k]		X								
Drug dispensing		X				X		X	X	
Drug accountability						X		X	X	X
Adverse event reporting		X	X	X	X	X	X	X	X	X
Review entry criteria for A3921024										X

ACR = American college of rheumatology, DAS = disease activity score, EQ-5D = self-report questionnaire (quality of life instrument) developed by the European Quality of Life (EuroQoL) Group, EuroQoL = European Quality of Life [Group], FACIT-Fatigue Scale = Functional Assessment of Chronic Illness Therapy-Fatigue Scale, HBsAg = hepatitis B surface antigen, HCG = human chorionic gonadotropin, HCV Ab = hepatitis C virus antibody, HIV = human immunodeficiency virus, IVRS = interactive voice response system, Mo = month, MOS Sleep Scale = Medical Outcomes Study Sleep Scale, PPD = purified protein derivative, RA = rheumatoid arthritis, SF-36 = Short Form (36 questions) Health Survey, Wk = week.

a. Screening Visit occurred within 1 month (30 days+10 day window) prior to the Baseline Visit.
b. Medical history included smoking status, average weekly alcohol consumption, family history of premature coronary heart disease.
c. Targeted physical examination consisted of weight, examination of heart, lungs, abdomen, lower extremities (peripheral edema) and lymph nodes.
d. Hematology included red blood cell count, white blood cell count with differential, hemoglobin, hematocrit and platelet count.
e. Chemistry panel included sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, creatine kinase, aspartate aminotransferase, alanine aminotransferase, albumin, total protein, bilirubin (direct, indirect and total), alkaline phosphatase, and gamma glutamyl transferase.
f. Lipid profile included fasting total cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides. Fasting apolipoprotein A-1 and B and other lipoprotein tests potentially including particle size measurements were obtained at Baseline and Month 3, 6, 9 and 12/End of Study.
g. Safety laboratories as appropriate for standard of care.
h. Urinary pregnancy testing (human chorionic gonadotropic) was required only for women who were of childbearing potential; may have been repeated more frequently if required by local practices, if a menstrual cycle was missed, or if potential pregnancy was otherwise suspected.
i. Molecular profiling included deoxyribonucleic acid sample at Baseline, and plasma and serum biomarker samples at Baseline and other timepoints. Only at sites participating in the molecular profiling (pharmacogenomic) research component.
j. All ESR tests performed after screening must have been done at a local laboratory that had the capability of reporting directly to the central laboratory, keeping the results blinded from the site personnel. If ESR could not be performed in a blinded manner, the site was not to perform ESR after screening.
k. Subjects in the United States reported daily via interactive voice response system for 2 weeks both the Patient's Assessment of Arthritis Pain and the Patient's Global Assessment of Arthritis.

Number of Subjects (Planned and Analyzed): In total, 750 subjects were planned to be enrolled in this study. The study enrolled 795 subjects: 52 in Australia, 37 in Chile, 218 in China, 29 in Colombia, 8 in Croatia, 6 in Denmark, 10 in Finland, 48 in Germany, 25 in Malaysia, 36 in Mexico, 65 in Poland, 19 in Russian Federation, 33 in Slovakia, 21 in Spain, 4 in Sweden, 32 in Thailand, 8 in the United Kingdom, 138 in the United States, 7 in Venezuela. Seven hundred and ninety-five subjects were randomized to treatment, and 792 received at least 1 dose of study medication; 651/792 (82.2%) subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Male and female (nonchildbearing potential) subjects at least 18 years of age, with a diagnosis of RA based on the ACR 1987 Revised Criteria. The subject had active disease as defined by both ≥4 tender or painful joints on motion and ≥4 joints swollen; and either an ESR >28 mm or a C-reactive protein (CRP) concentration >7 mg/dL. The subject had an inadequate response to at least one disease modifying antirheumatic drug (traditional or biologic) due to lack of efficacy or toxicity. Subject must remain on at least one background traditional disease modifying antirheumatic drug. No evidence of inadequately treated latent or active infection with *Mycobacterium tuberculosis*.

Subjects were excluded if they presented with blood dyscrasias including confirmed: hemoglobin <9 g/dL or hematocrit <30%; white blood cell count <3.0 x 10^9/L; absolute neutrophil count <1.2 x 10^9/L; platelet count <100 x 10^9/L; had a history of any other rheumatic autoimmune disease other than Sjogren's syndrome; had no malignancy or history of malignancy; had a history of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the Investigator, within the 6 months prior to the first dose of study drug.

Study Treatment: Subjects were randomized to 1 of the following treatment sequences: tofacitinib 5 mg BID; tofacitinib 10 mg BID; placebo → tofacitinib 5 mg; or placebo → tofacitinib 10 mg.

Efficacy Endpoints:

Primary Endpoints:

- Signs and symptoms as measured by ACR 20 at Month 6;
- Physical function as measured by the HAQ-DI change from Baseline at Month 3;
- Incidence of DAS28-4 (ESR) <2.6 at Month 6.

Secondary Endpoints:

- ACR20 Responder rates at times other than Month 6;
- ACR50 Responder rates;
- ACR70 Responder rates;

- Actual and change from Baseline of the 7 individual components (tender joint count, swollen joint count, patient assessment of arthritis pain, Physician Global Assessment of Arthritis, Patient Global Assessment of Arthritis, CRP, and HAQ-DI) of the ACR criteria variables (separate analyses);

- Actual and change from Baseline in DAS28 which included the following DAS: DAS28-3(CRP), and DAS28-4(ESR), that is, separate endpoints, analyzed separately;

- Incidences of DAS28-3(CRP) ≤3.2, and DAS28-4(ESR) ≤3.2 (separate endpoints, analyzed separately);

- Incidences of DAS28-4(ESR) <2.6 at timepoints other than Month 6;

- Incidences of DAS28-3(CRP) <2.6;

- DAS 28 response rates (No improvement vs improvement [Moderate improvement or Good improvement]), based on DAS28-3(CRP) and DAS28-4(ESR), (separate endpoints, analyzed separately);

- ACR70 Response for at least 6 Months;

- Durability of ACR20, ACR50, ACR70, DAS28 response rates: the durability of each of these endpoints, separate measures, was as follows:

  The proportion of subjects who first achieved the response at each post-baseline visit (eg, at Month 3) and, of these, the proportion of subjects that continued to sustain a response for the following consecutive visits (eg, Month 6 to Month 12);

- Actual and change from Baseline in the Short Form (36 questions) (SF-36) 8 domain scores and 2 component scores (separate analyses);

- Actual and change from Baseline in Work Limitations Questionnaire (WLQ) 4 domain scores and the work loss index (separate analyses);

- Actual and change from Baseline in the EuroQoL 5 dimension (EQ-5D);

- Actual and change from Baseline in the Medical Outcomes Study (MOS)-Sleep Scale;

- Actual and change from Baseline in the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale;

- Rates of clinically meaningful decrease in the HAQ-DI (decrease of at least 0.22, 0.3, 0.5, or 0.8 units) “HAQ-DI (0.22)”, “HAQ-DI (0.30)”, “HAQ-DI (0.5)”, “HAQ-DI (0.8)”, respectively;

- Rate of advancement at Month 3;

- Rate of erroneous advancement at Month 3.

Safety Evaluations:

- Incidence and severity of adverse events (AEs);
- Incidence and severity of clinical laboratory abnormalities;
- Summary of changes in physical examination compared to Baseline by subject;
- Mean change from Baseline in vital signs (blood pressure [BP], heart rate, and oral, temporal or tympanic temperature, weight) measurements;
- Categorical summary of absolute vital signs and vital sign changes compared to Baseline by subject.

Statistical Methods: In order to preserve Type I error in the primary analyses, each primary efficacy endpoint was assessed sequentially using gate-keeping or step-down approach where statistical significance was claimed for a given endpoint only if the prior endpoint in the sequence met the requirement for significance. Additionally, as there were 2 dose levels to be evaluated within each endpoint, the gate-keeping or step-down approach was also applied, ie, the high dose (10 mg BID) at a given endpoint could achieve significance only if the high dose at the prior endpoint was significant; the low dose (5 mg BID) at a given endpoint could achieve significance only if both the high dose at the same endpoint and the low dose at the prior endpoint were significant. For the primary endpoints, the placebo refers to the combined placebo data from the 2 placebo → tofacitinib treatment sequences in Months 3 and 6 analyses.

Secondary endpoints have been assessed statistically and p-values calculated with no protection of Type I error and significance declared for p-values ≤0.05.

Analysis set used for this study were as follows:

- The full analysis set (FAS) included all subjects who were randomized to the study and received at least 1 dose of the randomized investigational drug (tofacitinib or placebo). The primary analysis population for this study was defined by the FAS of subjects.
- Subjects who had a protocol deviation thought to affect the efficacy analysis were excluded from the per protocol (PP) efficacy analysis.
- The safety analysis set was defined as those subjects who received at least 1 dose of the investigational drug (tofacitinib or placebo). It was the same as the FAS.

Post Month 6, all subjects in the placebo group had been advanced to active drug (tofacitinib). In general, any analyses that incorporated post Month 6 data were meant to be descriptive in nature and the actual data were used for each sequence unless specified, although statistical testing could have been applied. In this case, changes from the Baseline within each sequence could have been compared.

For ACR20 and incidence of DAS28-4(ESR) <2.6 at Month 6, the normal approximation for the difference in binomial proportions was used.

For the change from Baseline in the HAQ-DI at Month 3, the mixed-effect model with repeated measures as treatment effect model was used.

Secondary analyses included the normal approximation for the difference in binomial proportions for the ACR variables (ACR20, ACR50, and ACR70) done in separate analyses. The binomial variables: DAS28 $\leq$3.2, incidence of DAS28 <2.6, DAS28 responses, and clinically meaningful decrease in HAQ-DI, were analyzed by considering the proportion of subjects responding to each endpoint and using the same normal approximation to the binomial for the analyses.

For change in HAQ-DI from Baseline to Month 6, the mixed-effect model with repeated measures as the treatment effect model was used.

In addition, change in HAQ-DI from Baseline after Month 6 was also analyzed for descriptive purposes; and the mixed effect model with repeated measures was applied as well to evaluate the effect post Month 6. Further analyses using the sequence effect model was conducted for the HAQ-DI actual values at each visit.

The other 6 components of the ACR criteria, DAS28, the 8 domains and 2 scores of SF-36, MOS-sleep scales, EuroQoL EQ-5D, the 4 domain scores and the work loss index of WLQ and FACIT fatigue scale were each analyzed in the same way as HAQ-DI is analyzed. Each endpoint's baseline values were used as covariates. The data from the RA health-care resources utilization was listed, and descriptive statistics were generated.

Number of days to the first ">1 day consecutive sequential decrease in pain" were analyzed using Kaplan-Meier and other related time-to-event methods for each of the "Patient Assessment of Arthritis Pain" and "Patient Global Assessment of Arthritis" endpoints.

Patient Global Assessment of Arthritis endpoints (time to first sequential decrease from Baseline and number of days required for a >1 day consecutive sequential decrease) were analyzed for study centers in the United States only. Results were tabulated and displayed graphically.

All the safety data, including the following, were summarized through appropriate data tabulations, descriptive statistics, and graphical presentations:

- AEs were summarized according to sponsor's standards;
- Safety laboratory tests were summarized according to the sponsor's standards; special attention was given to the following safety criteria: neutrophil counts, serum creatinine levels, platelet counts, liver function tests, events of anemia, hyperlipidemia and hypertension;
- Any cardiovascular safety endpoints adjudicated by the cardiovascular safety endpoint adjudication committee (CV SEAC) were summarized;

- Any potentially malignant tumor, suspicious lymphadenopathy, possible extranodal lympho proliferative disorder (LPD) adjudicated by the central pathologists was summarized;

- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials, were summarized. (This was done by written narratives);

- Abnormal changes in physical examination compared with Baseline were summarized;

- Change from Baseline in vital signs (BP, heart rate, temperature, and weight measurements) was summarized.

AEs were displayed for the period of time from Baseline to Month 3 (that is, AEs that occurred up to Month 3), for the period of time from Month 3 to Month 6 (that is, AEs that occurred after Month 3 and up to Month 6), and Month 6 to the end of treatment period (that is, AEs that occurred after Month 6).

Serious AE (SAE) presentations were derived from a combination of data contained within the clinical study database and the corporate safety database. The corporate safety database was a separate, centralized, AE monitoring database that was continuously updated based on rapidly communicated reports from the Investigators to the sponsor. The clinical study database was based on information provided from the case report form/data collection tools. Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database.

RESULTS

Subject Disposition and Demography: Table 3 summarizes subject disposition by treatment sequence.

Table 3. Subject Disposition by Treatment Sequence

No. (%) of Subjects	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo → Tofacitinib 5 mg BID	Placebo → Tofacitinib 10 mg BID
Screened: 1281				
Randomized: 795				
Assigned to Study Treatment	318	318	79	80
Treated	315[a]	318	79	80
Completed	261 (82.1)	252 (79.2)	71 (89.9)	67 (83.8)
Discontinued	54 (17.0)	66 (20.8)	8 (10.1)	13 (16.3)
Subject Died[b]	0	2 (0.6)	0	0
Related to Study Drug	31 (9.8)	34 (10.7)	3 (3.8)	4 (5.0)
Adverse event	14 (4.4)	20 (6.3)	0	0
Lack of efficacy	16 (5.1)	12 (3.8)	3 (3.8)	3 (3.8)
Other[c]	1 (0.3)	2 (0.6)	0	1 (1.3)
Not Related to Study Drug	23 (7.3)	30 (9.4)	5 (6.3)	9 (11.3)
Adverse event	6 (1.9)	9 (2.8)	2 (2.5)	3 (3.8)
Lost to follow-up	1 (0.3)	2 (0.6)	2 (2.5)	0
Other[c]	8 (2.5)	14 (4.4)	1 (1.3)	5 (6.3)
Subject no longer willing to participate in study	8 (2.5)	5 (1.6)	0	1 (1.3)

BID = twice daily, No. = number.

a. Two subjects were randomized, but not treated; the subjects were no longer willing to participate in the study. One more subject was randomized, but not treated; the subjects moved to another city and could no longer make the study visits.

b. Two deaths were reported during the study. Two additional subjects died after withdrawal from the study.

c. Other reasons for discontinuation included pregnancy, withdrawal due to request by the study team due to early termination, subject decided to withdraw from the study due to being out of town for a family calamity, loss of site staff, study terminated by the sponsor, subject noncompliant with hypertension medication, subject going abroad, subject changed jobs and could not complete study visits, and subject went to live in another city.

Demographic characteristics are summarized in Table 4.

Table 4. Demographic Characteristics

Demographic Characteristic Parameter	Tofacitinib 5 mg BID Male N=51	Tofacitinib 5 mg BID Female N=264	Tofacitinib 5 mg BID Total N=315	Tofacitinib 10 mg BID Male N=60	Tofacitinib 10 mg BID Female N=258	Tofacitinib 10 mg BID Total N=318
Age (years), n (%):						
18-44	11 (21.6)	64 (24.2)	75 (23.8)	12 (20.0)	66 (25.6)	78 (24.5)
45-64	32 (62.7)	162 (61.4)	194 (61.6)	40 (66.7)	158 (61.2)	198 (62.3)
≥65	8 (15.7)	38 (14.4)	46 (14.6)	8 (13.3)	34 (13.2)	42 (13.2)
Mean (SD)	53.7 (11.2)	52.5 (11.8)	52.7 (11.7)	52.8 (12.1)	51.7 (11.7)	51.9 (11.8)
Range	26-80	18-86	18-86	20-82	20-85	20-85
Race, n (%):						
White	32 (62.7)	141 (53.4)	173 (54.9)	40 (66.7)	134 (51.9)	174 (54.7)
Black	1 (2.0)	3 (1.1)	4 (1.3)	0	7 (2.7)	7 (2.2)
Asian	13 (25.5)	100 (37.9)	113 (35.9)	18 (30.0)	93 (36.0)	111 (34.9)
Other	5 (9.8)	20 (7.6)	25 (7.9)	2 (3.3)	24 (9.3)	26 (8.2)
Weight (kg):						
Mean (SD)	77.2 (16.1)	68.2 (18.9)	69.6 (18.8)	83.6 (16.7)	68.1 (18.0)	71.0 (18.7)
Range	46.1-117.5	38.0-186.9	38.0-186.9	52.0-124.7	34.7-148.8	34.7-148.8
Body mass index (kg/m^2):						
Mean (SD)	25.8 (4.6)	26.7 (7.0)	26.6 (6.7)	27.6 (4.5)	26.7 (6.6)	26.9 (6.3)
Range	16.3-36.7	16.0-70.3	16.0-70.3	18.9-38.5	15.1-58.1	15.1-58.1
Height (cm):						
Mean (SD)	172.7 (6.2)	159.5 (6.5)	161.6 (8.1)	173.7 (7.1)	159.6 (6.9)	162.2 (8.8)
Range	157.0-188.0	143.0-178.0	143.0-188.0	157.0-191.0	138.0 (180.0)	138.0-191.0
	Placebo →Tofacitinib 5 mg BID			**Placebo →Tofacitinib 10 mg BID**		
	Male N=16	**Female N=63**	**Total N=79**	**Male N=20**	**Female N=60**	**Total N=80**
Age (years), n (%):						
18-44	2 (12.5)	16 (25.4)	18 (22.8)	3 (15.0)	13 (21.7)	16 (20.0)
45-64	10 (62.5)	43 (68.3)	53 (67.1)	15 (75.0)	37 (61.7)	52 (65.0)
≥65	4 (25.0)	4 (6.3)	8 (10.1)	2 (10.0)	10 (16.7)	12 (15.0)
Mean (SD)	57.9 (9.5)	49.1 (11.0)	50.8 (11.2)	53.8 (8.3)	53.2 (11.6)	53.3 (10.8)
Range	38-70	18-68	18-70	41-70	18-73	18-73
Race, n (%):						
White	13 (81.3)	35 (55.6)	48 (60.8)	14 (70.0)	30 (50.0)	44 (55.0)
Black	0	2 (3.2)	2 (2.5)	0	2 (3.3)	2 (2.5)
Asian	2 (12.5)	22 (34.9)	24 (30.4)	6 (30.0)	21 (35.0)	27 (33.8)
Other	1 (6.3)	4 (6.3)	5 (6.3)	0	7 (11.7)	7 (8.8)

Table 4. Demographic Characteristics

	Placebo →Tofacitinib 5 mg BID			Placebo →Tofacitinib 10 mg BID		
	Male N=16	**Female N=63**	**Total N=79**	**Male N=20**	**Female N=60**	**Total N=80**
Weight (kg):						
Mean (SD)	74.9 (16.4)	71.1 (19.8)	71.9 (19.1)	77.0 (18.2)	68.9 (21.4)	70.9 (20.8)
Range	48.0-104.8	40.0-138.5	40.0-138.5	47.0-117.9	35.0-158.3	35.0-158.3
Body mass index (kg/m2):						
Mean (SD)	24.8 (4.3)	27.4 (7.4)	26.9 (7.0)	25.9 (5.7)	26.6 (7.0)	26.4 (6.7)
Range	17.2-32.7	15.8-54.1	15.8-54.1	16.7-40.8	16.2-54.1	16.2-54.1
Height (cm):						
Mean (SD)	173.2 (7.2)	161.0 (7.3)	163.5 (8.7)	172.2 (6.0)	160.2 (7.3)	163.2 (8.7)
Range	159.5-187.0	146.0-180.0	146.0-187.0	164.0-187.0	145.0-178.0	145.0-187.0
	All Placebo			**Total**		
	Male N=36	**Female N=123**	**Total N=159**	**Male N=147**	**Female N=645**	**Total N=792**
Age (years), n (%):						
18-44	5 (13.9)	29 (23.6)	34 (21.4)	28 (19.0)	159 (24.7)	187 (23.6)
45-64	25 (69.4)	80 (65.0)	105 (66.0)	97 (66.0)	400 (62.0)	497 (62.8)
≥65	6 (16.7)	14 (11.4)	20 (12.6)	22 (15.0)	86 (13.3)	108 (13.6)
Mean (SD)	55.6 (9.0)	51.1 (11.4)	52.1 (11.0)	53.8 (11.1)	51.9 (11.7)	52.3 (11.6)
Range	38-70	18-73	18-73	20-82	18-86	18-86
Race, n (%):						
White	27 (75.0)	65 (52.8)	92 (57.9)	99 (67.3)	340 (52.7)	439 (55.4)
Black	0	4 (3.3)	4 (2.5)	1 (0.7)	14 (2.2)	15 (1.9)
Asian	8 (22.2)	43 (35.0)	51 (32.1)	39 (26.5)	236 (36.6)	275 (34.7)
Other	1 (2.8)	11 (8.9)	12 (7.5)	8 (5.4)	55 (8.5)	63 (8.0)
Weight (kg):						
Mean (SD)	76.0 (17.2)	70.0 (20.5)	71.4 (19.9)	79.5 (16.9)	68.5 (18.9)	70.5 (19.0)
Range	47.0-117.9	35.0-158.3	35.0-158.3	46.1-124.7	34.7-186.9	34.7-186.9
Body mass index (kg/m2):						
Mean (SD)	25.4 (5.1)	27.0 (7.2)	26.7 (6.8)	26.4 (4.8)	26.8 (6.9)	26.7 (6.5)
Range	16.7-40.8	15.8-54.1	15.8-54.1	16.3-40.8	15.1-70.3	15.1-70.3
Height (cm):						
Mean (SD)	172.6 (6.5)	160.6 (7.3)	163.3 (8.7)	173.1 (6.6)	159.7 (6.8)	162.2 (8.5)
Range	159.5-187.0	145.0-180.0	145.0-187.0	157.0-191.0	138.0-180.0	138.0-191.0

Body mass index computed as weight/(height/100)^2.
BID = twice daily, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Efficacy Results:

Statistical significance of the efficacy primary objectives was determined using the step-down procedure. The ACR20 response rates at Month 6 were statistically significantly different for both tofacitinib doses compared with placebo. The differences from placebo for mean changes from Baseline in HAQ-DI at Month 3 were also statistically significantly different for both tofacitinib doses compared with placebo. The rate of subjects achieving a DAS28-4(ESR) <2.6 at Month 6 for tofacitinib 5 mg and 10 mg was also significantly different from placebo.

Improvements over time, in a dose-dependent fashion, were observed for ACR50, ACR70, and in the change from Baseline in DAS28-4(ESR).

Primary Efficacy Results:

ACR20 Response Rates at Month 6: Both tofacitinib doses demonstrated statistically significant by the step-down procedure (p-value <0.0001 for both doses) and clinically meaningful reductions in signs and symptoms of RA over placebo as measured by the ACR20 at Month 6 (Table 5).

Table 5. Normal Approximation to ACR20 Response Rates at Month 6 (FAS, NRI, Comparisons to Placebo)

Treatment	N	n	%	Difference from Comparator			
				Difference	95% CI for Difference		p-Value
					Lower	Upper	
Tofacitinib 5 mg BID	311	164	52.73	21.52	12.39	30.65	<0.0001
Tofacitinib 10 mg BID	309	180	58.25	27.04	17.94	36.13	<0.0001
Placebo	157	49	31.21	Not Applicable			

ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, LS mean = least squares mean, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation.

Changes from Baseline in HAQ-DI at Month 3: Both tofacitinib doses demonstrated statistically significant (significant by step-down procedure; p-value <0.0001) and clinically meaningful improvements in physical function over placebo as measured by the HAQ-DI at Month 3 (Table 6).

Table 6. Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Differences From Placebo)

Treatment	N	LS Mean	Differences From Placebo			
			LS Mean Difference	95% CI for Difference		p-Value
				Lower	Upper	
Tofacitinib 5 mg BID	292	-0.46	-0.26	-0.35	-0.16	<0.0001
Tofacitinib 10 mg BID	292	-0.56	-0.35	-0.44	-0.26	<0.0001
Placebo	147	-0.21	Not Applicable			

BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire - Disability Index, LS = least squares, N = number of subjects.

Rate of Subjects Achieving DAS28-4(ESR) <2.6 Versus Placebo at Month 6: The rate of subjects achieving DAS28-4(ESR) <2.6 at Month 6 for tofacitinib 5 mg and 10 mg (33 [13.69%] subjects and 41 [16.53%] subjects, respectively) were statistically significantly different from placebo by the step-down procedure (nominal p-values =0.0033 and 0.0001, respectively) (Table 7).

Table 7. Summary of Subjects Achieving DAS28-4(ESR) <2.6 at Month 6 (FAS, No Imputation, Comparisons to Placebo)

Treatment	N	n	%	Difference from Comparator			
				Difference	95% CI for Difference		p-Value
					Lower	Upper	
Tofacitinib 5 mg BID	241	33	13.69	8.54	2.83	14.25	0.0033
Tofacitinib 10 mg BID	248	41	16.53	11.38	5.45	17.31	0.0001
Placebo	136	7	5.15	Not applicable			

BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of subjects, n = number of subjects meeting prespecified criteria, CI = confidence interval.

ACR20 Response Rates at All Timepoints: ACR20 response rates were higher for subjects in the tofacitinib 5 mg and 10 mg sequences up to Month 3 compared with subjects in the placebo → tofacitinib 5 mg and placebo → tofacitinib 10 mg sequences. By Month 6, response rates for subjects in the tofacitinib 5 mg and 10 mg sequences were 63.34% and 65.70%, respectively, compared with 67.09% and 55.13% for subjects in the placebo → tofacitinib 5 mg and placebo → tofacitinib 10 mg sequences, respectively. By Month 12, response rates for subjects in the tofacitinib 5 mg and 10 mg sequences were 64.95% and 64.08%, respectively, compared with 62.03% and 62.82% for subjects in the placebo → tofacitinib 5 mg and placebo → tofacitinib 10 mg sequences, respectively. An initial slight increase in the percentage of subjects achieving an ACR20 response was noted for the placebo → tofacitinib treatment sequences; after Month 3 (ie, after placebo non responders advanced to tofacitinib), there was a continued increase. In general, ACR20 responses were consistent across treatment sequences taking into consideration that some of these subgroups contained small numbers of subjects (Table 8).

Table 8 Normal Approximation to ACR20 Response Rates per Visit (FAS, NRINAP), Comparisons Within Sequence

		N	n	Response Rate
Week 2 (NRINAP)	Tofacitinib 5 mg BID	311	85	27.33
	Tofacitinib 10 mg BID	307	99	32.25
	Placebo → 5 mg BID	79	10	12.66
	Placebo → 10 mg BID	77	7	9.09
Month 1 (NRINAP)	Tofacitinib 5 mg BID	311	120	38.59
	Tofacitinib 10 mg BID	309	150	48.54
	Placebo → 5 mg BID	79	21	26.58
	Placebo → 10 mg BID	78	15	19.23
Month 2 (NRINAP)	Tofacitinib 5 mg BID	311	168	54.02
	Tofacitinib 10 mg BID	309	199	64.4
	Placebo → 5 mg BID	79	20	25.32
	Placebo → 10 mg BID	78	21	26.92
Month 3 (NRINAP)	Tofacitinib 5 mg BID	311	178	57.23
	Tofacitinib 10 mg BID	309	200	64.72
	Placebo → 5 mg BID	79	24	30.38
	Placebo → 10 mg BID	78	22	28.21
Month 4.5 (NRINAP)	Tofacitinib 5 mg BID	311	183	58.84
	Tofacitinib 10 mg BID	309	198	64.08
	Placebo → 5 mg BID	79	44	55.7
	Placebo → 10 mg BID	78	34	43.59
Month 6 (NRINAP)	Tofacitinib 5 mg BID	311	197	63.34
	Tofacitinib 10 mg BID	309	203	65.7
	Placebo → 5 mg BID	79	53	67.09
	Placebo → 10 mg BID	78	43	55.13
Month 9 (NRINAP)	Tofacitinib 5 mg BID	311	188	60.45
	Tofacitinib 10 mg BID	309	215	69.58
	Placebo → 5 mg BID	79	55	69.62
	Placebo → 10 mg BID	78	52	66.67
Month 12 (NRINAP)	Tofacitinib 5 mg BID	311	202	64.95
	Tofacitinib 10 mg BID	309	198	64.08
	Placebo → 5 mg BID	79	49	62.03
	Placebo → 10 mg BID	78	49	62.82

Subjects who withdrew for any reason before Month 6, or subjects who were advanced to active tofacitinib after Month 3 have their values on or after withdrawing set to Non-Response in this analysis.
ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, N = number of subjects, n = number of subjects meeting prespecified criteria, NRINAP = nonresponder imputation no advancement penalty.

ACR50 Response Rates at All Timepoints: The differences for tofacitinib treatment from placebo in response rate were statistically significant for tofacitinib at all timepoints beginning at Week 2 for both the tofacitinib 5 mg and 10 mg doses. The response rate was numerically higher in the tofacitinib 10 mg dose than the tofacitinib 5 mg dose. Subjects in the tofacitinib 10 mg treatment sequence showed separation from the placebo → tofacitinib treatment sequences by Week 2. The response rate was numerically higher in the tofacitinib 10 mg sequence than in the tofacitinib 5 mg sequence at each visit. Subjects randomized to placebo showed clear improvements in ACR50 response rates after switching to tofacitinib

treatment at Months 3 or 6. In general, ACR50 responses were consistent across treatment sequences taking into consideration that some of these subgroups contained small numbers of subjects (Table 9).

Table 9. Normal Approximation to ACR50 Response Rates per Visit (FAS, NRI), Comparisons Within Sequence

		N	n	Response Rate
Week 2 (NRI)	Tofacitinib 5 mg BID	311	18	5.79
	Tofacitinib 10 mg BID	307	25	8.14
	Placebo → 5 mg BID	79	1	1.27
	Placebo → 10 mg BID	77	1	1.30
Month 1 (NRI)	Tofacitinib 5 mg BID	311	36	11.58
	Tofacitinib 10 mg BID	309	56	18.12
	Placebo → 5 mg BID	79	2	2.53
	Placebo → 10 mg BID	78	0	0
Month 2 (NRI)	Tofacitinib 5 mg BID	311	72	23.15
	Tofacitinib 10 mg BID	309	92	29.77
	Placebo → 5 mg BID	79	3	3.80
	Placebo → 10 mg BID	78	4	5.13
Month 3 (NRI)	Tofacitinib 5 mg BID	311	85	27.33
	Tofacitinib 10 mg BID	309	105	33.98
	Placebo → 5 mg BID	79	5	6.33
	Placebo → 10 mg BID	78	10	12.82
Month 4.5 (NRI)	Tofacitinib 5 mg BID	311	87	27.97
	Tofacitinib 10 mg BID	309	103	33.33
	Placebo → 5 mg BID	79	4	5.06
	Placebo → 10 mg BID	78	9	11.54
Month 6 (NRI)	Tofacitinib 5 mg BID	311	105	33.76
	Tofacitinib 10 mg BID	309	113	36.57
	Placebo → 5 mg BID	79	11	13.92
	Placebo → 10 mg BID	78	9	11.54
Month 9 (NRI)	Tofacitinib 5 mg BID	311	98	31.51
	Tofacitinib 10 mg BID	309	133	43.04
	Placebo → 5 mg BID	79	20	25.32
	Placebo → 10 mg BID	78	21	26.92
Month 12 (NRI)	Tofacitinib 5 mg BID	311	104	33.44
	Tofacitinib 10 mg BID	309	132	42.72
	Placebo → 5 mg BID	79	19	24.05
	Placebo → 10 mg BID	78	20	25.64

Subjects who withdrew for any reason before Month 6, or subjects who were advanced to active tofacitinib after Month 3 have their values on or after withdrawing set to Non-Response in this analysis.
ACR50 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation.

ACR70 Response Rates at All Timepoints: The percentage of subjects who achieved ACR70 by Month 6 for subjects treated with tofacitinib 5 mg was statistically significant compared with placebo. The percentage of subjects who achieved ACR70 by Month 6 for subjects treated with tofacitinib 10 mg was also statistically significant compared with placebo. The response rate was numerically higher for subjects who received tofacitinib 10 mg than for those who received tofacitinib 5 mg.

The response rates were numerically higher in the tofacitinib 10 mg sequence than in the tofacitinib 5 mg sequence. Response rates for the placebo → tofacitinib treatment sequences

remained relatively low through Month 6; after Month 6 (ie, after advancing to tofacitinib), there was a slight increase. By Month 12, the ACR70 response rate for the tofacitinib 10 mg treatment sequence was higher than for the other treatment sequences, with response rates for the tofacitinib 5 mg treatment sequence and the placebo → tofacitinib treatment sequences nearly indistinguishable. In general, ACR70 responses were consistent across treatment sequences taking into consideration that some of these subgroups contained small numbers of subjects (Table 10).

Table 10. Normal Approximation to ACR70 Response Rates per Visit (FAS, NRI), Comparisons Within Sequence

		N	n	Response Rate
Week 2 (NRI)	Tofacitinib 5 mg BID	311	1	0.32
	Tofacitinib 10 mg BID	307	7	2.28
	Placebo → 5 mg BID	79	0	0
	Placebo → 10 mg BID	77	0	0
Month 1 (NRI)	Tofacitinib 5 mg BID	311	11	3.54
	Tofacitinib 10 mg BID	309	22	7.12
	Placebo → 5 mg BID	79	0	0
	Placebo → 10 mg BID	78	0	0
Month 2 (NRI)	Tofacitinib 5 mg BID	311	28	9
	Tofacitinib 10 mg BID	309	32	10.36
	Placebo → 5 mg BID	79	0	0
	Placebo → 10 mg BID	78	2	2.56
Month 3 (NRI)	Tofacitinib 5 mg BID	311	26	8.36
	Tofacitinib 10 mg BID	309	44	14.24
	Placebo → 5 mg BID	79	1	1.27
	Placebo → 10 mg BID	78	2	2.56
Month 4.5 (NRI)	Tofacitinib 5 mg BID	311	37	11.90
	Tofacitinib 10 mg BID	309	56	18.12
	Placebo → 5 mg BID	79	1	1.27
	Placebo → 10 mg BID	78	4	5.13
Month 6 (NRI)	Tofacitinib 5 mg BID	311	41	13.18
	Tofacitinib 10 mg BID	309	50	16.18
	Placebo → 5 mg BID	79	2	2.53
	Placebo → 10 mg BID	78	3	3.85
Month 9 (NRI)	Tofacitinib 5 mg BID	311	44	14.15
	Tofacitinib 10 mg BID	309	78	25.24
	Placebo → 5 mg BID	79	8	10.13
	Placebo → 10 mg BID	78	9	11.54
Month 12 (NRI)	Tofacitinib 5 mg BID	311	60	19.29
	Tofacitinib 10 mg BID	309	79	25.57
	Placebo → 5 mg BID	79	11	13.92
	Placebo → 10 mg BID	78	16	20.51

Subjects who withdrew for any reason before Month 6, or subjects who were advanced to active tofacitinib after Month 3 have their values on or after withdrawing set to Non-Response in this analysis.
ACR70 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures,. BID = twice daily, FAS = full analysis set, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation.

Health Assessment Questionnaire – Disability Index: The results for the tofacitinib 5 mg and tofacitinib 10 mg subjects demonstrated statistically significantly decreased HAQ-DI scores at Month 3 compared with placebo; subjects who received tofacitinib 10 mg experienced numerically greater improvement compared with tofacitinib 5 mg. Decreases from Baseline in HAQ-DI scores were noted in the tofacitinib treatment sequences as early as Week 2 that continued through Month 12 (Table 11).

Table 11. Descriptive Statistics of HAQ-DI per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	311	1.44	0.69
	Tofacitinib 10 mg BID	315	1.43	0.68
	Placebo → 5 mg BID	79	1.45	0.64
	Placebo → 10 mg BID	78	1.24	0.66
Week 2	Tofacitinib 5 mg BID	310	1.24	0.69
	Tofacitinib 10 mg BID	305	1.14	0.67
	Placebo → 5 mg BID	79	1.35	0.66
	Placebo → 10 mg BID	77	1.20	0.66
Month 1	Tofacitinib 5 mg BID	304	1.12	0.67
	Tofacitinib 10 mg BID	303	1.01	0.65
	Placebo → 5 mg BID	77	1.29	0.67
	Placebo → 10 mg BID	77	1.12	0.66
Month 2	Tofacitinib 5 mg BID	299	1.03	0.68
	Tofacitinib 10 mg BID	300	0.93	0.66
	Placebo → 5 mg BID	76	1.26	0.62
	Placebo → 10 mg BID	74	1.13	0.64
Month 3	Tofacitinib 5 mg BID	293	0.98	0.67
	Tofacitinib 10 mg BID	292	0.88	0.67
	Placebo → 5 mg BID	74	1.23	0.65
	Placebo → 10 mg BID	74	1.09	0.70
Month 4.5	Tofacitinib 5 mg BID	284	0.97	0.68
	Tofacitinib 10 mg BID	289	0.84	0.67
	Placebo → 5 mg BID	73	1.07	0.66
	Placebo → 10 mg BID	74	0.92	0.62
Month 6	Tofacitinib 5 mg BID	278	0.91	0.67
	Tofacitinib 10 mg BID	279	0.81	0.65
	Placebo → 5 mg BID	73	1.03	0.63
	Placebo → 10 mg BID	71	0.83	0.63
Month 9	Tofacitinib 5 mg BID	266	0.89	0.68
	Tofacitinib 10 mg BID	264	0.71	0.64
	Placebo → 5 mg BID	72	0.85	0.65
	Placebo → 10 mg BID	70	0.7	0.64
Month 12	Tofacitinib 5 mg BID	258	0.86	0.68
	Tofacitinib 10 mg BID	250	0.73	0.64
	Placebo → 5 mg BID	70	0.81	0.68
	Placebo → 10 mg BID	67	0.73	0.69

BID = twice daily, HAQ-DI = Health Assessment Questionnaire-Disability Index, N = number of subjects; SD = standard deviation.

Rates of at Least 0.22 Improvements in HAQ-DI: Treatment with tofacitinib (5 mg and 10 mg) resulted in statistically significantly greater rates of improvement compared with placebo for Week 2 through Month 6. Response rates were numerically greater for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg.

In the tofacitinib treatment sequences, greater percentages of subjects with at least a 0.22 improvement in HAQ-DI were noted by Week 2 compared with the placebo → tofacitinib treatment sequences; in the tofacitinib sequences, the proportions of subjects increased through approximately Month 3. By Month 12, the rates of subjects achieving at least a 0.22 improvement in HAQ-DI were similar across all 4 treatment sequences. In general, changes in HAQ-DI were consistent across treatment sequences. The tofacitinib 5

mg treatment sequence in the "Other DMARDs without methotrexate and leflunomide" subgroup showed little change in HAQ-DI, but the numbers of subject in these subgroups were too small to draw conclusions from these data (Table 12). The rates of at least 0.3 and 0.5 improvements in HAQ-DI are summarized in Table 13 and Table 14.

Table 12. Normal Approximation to Rates of at Least 0.22 Improvement in HAQ-DI per Visit (FAS, NRI), Comparisons Within Sequence

		N	n	Response Rate
Week 2 (NRI)	Tofacitinib 5 mg BID	309	141	45.63
	Tofacitinib 10 mg BID	305	162	53.11
	Placebo → 5 mg BID	79	29	36.71
	Placebo → 10 mg BID	76	24	31.58
Month 1 (NRI)	Tofacitinib 5 mg BID	310	173	55.81
	Tofacitinib 10 mg BID	308	201	65.26
	Placebo → 5 mg BID	79	37	46.84
	Placebo → 10 mg BID	77	29	37.66
Month 2 (NRI)	Tofacitinib 5 mg BID	310	195	62.90
	Tofacitinib 10 mg BID	308	204	66.23
	Placebo → 5 mg BID	79	34	43.04
	Placebo → 10 mg BID	77	34	44.16
Month 3 (NRI)	Tofacitinib 5 mg BID	310	152	49.03
	Tofacitinib 10 mg BID	308	176	57.14
	Placebo → 5 mg BID	79	18	22.78
	Placebo → 10 mg BID	77	19	24.68
Month 4.5 (NRI)	Tofacitinib 5 mg BID	310	152	49.03
	Tofacitinib 10 mg BID	308	177	57.47
	Placebo → 5 mg BID	79	24	30.38
	Placebo → 10 mg BID	77	18	23.38
Month 6 (NRI)	Tofacitinib 5 mg BID	310	154	49.68
	Tofacitinib 10 mg BID	308	171	55.52
	Placebo → 5 mg BID	79	22	27.85
	Placebo → 10 mg BID	77	15	19.48
Month 9 (NRI)	Tofacitinib 5 mg BID	310	146	47.10
	Tofacitinib 10 mg BID	308	179	58.12
	Placebo → 5 mg BID	79	26	32.91
	Placebo → 10 mg BID	77	23	29.87
Month 12 (NRI)	Tofacitinib 5 mg BID	310	150	48.39
	Tofacitinib 10 mg BID	308	167	54.22
	Placebo → 5 mg BID	79	26	32.91
	Placebo → 10 mg BID	77	22	28.57

Subjects who withdrew for any reason before Month 6, or subjects who were advanced to active tofacitinib after Month 3 have their values on or after withdrawing set to Non-Response in this analysis.
BID = twice daily, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire-Disability Index, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation.

Table 13 Normal Approximation to Rates of at Least 0.3 Improvement in HAQ-DI per Visit (FAS, NRI), Comparisons Within Sequence

		N	n	Response Rate
Week 2 (NRI)	Tofacitinib 5 mg BID	309	109	35.28
	Tofacitinib 10 mg BID	305	126	41.31
	Placebo → 5 mg BID	79	15	18.99
	Placebo → 10 mg BID	76	14	18.42
Month 1 (NRI)	Tofacitinib 5 mg BID	310	126	40.65
	Tofacitinib 10 mg BID	308	159	51.62
	Placebo → 5 mg BID	79	25	31.65
	Placebo → 10 mg BID	77	20	25.97
Month 2 (NRI)	Tofacitinib 5 mg BID	310	164	52.9
	Tofacitinib 10 mg BID	308	169	54.87
	Placebo → 5 mg BID	79	26	32.91
	Placebo → 10 mg BID	77	24	31.17
Month 3 (NRI)	Tofacitinib 5 mg BID	310	135	43.55
	Tofacitinib 10 mg BID	308	159	51.62
	Placebo → 5 mg BID	79	13	16.46
	Placebo → 10 mg BID	77	15	19.48
Month 4.5 (NRI)	Tofacitinib 5 mg BID	310	138	44.52
	Tofacitinib 10 mg BID	308	163	52.92
	Placebo → 5 mg BID	79	18	22.78
	Placebo → 10 mg BID	77	16	20.78
Month 6 (NRI)	Tofacitinib 5 mg BID	310	138	44.52
	Tofacitinib 10 mg BID	308	152	49.35
	Placebo → 5 mg BID	79	17	21.52
	Placebo → 10 mg BID	77	14	18.18
Month 9 (NRI)	Tofacitinib 5 mg BID	310	136	43.87
	Tofacitinib 10 mg BID	308	162	52.6
	Placebo → 5 mg BID	79	25	31.65
	Placebo → 10 mg BID	77	19	24.68
Month 12 (NRI)	Tofacitinib 5 mg BID	310	133	42.9
	Tofacitinib 10 mg BID	308	152	49.35
	Placebo → 5 mg BID	79	24	30.38
	Placebo → 10 mg BID	77	18	23.38

Subjects who withdrew for any reason before Month 6, or subjects who were advanced to active tofacitinib after Month 3 have their values on or after withdrawing set to Non-Response in this analysis.
BID = twice daily, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire-Disability Index, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation.

Table 14 Normal Approximation to Rates of at Least 0.5 Improvement in HAQ-DI per Visit (FAS, NRI), Comparisons Within Sequence

		N	n	Response Rate
Week 2 (NRI)	Tofacitinib 5 mg BID	309	79	25.57
	Tofacitinib 10 mg BID	305	87	28.52
	Placebo → 5 mg BID	79	8	10.13
	Placebo → 10 mg BID	76	8	10.53
Month 1 (NRI)	Tofacitinib 5 mg BID	310	103	33.23
	Tofacitinib 10 mg BID	308	124	40.26
	Placebo → 5 mg BID	79	17	21.52
	Placebo → 10 mg BID	77	15	19.48
Month 2 (NRI)	Tofacitinib 5 mg BID	310	130	41.94
	Tofacitinib 10 mg BID	308	152	49.35
	Placebo → 5 mg BID	79	23	29.11
	Placebo → 10 mg BID	77	19	24.68
Month 3 (NRI)	Tofacitinib 5 mg BID	310	115	37.1
	Tofacitinib 10 mg BID	308	135	43.83
	Placebo → 5 mg BID	79	10	12.66
	Placebo → 10 mg BID	77	12	15.58
Month 4.5 (NRI)	Tofacitinib 5 mg BID	310	120	38.71
	Tofacitinib 10 mg BID	308	140	45.45
	Placebo → 5 mg BID	79	12	15.19
	Placebo → 10 mg BID	77	12	15.58
Month 6 (NRI)	Tofacitinib 5 mg BID	310	119	38.39
	Tofacitinib 10 mg BID	308	138	44.81
	Placebo → 5 mg BID	79	15	18.99
	Placebo → 10 mg BID	77	11	14.29
Month 9 (NRI)	Tofacitinib 5 mg BID	310	127	40.97
	Tofacitinib 10 mg BID	308	146	47.4
	Placebo → 5 mg BID	79	24	30.38
	Placebo → 10 mg BID	77	16	20.78
Month 12 (NRI)	Tofacitinib 5 mg BID	310	121	39.03
	Tofacitinib 10 mg BID	308	143	46.43
	Placebo → 5 mg BID	79	22	27.85
	Placebo → 10 mg BID	77	15	19.48

Subjects who withdrew for any reason before Month 6, or subjects who were advanced to active tofacitinib after Month 3 have their values on or after withdrawing set to Non-Response in this analysis.
BID = twice daily, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire-Disability Index, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation.

DAS28-4(ESR): Treatment with tofacitinib (5 and 10 mg) resulted in statistically significant improvements from Baseline in DAS28-4(ESR) at Month 3 and Month 6 compared with placebo. The decrease from Baseline was slightly larger for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg.

The tofacitinib treatment sequences had a numerically greater decrease from Baseline at Month 3 and Month 6 compared with the placebo → tofacitinib treatment sequences in DAS28-4(ESR). An initial decrease from Baseline was noted for the placebo → tofacitinib treatment sequences at Month 3; after Months 3 and 6 (ie, after advancing to tofacitinib), a further decrease was observed.

The rates of subjects achieving DAS28-4(ESR) ≤3.2 with treatment with tofacitinib (5 mg and 10 mg) resulted in statistically significantly greater response rates compared with placebo at Month 3 and Month 6. Subjects in the tofacitinib treatment sequences showed a response by Month 3; the response rates were relatively stable at Month 6.

The rates of subjects achieving DAS28-4(ESR) <2.6 were greater for subjects who received tofacitinib 5 mg and tofacitinib 10 mg at Month 6 than the response rate for placebo, and the differences were statistically significant. The rates of subjects achieving DAS28-4(ESR) <2.6 through Month 12 in the last observation carried forward (LOCF) imputation were similar response rates at Month 12.

Treatment with tofacitinib (5 mg and 10 mg) resulted in statistically significantly greater response rates with DAS28-4(ESR) response ('good' or 'moderate') compared with placebo at all timepoints. Approximately three-fourths of subjects in the tofacitinib treatment sequences had achieved DAS28-4(ESR) response by Month 3; the response rates were relatively stable at Month 6. In the LOCF imputation, all treatment sequences demonstrated similar response rates at Month 12 (Table 15).

Table 15. Descriptive Statistics of DAS28-4(ESR) per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	309	6.29	0.96
	Tofacitinib 10 mg BID	313	6.36	1.01
	Placebo → 5 mg BID	79	6.44	0.90
	Placebo → 10 mg BID	79	6.16	0.92
Month 3	Tofacitinib 5 mg BID	260	4.41	1.39
	Tofacitinib 10 mg BID	263	4.20	1.30
	Placebo → 5 mg BID	70	5.39	1.22
	Placebo → 10 mg BID	70	5.24	1.30
Month 6	Tofacitinib 5 mg BID	241	4.14	1.34
	Tofacitinib 10 mg BID	248	3.84	1.26
	Placebo → 5 mg BID	69	4.40	1.20
	Placebo → 10 mg BID	67	4.14	1.19
Month 12	Tofacitinib 5 mg BID	220	3.82	1.30
	Tofacitinib 10 mg BID	226	3.50	1.11
	Placebo → 5 mg BID	63	3.76	1.31
	Placebo → 10 mg BID	62	3.62	1.19

BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, N = number of subjects, SD = standard deviation.

ESR: Treatment with tofacitinib (5 mg and 10 mg) resulted in statistically significant decreases from Baseline in ESR at Month 3 and Month 6 compared with placebo. The tofacitinib treatment sequences had decreases from Baseline in ESR at Month 3; while the values remained stable through Month 12. The placebo → tofacitinib treatment sequences had smaller decreases at Month 3 (Table 16).

Table 16. Descriptive Statistics of Erythrocyte Sedimentation Rate (mm/hr) per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	311	50.46	28.71
	Tofacitinib 10 mg BID	315	51.94	28.46
	Placebo → 5 mg BID	79	51.04	23.72
	Placebo → 10 mg BID	79	49.29	27.72
Month 3	Tofacitinib 5 mg BID	261	33.67	24.5
	Tofacitinib 10 mg BID	263	31.06	22.58
	Placebo → 5 mg BID	70	45.24	25.40
	Placebo → 10 mg BID	70	44.19	25.60
Month 6	Tofacitinib 5 mg BID	242	32.02	21.85
	Tofacitinib 10 mg BID	248	29.82	18.98
	Placebo → 5 mg BID	69	33.46	23.17
	Placebo → 10 mg BID	67	34.63	22.32
Month 12	Tofacitinib 5 mg BID	221	32.28	22.11
	Tofacitinib 10 mg BID	227	29.55	20.54
	Placebo → 5 mg BID	63	31.40	18.93
	Placebo → 10 mg BID	62	31.84	23.00

BID = twice daily, N = number of subjects, SD = standard deviation.

DAS28-3(CRP): Subjects who received tofacitinib had statistically significant decreases from Baseline in DAS28-3(CRP) compared with placebo by Week 2 that continued through Month 6. Changes from Baseline were greater for subjects who received tofacitinib 10 mg group compared with tofacitinib 5 mg. Subjects in the tofacitinib treatment sequences had pronounced decreases from Baseline by Week 2 that continued through Month 12. Decreases in the tofacitinib 10 mg sequence were numerically larger than those in the tofacitinib 5 mg sequence. By Month 12, all treatment sequences showed similar decreases in DAS28-3(CRP).

Subjects in the tofacitinib treatment sequences began to achieve DAS28-3(CRP) ≤3.2 by Week 2; response rates increased through Month 6. The response rates were higher in the tofacitinib 10 mg sequence than in the tofacitinib 5 mg sequence. After Month 6 (ie, after advancing to tofacitinib) there was an increase in the proportion of subjects in the placebo → tofacitinib treatment sequences who achieved DAS28-3(CRP) ≤3.2.

Subjects who received tofacitinib 5 mg or 10 mg had statistically significantly improved DAS28-3(CRP) <2.6 response rates for Week 2 through Month 6 compared with placebo. The response rates were numerically greater for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg. The percentages of subjects in the tofacitinib treatment sequences who achieved DAS28-3(CRP) <2.6 increased at each timepoint through Month 12. Subjects in the tofacitinib 10 mg sequence achieved DAS28-3(CRP) <2.6 at a greater frequency than subjects in the tofacitinib 5 mg sequence. The percentages of subjects in the placebo → tofacitinib treatment sequences who achieved DAS28-3(CRP) <2.6 remained near Baseline levels prior to Month 3. After Months 3 and 6 (ie, after advancing to tofacitinib), there was an increase in the percentage of subjects in the placebo → tofacitinib treatment sequences who achieved DAS28-3(CRP) <2.6.

Treatment with tofacitinib (5 mg and 10 mg) resulted in statistically significant improvements in DAS28-3(CRP) response rates ('good' or 'moderate') compared with placebo from Week 2 through Month 6. A large percentage of subjects in the tofacitinib treatment sequences showed response by Week 2, with response rates increasing through approximately Month 3 and then plateauing through Month 12. An initial response was noted for subjects in the placebo → tofacitinib treatment sequences; after Month 3 and 6 (ie, after advancement to tofacitinib), the response rates increased. By Month 12, all treatment sequences showed a similar response rate in the LOCF analysis group (Table 17).

Table 17. Descriptive Statistics of DAS28-3(CRP) per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	312	5.21	0.92
	Tofacitinib 10 mg BID	315	5.26	0.96
	Placebo → 5 mg BID	79	5.34	0.85
	Placebo → 10 mg BID	79	5.09	0.97
Week 2	Tofacitinib 5 mg BID	309	4.41	1.10
	Tofacitinib 10 mg BID	304	4.18	1.09
	Placebo → 5 mg BID	79	5.01	1.05
	Placebo → 10 mg BID	77	4.82	0.96
Month 1	Tofacitinib 5 mg BID	304	4.08	1.13
	Tofacitinib 10 mg BID	300	3.83	1.12
	Placebo → 5 mg BID	75	4.76	1.19
	Placebo → 10 mg BID	76	4.60	0.97
Month 2	Tofacitinib 5 mg BID	294	3.70	1.20
	Tofacitinib 10 mg BID	300	3.49	1.15
	Placebo → 5 mg BID	75	4.63	1.15
	Placebo → 10 mg BID	73	4.55	1.19
Month 3	Tofacitinib 5 mg BID	293	3.62	1.22
	Tofacitinib 10 mg BID	291	3.44	1.15
	Placebo → 5 mg BID	74	4.53	1.14
	Placebo → 10 mg BID	73	4.49	1.18
Month 4.5	Tofacitinib 5 mg BID	281	3.46	1.27
	Tofacitinib 10 mg BID	286	3.15	1.12
	Placebo → 5 mg BID	73	3.95	1.19
	Placebo → 10 mg BID	74	3.68	1.10
Month 6	Tofacitinib 5 mg BID	279	3.39	1.21
	Tofacitinib 10 mg BID	278	3.09	1.13
	Placebo → 5 mg BID	73	3.73	1.11
	Placebo → 10 mg BID	72	3.41	1.15
Month 9	Tofacitinib 5 mg BID	267	3.21	1.14
	Tofacitinib 10 mg BID	263	2.88	1.05
	Placebo → 5 mg BID	72	3.22	1.05
	Placebo → 10 mg BID	68	2.83	0.93
Month 12	Tofacitinib 5 mg BID	258	3.08	1.19
	Tofacitinib 10 mg BID	250	2.81	1.04
	Placebo → 5 mg BID	70	3.03	1.15
	Placebo → 10 mg BID	67	2.99	1.06

BID = twice daily, CRP = C-reactive protein, DAS = Disease Activity Score, N = number of subjects, SD = standard deviation.

CRP: Treatment with tofacitinib (5 mg and 10 mg) resulted in statistically significant decreases from Baseline in CRP concentrations compared with placebo from Week 2 through Month 6. The decreases from Baseline were observed as early as Week 2 for the tofacitinib treatment sequences; the values stabilized through Month 12. Mean CRP values for the placebo → tofacitinib 5 mg treatment sequence decreased from Week 2 through Month 12 with the most pronounced decrease occurring after Month 3 and 6 (ie, after placebo subjects advanced to tofacitinib treatment). Mean CRP values for the placebo → tofacitinib 10 mg treatment sequence were sporadic from Baseline to Month 3 (ie, after nonresponders advanced to tofacitinib treatment), at which point values decreased through Month 12. At Month 12, all treatment sequences showed a similar decrease in CRP levels (Table 18).

Table 18. Descriptive Statistics of C-Reactive Protein (mg/L) per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	312	17.68	21.44
	Tofacitinib 10 mg BID	313	17.73	21.88
	Placebo → 5 mg BID	79	16.88	16.47
	Placebo → 10 mg BID	79	16.54	18.2
Week 2	Tofacitinib 5 mg BID	299	8.3	13.27
	Tofacitinib 10 mg BID	282	6.91	14.56
	Placebo → 5 mg BID	79	19.41	25.38
	Placebo → 10 mg BID	77	15.58	14.2
Month 1	Tofacitinib 5 mg BID	296	7.02	11.85
	Tofacitinib 10 mg BID	273	6.12	12.81
	Placebo → 5 mg BID	75	17.48	17.74
	Placebo → 10 mg BID	75	16.98	19.63
Month 2	Tofacitinib 5 mg BID	282	6.1	12.64
	Tofacitinib 10 mg BID	284	5.64	11.41
	Placebo → 5 mg BID	75	13.89	14.1
	Placebo → 10 mg BID	73	15.18	14.85
Month 3	Tofacitinib 5 mg BID	281	6.30	11.69
	Tofacitinib 10 mg BID	274	5.82	9.44
	Placebo → 5 mg BID	74	13.07	13.17
	Placebo → 10 mg BID	73	18.24	19.82
Month 4.5	Tofacitinib 5 mg BID	269	6.08	9.93
	Tofacitinib 10 mg BID	252	4.89	8.21
	Placebo → 5 mg BID	72	11.36	15.63
	Placebo → 10 mg BID	73	10.17	12.24
Month 6	Tofacitinib 5 mg BID	255	5.98	8.49
	Tofacitinib 10 mg BID	249	5.47	11.65
	Placebo → 5 mg BID	72	9.09	11.8
	Placebo → 10 mg BID	68	8.94	11.43
Month 9	Tofacitinib 5 mg BID	256	6.35	9.26
	Tofacitinib 10 mg BID	235	5.71	14.89
	Placebo → 5 mg BID	69	5.88	7.26
	Placebo → 10 mg BID	63	4.61	7.23
Month 12	Tofacitinib 5 mg BID	245	6.07	9.34
	Tofacitinib 10 mg BID	231	4.63	7.91
	Placebo → 5 mg BID	68	5.56	8.67
	Placebo → 10 mg BID	58	7.48	12.49

BID = twice daily, N = number of subjects, SD = standard deviation.

Patient Global Assessment of Arthritis: Treatment with tofacitinib (5 mg and 10 mg) resulted in statistically significant decreases in Patient Global Assessment of Arthritis from Baseline compared with placebo at Week 2 through Month 6. The decreases from Baseline were numerically greater for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg. The tofacitinib treatment sequences demonstrated decreases (improvements) from Baseline Patient Global Assessment of Arthritis beginning at Week 2; the decreases continued through approximately Month 2, stabilized through Month 6, and decreased further through Month 12. At Month 12, all treatment sequences showed similar changes in Patient Global Assessment Scores (Table 19).

Table 19. Descriptive Statistics of Patient Global Assessment per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	311	59.03	22.89
	Tofacitinib 10 mg BID	315	60.22	22.53
	Placebo → 5 mg BID	79	59.10	23.20
	Placebo → 10 mg BID	79	56.75	23.55
Week 2	Tofacitinib 5 mg BID	310	46.59	22.52
	Tofacitinib 10 mg BID	306	42.99	22.16
	Placebo → 5 mg BID	79	50.61	25.58
	Placebo → 10 mg BID	77	51.95	22.36
Month 1	Tofacitinib 5 mg BID	303	40.50	23.29
	Tofacitinib 10 mg BID	303	36.53	21.42
	Placebo → 5 mg BID	77	47.03	24.93
	Placebo → 10 mg BID	77	45.47	23.63
Month 2	Tofacitinib 5 mg BID	299	37.18	22.52
	Tofacitinib 10 mg BID	301	33.80	22.21
	Placebo → 5 mg BID	76	50.91	24.43
	Placebo → 10 mg BID	74	49.92	22.79
Month 3	Tofacitinib 5 mg BID	294	36.27	22.64
	Tofacitinib 10 mg BID	292	33.43	22.55
	Placebo → 5 mg BID	74	47.49	24.5
	Placebo → 10 mg BID	74	46.70	27.82
Month 4.5	Tofacitinib 5 mg BID	284	35.92	22.69
	Tofacitinib 10 mg BID	289	34.05	22.09
	Placebo → 5 mg BID	73	38.85	24.44
	Placebo → 10 mg BID	74	36.89	21.54
Month 6	Tofacitinib 5 mg BID	279	33.75	23.01
	Tofacitinib 10 mg BID	280	31.31	21.55
	Placebo → 5 mg BID	73	34.26	23.33
	Placebo → 10 mg BID	71	33.21	21.80
Month 9	Tofacitinib 5 mg BID	266	32.06	22.49
	Tofacitinib 10 mg BID	264	28.01	20.81
	Placebo → 5 mg BID	72	28.97	20.07
	Placebo → 10 mg BID	70	28.56	22.74
Month 12	Tofacitinib 5 mg BID	258	30.64	22.03
	Tofacitinib 10 mg BID	250	27.94	20.39
	Placebo → 5 mg BID	70	28.71	23.05
	Placebo → 10 mg BID	66	28.20	24.29

BID = twice daily, N = number of subjects, SD = standard deviation.

Physician Global Assessment of Arthritis: Treatment with tofacitinib (5 and 10 mg) resulted in statistically significant decreases from Baseline in Physician Global Assessment of Arthritis compared with placebo at Week 2 through Month 6. The decreases from Baseline were greater for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg. The tofacitinib treatment sequences demonstrated decreases (improvements) from Baseline beginning at Week 2; the decreases continued through Month 12. An initial decrease in Physician Global Assessment of Arthritis was noted for the placebo → tofacitinib treatment sequences. Decreases (improvements) continued in the placebo → tofacitinib treatment sequences after Months 3 and 6 (ie, when placebo subjects were advanced to tofacitinib therapy). At Month 12, all treatment sequences showed a similar change in Physician Global Assessments (Table 20).

Table 20. Descriptive Statistics of Physician Global Assessment per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	310	60.48	17.83
	Tofacitinib 10 mg BID	313	59.66	17.03
	Placebo → 5 mg BID	79	58.97	15.74
	Placebo → 10 mg BID	79	58.78	17.36
Week 2	Tofacitinib 5 mg BID	308	46.41	20.14
	Tofacitinib 10 mg BID	304	43.79	18.17
	Placebo → 5 mg BID	79	48.16	19.43
	Placebo → 10 mg BID	76	50.02	18.42
Month 1	Tofacitinib 5 mg BID	302	38.35	19.92
	Tofacitinib 10 mg BID	303	34.31	18.70
	Placebo → 5 mg BID	77	41.98	21.78
	Placebo → 10 mg BID	77	43.74	18.44
Month 2	Tofacitinib 5 mg BID	299	32.54	19.36
	Tofacitinib 10 mg BID	299	29.4	17.36
	Placebo → 5 mg BID	76	40.20	21.21
	Placebo → 10 mg BID	74	42.33	19.66
Month 3	Tofacitinib 5 mg BID	293	31.97	20.25
	Tofacitinib 10 mg BID	292	29.21	19.31
	Placebo → 5 mg BID	74	40.04	20.81
	Placebo → 10 mg BID	74	39.04	21.5
Month 4.5	Tofacitinib 5 mg BID	283	29.45	19.84
	Tofacitinib 10 mg BID	288	26.11	17.54
	Placebo → 5 mg BID	73	31.17	20.77
	Placebo → 10 mg BID	74	31.35	19.35
Month 6	Tofacitinib 5 mg BID	278	25.83	17.29
	Tofacitinib 10 mg BID	280	23.69	16.62
	Placebo → 5 mg BID	73	26.49	17.79
	Placebo → 10 mg BID	72	27.29	17.45
Month 9	Tofacitinib 5 mg BID	265	24.36	17.67
	Tofacitinib 10 mg BID	264	20.09	14.23
	Placebo → 5 mg BID	72	22.70	15.42
	Placebo → 10 mg BID	70	20.63	17.35
Month 12	Tofacitinib 5 mg BID	257	21.52	17.14
	Tofacitinib 10 mg BID	249	18.12	14.50
	Placebo → 5 mg BID	70	19.01	15.01
	Placebo → 10 mg BID	67	17.59	15.21

BID = twice daily, N = number of subjects, SD = standard deviation.

Pain: Treatment with tofacitinib (5 and 10 mg) resulted in statistically significant decreases in pain from Baseline in pain compared with placebo at Week 2 through Month 6. The decreases from Baseline were numerically greater for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg. The tofacitinib treatment sequences demonstrated decreases (improvements) from Baseline beginning at Week 2; the decreases continued somewhat rapidly through Month 3, then continued to decrease though at a slower rate through Month 12. At Month 12, all treatment sequences showed a similar change in pain scores (Table 21).

Table 21. Descriptive Statistics of Pain Visual Analog Scale (VAS) per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	311	57.08	23.82
	Tofacitinib 10 mg BID	315	58.58	22.19
	Placebo → 5 mg BID	79	58.34	22.62
	Placebo → 10 mg BID	79	55.87	23.14
Week 2	Tofacitinib 5 mg BID	310	46.81	22.82
	Tofacitinib 10 mg BID	306	41.85	22.49
	Placebo → 5 mg BID	79	51.33	25.75
	Placebo → 10 mg BID	77	50.68	23.21
Month 1	Tofacitinib 5 mg BID	304	40.17	23.20
	Tofacitinib 10 mg BID	303	37.08	22.14
	Placebo → 5 mg BID	77	47.09	25.66
	Placebo → 10 mg BID	77	44.30	24.42
Month 2	Tofacitinib 5 mg BID	299	36.40	22.63
	Tofacitinib 10 mg BID	301	32.84	21.71
	Placebo → 5 mg BID	76	48.34	23.34
	Placebo → 10 mg BID	74	46.23	25.35
Month 3	Tofacitinib 5 mg BID	294	34.92	23.03
	Tofacitinib 10 mg BID	292	32.96	23.10
	Placebo → 5 mg BID	74	46.35	26.10
	Placebo → 10 mg BID	74	46.84	28.32
Month 4.5	Tofacitinib 5 mg BID	284	34.43	22.68
	Tofacitinib 10 mg BID	289	32.62	21.74
	Placebo → 5 mg BID	73	37.26	22.39
	Placebo → 10 mg BID	74	36.62	24.23
Month 6	Tofacitinib 5 mg BID	279	31.07	21.84
	Tofacitinib 10 mg BID	280	29.94	21.53
	Placebo → 5 mg BID	73	34.29	23.42
	Placebo → 10 mg BID	71	31.89	22.67
Month 9	Tofacitinib 5 mg BID	267	30.78	22.28
	Tofacitinib 10 mg BID	264	27.13	20.77
	Placebo → 5 mg BID	72	29.50	21.34
	Placebo → 10 mg BID	70	25.26	21.96
Month 12	Tofacitinib 5 mg BID	258	30.18	23.11
	Tofacitinib 10 mg BID	250	25.43	20.57
	Placebo → 5 mg BID	70	28.20	22.46
	Placebo → 10 mg BID	67	25.39	22.71

BID = twice daily, N = number of subjects, SD = standard deviation.

Tender Joint Counts: Treatment with tofacitinib 10 mg resulted in statistically significant decreases from Baseline in tender joint counts compared with placebo at Week 2 through Month 6. Treatment with tofacitinib 5 mg resulted in statistically significant decreases from Baseline in tender joint counts compared with placebo at Month 1 through Month 6. The decreases from Baseline were slightly larger for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg.

The tofacitinib treatment sequences demonstrated decreases from Baseline in tender joint counts beginning at Week 2; the decreases continued through Month 12. The changes from Baseline were statistically significant (p-value <0.0001) at each timepoint for the tofacitinib treatment sequences. An initial decrease in tender joint counts was noted for subjects in the

placebo → tofacitinib treatment sequences; after Month 3 (ie, after nonresponders advanced to tofacitinib) and Month 6 (ie, remaining placebo subjects were advanced to tofacitinib), there was a continued decrease. At Month 12, all treatment sequences had a similar change in tender joint count (Table 22).

Table 22. Descriptive Statistics of Tender-Joint Counts per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	312	25.00	15.26
	Tofacitinib 10 mg BID	315	26.57	16.10
	Placebo → 5 mg BID	79	27.23	16.78
	Placebo → 10 mg BID	79	21.86	13.01
Week 2	Tofacitinib 5 mg BID	311	19.40	15.52
	Tofacitinib 10 mg BID	306	18.31	14.34
	Placebo → 5 mg BID	79	22.86	16.56
	Placebo → 10 mg BID	77	18.75	11.93
Month 1	Tofacitinib 5 mg BID	305	16.66	14.59
	Tofacitinib 10 mg BID	304	15.1	14.18
	Placebo → 5 mg BID	78	21.44	18.29
	Placebo → 10 mg BID	77	16.26	10.88
Month 2	Tofacitinib 5 mg BID	301	13.8	14.38
	Tofacitinib 10 mg BID	302	11.83	12.89
	Placebo → 5 mg BID	76	19.63	16.55
	Placebo → 10 mg BID	75	17.83	14.53
Month 3	Tofacitinib 5 mg BID	294	12.47	13.23
	Tofacitinib 10 mg BID	292	11.35	13.18
	Placebo → 5 mg BID	74	18.84	17.24
	Placebo → 10 mg BID	74	15.05	12.39
Month 4.5	Tofacitinib 5 mg BID	285	11.66	14.31
	Tofacitinib 10 mg BID	289	9.31	11.32
	Placebo → 5 mg BID	73	13.32	13.58
	Placebo → 10 mg BID	74	11.57	11.11
Month 6	Tofacitinib 5 mg BID	279	10.57	12.50
	Tofacitinib 10 mg BID	280	9.08	11.48
	Placebo → 5 mg BID	73	12.01	14.13
	Placebo → 10 mg BID	72	9.76	11.39
Month 9	Tofacitinib 5 mg BID	267	9.04	10.89
	Tofacitinib 10 mg BID	264	7.17	9.53
	Placebo → 5 mg BID	72	8.68	11.41
	Placebo → 10 mg BID	70	7.59	10.47
Month 12	Tofacitinib 5 mg BID	258	8.03	11.00
	Tofacitinib 10 mg BID	250	6.75	9.94
	Placebo → 5 mg BID	70	8.49	13.06
	Placebo → 10 mg BID	67	6.42	7.56

BID = twice daily, N = number of subjects, SD = standard deviation.

Swollen Joint Counts: Treatment with tofacitinib 10 mg resulted in statistically significant decreases from Baseline in swollen joint counts compared with placebo at Month 1 through Month 6. The decreases from Baseline were slightly larger for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg.

The tofacitinib treatment sequences demonstrated decreases from Baseline in swollen joint counts beginning at Week 2; the decreases continued through Month 12. An initial decrease in swollen joint counts was noted for subjects in the placebo → tofacitinib treatment sequences; after Month 3 (ie, after nonresponders advanced to tofacitinib) and Month 6 (ie, remaining placebo subjects were advanced to tofacitinib), there was a continued decrease. At Month 12, all treatment sequences showed a similar decrease in swollen joint count (Table 23).

Table 23. Descriptive Statistics of Swollen-Joint Counts per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	312	14.49	10.26
	Tofacitinib 10 mg BID	315	14.41	9.72
	Placebo → 5 mg BID	79	14.58	9.65
	Placebo → 10 mg BID	79	13.91	8.62
Week 2	Tofacitinib 5 mg BID	311	10.94	10.89
	Tofacitinib 10 mg BID	306	10.22	9.04
	Placebo → 5 mg BID	79	11.78	9.11
	Placebo → 10 mg BID	77	11.31	8.54
Month 1	Tofacitinib 5 mg BID	305	8.94	9.64
	Tofacitinib 10 mg BID	304	8.15	8.47
	Placebo → 5 mg BID	78	11.56	11.11
	Placebo → 10 mg BID	77	9.71	7.42
Month 2	Tofacitinib 5 mg BID	301	7.91	9.88
	Tofacitinib 10 mg BID	302	6.54	8.07
	Placebo → 5 mg BID	76	9.71	8.96
	Placebo → 10 mg BID	75	10.71	11.87
Month 3	Tofacitinib 5 mg BID	294	6.93	8.64
	Tofacitinib 10 mg BID	292	5.96	6.72
	Placebo → 5 mg BID	74	9.91	9.48
	Placebo → 10 mg BID	74	9.15	8.75
Month 4.5	Tofacitinib 5 mg BID	285	6.36	8.95
	Tofacitinib 10 mg BID	289	5.02	6.37
	Placebo → 5 mg BID	73	6.70	8.70
	Placebo → 10 mg BID	74	5.95	6.19
Month 6	Tofacitinib 5 mg BID	279	5.56	8.49
	Tofacitinib 10 mg BID	280	4.58	5.89
	Placebo → 5 mg BID	73	6.97	8.93
	Placebo → 10 mg BID	72	6.10	8.22
Month 9	Tofacitinib 5 mg BID	267	4.56	6.36
	Tofacitinib 10 mg BID	264	3.27	4.60
	Placebo → 5 mg BID	72	4.78	5.30
	Placebo → 10 mg BID	70	3.94	6.88
Month 12	Tofacitinib 5 mg BID	258	4.02	6.08
	Tofacitinib 10 mg BID	250	3.01	4.06
	Placebo → 5 mg BID	70	4.16	5.10
	Placebo → 10 mg BID	67	3.45	5.57

BID = twice daily, N = number of subjects, SD = standard deviation.

SF-36 (Version 2, Acute): Score improvements for subjects who received tofacitinib 10 mg were numerically greater than for those who received tofacitinib 5 mg. Subjects in both tofacitinib treatment sequences had increases (improvements) from Baseline in each of the

SF-36 domain scores at Month 1; the increases continued or remained stable through Month 12. An initial increase from Baseline in each of the SF-36 domain scores was noted for subjects in the placebo → tofacitinib treatment sequences at Month 1; after Month 3 (ie, after nonresponders advanced to tofacitinib) and Month 6 (ie, after remaining placebo subjects were advanced to tofacitinib), there was a continued increase. At Month 12, all treatment sequences showed similar changes in SF-36 domain scores (Table 24).

Increases (improvements) from Baseline were noted in each of the tofacitinib sequences and in the placebo → tofacitinib 10 mg sequence for the SF-36 mental component at Month 1 through Month 12. Increases (improvements) were also noted in the SF-36 physical component scores in each of the treatment sequences from Month 1 through Month 12, with larger increases in the tofacitinib treatment sequences compared with the placebo → tofacitinib sequences from Month 1 through Month 3. At Month 12, all treatment sequences showed a similar change in SF-36 component scores.

Table 24 36-Item Short-Form Health Survey (SF-36) Score per Visit, Comparisons to Placebo

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Baseline: physical functioning (N=312, 315, 158)	32.53±9.58	31.74±9.62	32.76±9.59
Baseline: role physical (N=312, 315, 158)	33.73±9.74	33.15±9.43	33.91±9.57
Baseline: social functioning (N=312, 315, 158)	36.22±11.15	37.04±10.27	36.87±11.63
Baseline: bodily pain (N=312, 315, 158)	33.38±7.25	33.94±7.28	34.22±7.47
Baseline: mental health (N=312, 315, 158)	39.94±12.52	41.05±10.54	41.50±11.38
Baseline: role emotional (N=312, 315, 158)	35.51±13.65	34.91±13.00	35.36±12.97
Baseline: vitality (N=312, 315, 158)	40.84±10.29	40.87±8.89	41.33±9.37
Baseline: general health (N=312, 315, 158)	33.95±9.14	34.27±8.58	34.65±8.32
Baseline: mental component (N=312, 315, 158)	40.86±12.59	41.56±11.14	41.67±11.57
Baseline: physical component (N=312, 315, 158)	32.44±7.82	32.02±7.46	32.74±7.60
Month 1: physical functioning (N=303, 302, 154)	36.17±10.33	36.71±10.08	33.95±9.72
Month 1: role physical (N=303, 301, 154)	38.20±10.33	39.00±9.60	37.15±9.41
Month 1: social functioning (N=303, 302, 154)	40.25±10.99	41.96±9.73	39.29±9.92
Month 1: bodily pain (N=303, 302, 154)	39.02±7.86	40.70±7.69	36.87±7.14
Month 1: mental health (N=303, 302, 153)	43.40±11.43	44.70±10.00	42.79±11.04
Month 1: role emotional (N=303, 301, 154)	38.36±12.79	39.27±11.91	38.18±12.97
Month 1: vitality (N=303, 302, 153)	45.87±10.17	46.71±8.76	43.74±9.00
Month 1: general health (N=303, 302, 154)	37.86±9.45	38.81±8.65	36.39±8.35
Month 1: mental component (N=303, 301, 153)	44.04±11.64	45.32±10.13	43.80±11.22
Month 1: physical component (N=303, 301, 153)	37.12±8.31	37.94±7.96	34.86±7.48
Month 3: physical functioning (N=294, 291, 147)	37.15±10.47	38.29±10.60	34.35±10.42
Month 3: role physical (N=294, 292, 147)	39.25±9.91	40.57±9.69	36.50±9.76
Month 3: social functioning (N=294, 292, 147)	41.51±10.46	42.44±9.92	38.62±11.04

Table 24 36-Item Short-Form Health Survey (SF-36) Score per Visit, Comparisons to Placebo

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Month 3: bodily pain (N=294, 292, 147)	40.22±8.24	41.82±8.70	37.50±8.26
Month 3: mental health (N=294, 292, 147)	44.69±10.45	45.15±10.28	42.68±10.88
Month 3: role emotional (N=293, 291, 146)	38.36±11.98	39.81±12.04	37.42±13.23
Month 3: vitality (N=294, 292, 147)	47.05±9.71	47.22±9.05	43.84±9.68
Month 3: general health (N=294, 291, 147)	38.98±9.69	39.45±9.19	35.56±9.37
Month 3: mental component (N=293, 290, 146)	44.96±10.75	45.35±10.26	43.10±11.12
Month 3: physical component (N=293, 290, 146)	38.26±8.46	39.53±8.58	34.90±8.37
Month 6: physical functioning (N=279, 280, 68)	38.55±10.60	39.42±10.38	38.18±9.63
Month 6: role physical (N=279, 279, 68)	39.86±9.82	41.02±9.41	40.27±8.86
Month 6: social functioning (N=279, 280, 68)	41.97±10.22	43.36±10.01	43.67±9.96
Month 6: bodily pain (N=279, 280, 68)	41.01±8.17	42.12±8.45	41.91±7.74
Month 6: mental health (N=279, 280, 68)	44.43±10.26	45.01±10.27	44.12±10.13
Month 6: role emotional (N=279, 279, 68)	39.37±12.11	40.49±11.79	39.81±12.38
Month 6: vitality (N=279, 280, 68)	47.02±9.82	47.80±9.55	46.67±8.93
Month 6: general health (N=279, 280, 68)	40.03±9.51	39.71±9.17	38.10±9.05
Month 6: mental component (N=279, 279, 68)	44.73±10.59	45.63±10.29	45.13±11.02
Month 6: physical component (N=279, 279, 68)	39.49±8.64	40.24±8.43	39.24±7.19

BID = twice daily, N = number of subjects.

Increases (improvements) from Baseline were noted in each of the tofacitinib sequences and in the placebo → tofacitinib 10 mg sequence for the SF-36 mental component at Month 1 through Month 12. Increases (improvements) were also noted in the SF-36 physical component scores in each of the treatment sequences from Month 1 through Month 12, with larger increases in the tofacitinib treatment sequences compared with the placebo → tofacitinib sequences from Month 1 through Month 3. At Month 12, all treatment sequences showed a similar change in SF-36 component scores (Table 25).

Table 25. 36-Item Short-Form Health Survey (SF-36) at Month 9 and 12, Comparisons Within Sequence

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo →Tofacitinib 5 mg BID	Placebo →Tofacitinib 10 mg BID
	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Month 9: physical functioning (N=267, 263, 72, 70)	39.40±10.60	40.67±10.12	38.86±10.47	40.83±9.76
Month 9 :role physical (N=267, 263, 72, 70)	40.21±9.99	42.03±9.05	41.44±9.70	42.99±9.18
Month 9: social functioning (N=267, 264, 72, 70)	42.43±9.97	43.67±9.60	43.26±11.23	44.11±10.32
Month 9: bodily pain (N=267, 264, 72, 70)	41.83±8.89	43.37±8.45	42.31±8.42	44.03±8.26
Month 9: mental health (N=267, 264, 72, 70)	45.49±10.69	46.03±10.67	46.12±10.49	45.11±10.51
Month 9: role emotional (N=267, 264, 72, 70)	40.55±11.54	42.16±11.43	40.75±12.67	41.02±11.46
Month 9: vitality (N=267, 264, 72, 70)	48.39±9.53	48.70±9.41	48.38±8.71	47.29±10.43
Month 9: general health (N=266, 264, 72, 70)	39.77±9.63	40.57±9.29	40.38±9.04	40.08±9.50
Month 9: mental component (N=266, 262, 72, 70)	45.97±10.45	46.61±10.74	46.42±11.01	45.22±11.40
Month 9: physical component (N=266, 262, 72, 70)	39.79±8.60	41.15±8.15	40.07±7.97	42.05±6.93
Month 12: physical functioning (N=258, 250, 70, 67)	39.07±11.18	40.38±10.24	38.61±11.38	39.85±10.97
Month 12: role physical (N=258, 250, 70, 67)	40.51±9.99	42.11±9.31	42.51±9.72	43.16±9.51
Month 12: social functioning (N=258, 250, 70, 67)	42.69±10.14	43.63±9.71	44.27±9.72	44.36±10.30
Month 12: bodily pain (N=258, 250, 70, 67)	41.95±8.77	43.28±8.70	42.59±9.07	45.49±8.11
Month 12: mental health (N=258, 250, 70, 67)	44.86±10.63	45.52±10.27	46.10±10.81	45.65±11.29
Month 12: role emotional (N=258, 250, 70, 67)	40.02±12.10	41.37±11.79	42.92±11.80	42.40±11.92
Month 12: vitality (N=258, 250, 70, 67)	48.08±9.83	48.12±9.22	49.77±9.52	47.75±10.45
Month 12: general health (N=258, 250, 70, 67)	39.63±9.64	39.88±8.88	40.86±9.34	39.43±10.35
Month 12: mental component (N=258, 250, 70, 67)	45.39±10.69	45.92±10.65	47.84±11.04	46.33±11.21
Month 12: physical component (N=258, 250, 70, 67)	39.94±8.83	41.13±8.13	40.16±9.14	41.62±8.16

BID = twice daily, N = number of subjects.

MOS Sleep Scale (MOS-SS): Treatment with tofacitinib 10 mg resulted in statistically significant improvements from Baseline compared with placebo at Month 3 in the sleep problems, overall sleep problems, somnolence, sleep disturbance, and adequacy subscales; the Sleep Problems Index II (9-item scale) was used for this analysis. In the tofacitinib

treatment sequences, improvement was most marked at Month 3 and scores generally remained stable through Month 12; the Sleep Problems Index II (9-item scale) was used for this analysis (Table 26 and Table 27).

Table 26. Medical Outcomes Study Sleep Scale (MOS-SS) at Baseline, Month 1, 3 and 6, Comparisons to Placebo

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Baseline: sleep scale score (N=312, 313, 158)	41.05±20.68	40.89±18.47	39.75±18.25
Baseline: sleep problem index (N=312, 314, 158)	39.51±21.22	40.08±19.02	37.87±18.37
Baseline: somnolence (N=312, 314, 158)	34.38±21.95	36.09±21.59	34.94±17.94
Baseline: snoring (N=310, 314, 157)	32.26±30.31	31.27±31.27	33.76±32.09
Baseline: quantity (N=312, 313, 158)	6.88±2.13	6.72±1.55	6.82±1.51
Baseline: sleep disturbance (N=312, 313, 158)	44.39±26.68	41.58±24.61	41.20±25.42
Baseline: awaken short of breath (N=312, 314, 158)	18.91±24.38	19.81±24.38	17.34±21.78
Baseline: adequacy (N=312, 314, 158)	47.56±28.78	44.97±26.89	46.84±25.69
Month 1: overall sleep problem (N=301, 301, 154)	36.51±19.94	34.77±17.79	37.09±18.02
Month 1: sleep problem summary (N=301, 301, 154)	35.87±20.50	34.45±17.94	35.95±18.32
Month 1: somnolence (N=301, 302, 154)	31.58±21.01	30.49±20.05	33.33±19.02
Month 1: snoring (N=300, 302, 153)	29.87±29.33	28.74±30.29	32.03±29.68
Month 1: quantity (N=301, 301, 154)	6.90±1.54	7.02±1.55	6.81±1.54
Month 1: sleep disturbance (N=301, 302, 154)	38.43±26.01	34.64±24.20	37.42±24.86
Month 1: awaken short of breath (N=301, 301, 154)	18.34±23.41	17.21±21.91	14.94±20.01
Month 1: adequacy (N=301, 302, 154)	52.92±27.91	51.52±26.23	49.16±23.51
Month 3: overall sleep problem (N=292, 292, 146)	35.10±18.58	34.06±17.33	38.66±17.32
Month 3: sleep problem summary (N=292, 292, 146)	34.41±19.04	33.80±17.65	37.97±17.21
Month 3: somnolence (N=292, 292, 146)	30.07±19.89	28.90±18.75	35.43±20.29
Month 3: snoring (N=290, 292, 144)	31.31±29.56	31.78±30.23	31.81±29.77
Month 3: quantity (N=293, 292, 147)	6.87±1.54	6.96±1.46	6.76±1.55
Month 3: sleep disturbance (N=292, 292, 146)	36.67±23.98	33.69±23.01	37.77±24.18
Month 3: awaken short of breath (N=292, 292, 146)	19.38±24.67	17.26±21.19	18.08±21.57

Table 26. Medical Outcomes Study Sleep Scale (MOS-SS) at Baseline, Month 1, 3 and 6, Comparisons to Placebo

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Month 3: adequacy (N=292, 292, 146)	54.66±27.42	51.58±26.71	45.82±25.54
Month 6: overall sleep problem (N=277, 280, 68)	33.92±19.36	33.11±16.94	34.87±18.29
Month 6: sleep problem summary (N=277, 280, 68)	33.26±19.87	33.30±17.17	34.85±18.81
Month 6: somnolence (N=277, 280, 68)	31.12±20.03	29.81±18.23	30.29±19.19
Month 6: snoring (N=271, 280, 68)	31.14±28.98	32.07±29.21	31.47±29.79
Month 6: quantity (N=278, 279, 68)	6.86±1.52	6.94±1.42	6.82±1.41
Month 6: sleep disturbance (N=277, 280, 68)	34.48±24.11	31.33±21.96	34.78±24.36
Month 6: awaken short of breath (N=277, 280, 68)	17.62±19.89	17.57±20.87	17.06±24.98
Month 6: adequacy (N=277, 280, 68)	54.40±28.34	51.64±26.36	50.29±26.76

Sleep Scale Score is an index measure that assesses sleep disturbance constructed from 9 items on the MOS.
BID = twice daily, N = number of subjects.

Table 27. Medical Outcome Study (MOS) Sleep Scale at Month 12: Comparisons Within Sequence

	Tofacitinib 5 mg BID Mean ± Standard Deviation	Tofacitinib 10 mg BID Mean ± Standard Deviation	Placebo →Tofacitinib 5 mg BID Mean ± Standard Deviation	Placebo →Tofacitinib 10 mg BID Mean ± Standard Deviation
Overall sleep problem (N=256, 249, 70, 66)	34.17±18.71	32.24±17.13	31.74±17.41	33.58±17.44
Sleep problem summary (N=256, 249, 70, 66)	33.71±19.11	32.58±17.42	30.95±17.09	32.53±17.89
Somnolence (N=256, 249, 70, 66)	29.30±19.09	27.93±17.70	30.86±21.18	28.48±15.45
Snoring (N=252, 249, 70, 65)	30.32±28.59	32.37±29.70	31.43±31.13	31.38±27.58
Quantity (N=258, 247, 69, 66)	6.94±1.51	7.04±1.30	6.83±1.36	6.95±1.42
Sleep disturbance (N=257, 249, 70, 66)	34.78±24.31	31.75±21.95	29.41±24.04	35.63±22.81
Awaken short of breath (N=256, 249, 70, 66)	19.77±24.38	17.19±21.25	17.71±19.42	14.85±17.30
Adequacy (N=256, 249, 70, 66)	54.38±26.14	53.29±25.26	55.00±25.01	55.76±26.37

BID = twice daily, N = number of subjects.

All 4 treatment sequences had small LS mean changes from Baseline in the MOS-SS Sleep Quantity subscale at Month 3 and Month 6; there were no statistically significant differences between tofacitinib and placebo at these timepoints. The changes from Baseline were not statistically significant for any of the 4 treatment sequences at any of the timepoints with the exception of the tofacitinib 10 mg sequence at Month 1 (p=0.0025) and Month 2 (p=0.0030). The proportions of subjects in each treatment sequence achieving optimal sleep were stable from Month 1 to Month 6 (Table 28 and Table 29).

Table 28. Number of Subjects With Optimal Sleep Assessed Using Medical Outcomes Study Sleep Scale (MOS-SS) at Baseline, Month 1, 3 and 6: Comparisons to Placebo

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Baseline (N=312, 315, 158)	139	139	70
Month 1 (N=305, 303, 155)	155	145	72
Month 3 (N=294, 292, 147)	139	152	65
Month 6 (N=278, 280, 145)	142	143	66

BID = twice daily, N = number of subjects.

Table 29. Number of Subjects With Optimal Sleep Assessed Using Medical Outcomes Study Sleep Scale (MOS-SS) at Month 12: Comparisons Within Sequence

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo →Tofacitinib 5 mg BID	Placebo →Tofacitinib 10 mg BID
Number of Subjects Analyzed	258	250	70	67
Subjects With Optimal Sleep	134	144	37	36

BID = twice daily.

FACIT Fatigue Scale: Subjects who received tofacitinib 5 mg and tofacitinib 10 mg showed statistically significant improvements from Baseline in the FACIT Fatigue Scale at Month 3 and Month 6 compared with placebo. The changes from Baseline for subjects who received tofacitinib 10 mg were numerically greater than for those who received tofacitinib 5 mg at Month 3 and Month 6.

All 4 treatment sequences had greater changes from Baseline at Month 6 compared with Month 3 except for tofacitinib 10 mg which had little change; changes from Baseline were numerically greater in the tofacitinib 10 mg treatment sequence compared with the tofacitinib 5 mg sequence. After Month 3 (ie, after nonresponders advanced to tofacitinib), subjects in the placebo → tofacitinib treatment sequences had increases in FACIT Fatigue Scale scores (Table 30).

Table 30. Descriptive Statistics of FACIT - Fatigue Scale per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	312	29.01	11.10
	Tofacitinib 10 mg BID	314	28.65	9.49
	Placebo → 5 mg BID	79	28.47	9.15
	Placebo → 10 mg BID	79	30.98	8.66
Month 1	Tofacitinib 5 mg BID	301	33.16	10.75
	Tofacitinib 10 mg BID	302	33.94	8.91
	Placebo → 5 mg BID	76	30.86	9.95
	Placebo → 10 mg BID	77	32.69	9.17
Month 3	Tofacitinib 5 mg BID	294	34.38	10.07
	Tofacitinib 10 mg BID	292	34.99	9.20
	Placebo → 5 mg BID	73	31.38	9.83
	Placebo → 10 mg BID	74	31.43	10.13
Month 6	Tofacitinib 5 mg BID	277	35.14	9.91
	Tofacitinib 10 mg BID	280	35.01	9.45
	Placebo → 5 mg BID	73	34.68	10.07
	Placebo → 10 mg BID	71	35.03	9.35
Month 12	Tofacitinib 5 mg BID	258	35.02	9.83
	Tofacitinib 10 mg BID	249	36.34	9.15
	Placebo → 5 mg BID	70	36.93	9.19
	Placebo → 10 mg BID	67	36.07	9.64

BID = twice daily, FACIT = functional assessment of chronic illness therapy, N = number of subjects, SD = standard deviation.

EuroQoL EQ-5D: Tofacitinib treatment (5 and 10 mg) resulted in statistically significant improvements in the utility score compared with placebo; changes were numerically greater for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg.

The tofacitinib treatment sequences had numerically greater improvements from Baseline at Month 3 compared with placebo; the increases were maintained through Month 12 for the tofacitinib treatment sequences. Utility score increases in the tofacitinib 10 mg sequence were slightly greater than the increases in the tofacitinib 5 mg sequence. The mean changes from Baseline for the tofacitinib treatment sequences were statistically significant compared with placebo at Months 3 and 6. A smaller mean increase was noted in the EuroQoL EQ-5D health state profile for the placebo → tofacitinib treatment sequences by Month 3 compared with the tofacitinib treatment sequences. After Months 3 and 6 (ie, after placebo subjects advanced to tofacitinib) the placebo → tofacitinib treatment sequences had a mean increase in EuroQoL EQ-5D health state profile scores (Table 31).

Table 31. Descriptive Statistics of EuroQol EQ-5D Health State Profile-Utility Score per Visit, Comparisons Within Sequence

Visit	Treatment	N	Mean	SD
Baseline	Tofacitinib 5 mg BID	311	0.46	0.31
	Tofacitinib 10 mg BID	314	0.48	0.29
	Placebo → 5 mg BID	79	0.47	0.28
	Placebo → 10 mg BID	79	0.55	0.25
Month 3	Tofacitinib 5 mg BID	294	0.63	0.24
	Tofacitinib 10 mg BID	291	0.68	0.24
	Placebo → 5 mg BID	73	0.56	0.27
	Placebo → 10 mg BID	74	0.56	0.3
Month 6	Tofacitinib 5 mg BID	277	0.66	0.23
	Tofacitinib 10 mg BID	280	0.70	0.21
	Placebo → 5 mg BID	73	0.63	0.26
	Placebo → 10 mg BID	71	0.68	0.21
Month 12	Tofacitinib 5 mg BID	258	0.68	0.23
	Tofacitinib 10 mg BID	249	0.70	0.21
	Placebo → 5 mg BID	70	0.66	0.24
	Placebo → 10 mg BID	67	0.69	0.23

BID = twice daily, EQ-5D = a self-report questionnaire (a quality of life instrument) developed by the European Quality of Life (EuroQoL) Group, N = number of subjects, SD = standard deviation.

Work Limitations Questionnaire: There were no statistically significant differences between treatment with tofacitinib and placebo at Month 3 or Month 6 for any of the subscales of the Work Limitations Questionnaire except for the Physical Demands Scale (Month 3 tofacitinib 5 mg and 10 mg, p=0.0089 and p=0.0246, respectively). There were, however, statistically significant improvements over time within the tofacitinib 5 mg and tofacitinib 10 mg sequences at Months 3, 6, and 12 for the Time Management Scale, Mental/Interpersonal Demands Scale, Output Demands Scale and, Work Loss Index (Table 32 and Table 33).

Table 32. Work Limitations Questionnaire (WLQ) Score at Baseline, Month 3 and 6: Comparisons to Placebo

	Tofacitinib 5 mg BID Mean ± Standard Deviation	Tofacitinib 10 mg BID Mean ± Standard Deviation	Placebo Mean ± Standard Deviation
Baseline: time management (N=152, 149, 80)	47.13±27.40	46.05±27.83	39.98±24.44
Baseline: physical demands (N=154, 154, 86)	48.08±25.92	50.83±25.34	51.88±24.98
Baseline: mental demands (N=158, 154, 83)	36.58±26.35	35.86±25.72	30.31±24.19
Baseline: output demands (N=153, 149, 79)	41.93±27.66	38.76±28.34	32.72±25.35
Baseline: work loss index (N=164, 163, 90)	11.25±6.04	10.76±6.16	9.22±5.28
Month 3: time management (N=139, 131, 69)	38.56±30.11	37.39±30.53	36.99±28.24
Month 3: physical demands (N=135, 132, 66)	43.14±26.03	45.07±30.63	52.78±24.73
Month 3: mental demands (N=142, 136, 72)	30.43±27.99	31.60±29.49	28.15±23.69
Month 3: output demands (N=136, 132, 68)	32.23±27.77	33.43±30.58	27.33±24.32
Month 3: work loss index (N=145, 138, 73)	9.29±6.32	9.64±7.10	8.77±5.47
Month 6: time management (N=112, 108, 27)	34.43±28.40	35.73±31.85	33.77±31.88
Month 6: physical demands (N=114, 110, 24)	48.72±29.30	41.75±30.91	48.13±32.45
Month 6: mental demands (N=115, 112, 27)	25.94±26.35	27.98±28.18	22.34±26.57
Month 6: output demands (N=111, 111, 26)	28.92±26.55	28.98±28.12	29.52±29.09
Month 6: work loss index (N=116, 114, 28)	8.73±6.26	8.71±6.64	8.03±6.64

BID = twice daily, N = number of subjects.

Table 33. Work Limitations Questionnaire (WLQ) Score at Month 12: Comparisons Within Sequence

	Tofacitinib 5 mg BID Mean ± Standard Deviation	Tofacitinib 10 mg BID Mean ± Standard Deviation	Placebo →Tofacitinib 5 mg BID Mean ± Standard Deviation	Placebo →Tofacitinib 10 mg BID Mean ± Standard Deviation
Time management (N=105, 98, 35, 31)	37.01±30.03	35.29±31.80	30.82±29.59	36.57±30.80
Physical demands (N=105, 97, 36, 28)	44.15±27.91	42.41±31.59	47.15±30.40	40.82±30.86
Mental demands (N=108, 100, 36, 32)	27.27±26.33	27.42±27.56	20.70±26.37	33.05±29.78
Output demands (N=105, 95, 35, 29)	26.75±25.54	25.67±27.25	22.54±25.05	28.43±27.66
Work loss index (N=108, 101, 38, 32)	8.65±6.12	8.28±6.59	7.06±5.81	8.89±6.29

BID = twice daily, N = number of subjects.

Rate of advancement at Month 3: Seventy subjects were not reassigned to tofacitinib 5 mg BID group and 57 subjects were not reassigned to tofacitinib 10 mg BID group after Month 6 or Month 3. Seventy seven subjects were reassigned to Placebo group after Month 3.

Rate of erroneous advancement at Month 3: Eighty subjects in tofacitinib 5 mg BID group, 58 subjects in tofacitinib 10 mg BID group, 38 subjects in placebo → tofacitinib 5 mg BID group and 40 subjects in placebo → tofacitinib 10 mg BID group were found advanced according to Impala data and no java transaction services data were found in oracle clinical.

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 34

Table 34. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term in > 5% of Subjects

Number (%) of Subjects with Adverse Events by: System Organ Class and Preferred Term	Tofacitinib 5 mg BID n (%)	n1	n2	Tofacitinib 10 mg BID n (%)	n1	n2	Placebo n (%)	n1	n2
Evaluable for adverse events	315			318			159		
With adverse events	117 (37.1)			122 (38.4)			63 (39.6)		
Gastrointestinal disorders	33 (10.5)	45	34	23 (7.2)	30	16	13 (8.2)	15	10
Diarrhoea	19 (6.0)	23	17	13 (4.1)	14	7	9 (5.7)	9	7
Nausea	17 (5.4)	22	17	12 (3.8)	16	9	6 (3.8)	6	3
Infections and infestations	68 (21.6)	99	51	74 (23.3)	115	60	40 (25.2)	53	27
Bronchitis	12 (3.8)	12	6	11 (3.5)	14	9	9 (5.7)	12	7
Nasopharyngitis	22 (7.0)	28	9	18 (5.7)	23	8	13 (8.2)	14	5
Upper respiratory tract infection	36 (11.4)	49	32	41 (12.9)	59	36	17 (10.7)	17	11
Urinary tract infection	9 (2.9)	10	4	17 (5.3)	19	7	9 (5.7)	10	4
Investigations	16 (5.1)	19	15	30 (9.4)	36	29	8 (5.0)	9	6
Alanine aminotransferase increased	7 (2.2)	8	7	17 (5.3)	17	14	4 (2.5)	5	4
Blood creatine phosphokinase increased	10 (3.2)	11	8	17 (5.3)	19	15	4 (2.5)	4	2
Nervous system disorders	13 (4.1)	17	11	19 (6.0)	28	19	11 (6.9)	12	4
Headache	13 (4.1)	17	11	19 (6.0)	28	19	11 (6.9)	12	4
Respiratory, thoracic and mediastinal disorders	4 (1.3)	6	1	8 (2.5)	8	4	9 (5.7)	9	2
Cough	4 (1.3)	6	1	8 (2.5)	8	4	9 (5.7)	9	2

Except for 'n1' and 'n2' Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v13.1) coding dictionary applied.
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.
BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; v = version.

Treatment-emergent SAEs (all causalities and treatment-related) by SOC and preferred term in either treatment group are summarized in Table 35.

Table 35. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by: System Organ Class and Preferred Term	Tofacitinib 5 mg BID n (%)	n1	n2	Tofacitinib 10 mg BID n (%)	n1	n2	Placebo n (%)	n1	n2
Number (%) of Subjects:									
Evaluable for adverse events	315			318			159		
With adverse events	20 (6.3)			23 (7.2)			8 (5.0)		
Blood and lymphatic system disorders	0	0	0	1 (0.3)	1	0	0	0	0
Thrombocytopenia	0	0	0	1 (0.3)	1	0	0	0	0
Cardiac disorders	2 (0.6)	2	0	2 (0.6)	2	0	0	0	0
Angina pectoris	1 (0.3)	1	0	0	0	0	0	0	0
Atrial fibrillation	0	0	0	1 (0.3)	1	0	0	0	0
Bradycardia	1 (0.3)	1	0	0	0	0	0	0	0
Cardiac failure acute	0	0	0	1 (0.3)	1	0	0	0	0
Gastrointestinal disorders	4 (1.3)	4	0	2 (0.6)	2	1	0	0	0
Colitis	1 (0.3)	1	0	0	0	0	0	0	0
Constipation	0	0	0	1 (0.3)	1	0	0	0	0
Duodenal ulcer haemorrhage	1 (0.3)	1	0	0	0	0	0	0	0
Pancreatitis	1 (0.3)	1	0	0	0	0	0	0	0
Peritonitis	0	0	0	1 (0.3)	1	1	0	0	0
Salivary gland calculus	1 (0.3)	1	0	0	0	0	0	0	0
General disorders and administration site conditions	2 (0.6)	2	0	1 (0.3)	1	0	1 (0.6)	1	0
Chest pain	2 (0.6)	2	0	1 (0.3)	1	0	1 (0.6)	1	0
Hepatobiliary disorders	3 (1.0)	4	1	1 (0.3)	1	0	1 (0.6)	1	0
Bile duct stone	1 (0.3)	1	0	0	0	0	0	0	0
Biliary colic	1 (0.3)	1	0	0	0	0	0	0	0
Biliary dyskinesia	0	0	0	0	0	0	1 (0.6)	1	0
Cholecystitis	2 (0.6)	2	1	0	0	0	0	0	0
Cholelithiasis	0	0	0	1 (0.3)	1	0	0	0	0
Infections and infestations	2 (0.6)	2	2	6 (1.9)	7	6	0	0	0
Bronchiectasis	0	0	0	1 (0.3)	1	1	0	0	0
Bronchitis	1 (0.3)	1	1	0	0	0	0	0	0
Diabetic foot infection	0	0	0	1 (0.3)	1	1	0	0	0
Herpes zoster disseminated	1 (0.3)	1	1	0	0	0	0	0	0
Pneumonia	0	0	0	2 (0.6)	2	1	0	0	0
Pneumonia cryptococcal	0	0	0	1 (0.3)	1	1	0	0	0
Pulmonary tuberculosis	0	0	0	2 (0.6)	2	2	0	0	0

Table 35. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by: System Organ Class and Preferred Term	Tofacitinib 5 mg BID n (%)	n1	n2	Tofacitinib 10 mg BID n (%)	n1	n2	Placebo n (%)	n1	n2
Injury, poisoning and procedural complications	3 (1.0)	3	0	3 (0.9)	3	0	1 (0.6)	1	0
Femur fracture	1 (0.3)	1	0	0	0	0	0	0	0
Foot fracture	0	0	0	1 (0.3)	1	0	0	0	0
Joint dislocation	1 (0.3)	1	0	0	0	0	0	0	0
Muscle injury	1 (0.3)	1	0	0	0	0	0	0	0
Tendon injury	0	0	0	0	0	0	1 (0.6)	1	0
Tendon rupture	0	0	0	2 (0.6)	2	0	0	0	0
Metabolism and nutrition disorders	0	0	0	2 (0.6)	2	0	0	0	0
Hypoglycaemia	0	0	0	1 (0.3)	1	0	0	0	0
Type 2 diabetes mellitus	0	0	0	1 (0.3)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	5 (1.6)	5	0	1 (0.3)	2	0	3 (1.9)	3	0
Arthralgia	1 (0.3)	1	0	0	0	0	0	0	0
Fistula	0	0	0	1 (0.3)	1	0	0	0	0
Foot deformity	0	0	0	1 (0.3)	1	0	0	0	0
Fracture nonunion	1 (0.3)	1	0	0	0	0	0	0	0
Osteoarthritis	1 (0.3)	1	0	0	0	0	1 (0.6)	1	0
Rheumatoid arthritis	2 (0.6)	2	0	0	0	0	2 (1.3)	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	3 (0.9)	3	1	0	0	0
Breast cancer	0	0	0	1 (0.3)	1	1	0	0	0
Metastasis	0	0	0	1 (0.3)	1	0	0	0	0
Thyroid adenoma	0	0	0	1 (0.3)	1	0	0	0	0
Nervous system disorders	2 (0.6)	2	0	2 (0.6)	2	0	1 (0.6)	1	0
Amnesia	0	0	0	1 (0.3)	1	0	0	0	0
Cerebrovascular accident	1 (0.3)	1	0	0	0	0	0	0	0
Epilepsy	0	0	0	0	0	0	1 (0.6)	1	0
Syncope	0	0	0	1 (0.3)	1	0	0	0	0
Transient ischaemic attack	1 (0.3)	1	0	0	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	0	0	1 (0.6)	1	0
Menorrhagia	0	0	0	0	0	0	1 (0.6)	1	0
Respiratory, thoracic and mediastinal disorders	2 (0.6)	2	0	1 (0.3)	2	2	0	0	0
Asthma	1 (0.3)	1	0	0	0	0	0	0	0
Pulmonary embolism	1 (0.3)	1	0	0	0	0	0	0	0

Table 35. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by: System Organ Class and Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Placebo		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Pulmonary hypertension	0	0	0	1 (0.3)	1	1	0	0	0
Respiratory failure	0	0	0	1 (0.3)	1	1	0	0	0
Skin and subcutaneous tissue disorders	1 (0.3)	1	0	0	0	0	0	0	0
Angioedema	1 (0.3)	1	0	0	0	0	0	0	0
Vascular disorders	1 (0.3)	1	0	1 (0.3)	1	0	0	0	0
Hypotension	1 (0.3)	1	0	0	0	0	0	0	0
Peripheral vascular disorder	0	0	0	1 (0.3)	1	0	0	0	0

Except for 'n1' and 'n2' Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v13.1) coding dictionary applied.
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.
BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; v = version.

Tofacitinib was generally well-tolerated. A total of 4 subjects died; 2 of the deaths occurred while the subjects were still in the study and 2 occurred after the subject had already been withdrawn (Table 36).

Table 36. Death Summary

Number (%) of Subjects with Adverse Events by: System Organ Class and Preferred Term	Number of Subjects with Fatal Adverse Events[a] Tofacitinib 5 mg BID n	n1	Tofacitinib 10 mg BID n	n1
Number (%) of Subjects:				
Evaluable for adverse events	315		318	
Cardiac disorders	1	0	1	0
Cardiac failure acute	0	0	1	0
Cardiopulmonary failure	1	0	0	0
Infections and infestations	0	0	1	1
Infection	0	0	1	1
Injury, poisoning and procedural complications	1	0	0	0
Craniocerebral injury	1	0	0	0
Total Number of Fatalities from Adverse Events[b]	2		2	
Total Number of Deaths all causes	2		2	

A subject death was associated with more than one treatment if the first onset date of the case falls within multiple treatment group periods.
A fatality was associated with multiple events.
n: The number of adverse events associated with a fatality.
n1: The number of adverse events associated with a fatality and thought to be associated or related to treatment.
MedDRA (v17.0) coding dictionary applied.
BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Total number of deaths in this reporting group thought to be causally related to adverse events.
b. Total number of deaths (all causes) in this reporting group. This includes deaths not related to the trial.

The most common TEAEs (all causalities) by Medical Dictionary for Regulatory Activities system organ class (MedDRA SOC) up to Month 3, overall, were gastrointestinal disorders, infections and infestations, and musculoskeletal and connective tissue disorders. The most commonly experienced AEs by preferred term for the tofacitinib 5 mg dose were upper respiratory tract infection, nasopharyngitis, and diarrhea. The most commonly experienced AEs by preferred term for the tofacitinib 10 mg dose were upper respiratory tract infection and headache and diarrhea. The most commonly experienced AEs by preferred term for placebo were nasopharyngitis, upper respiratory tract infection, and diarrhea, RA, and headache.

Upper respiratory tract infection and hypertension occurred more frequently in the tofacitinib groups compared with placebo, whereas RA (exacerbation) occurred more frequently in the placebo group. The frequency of alanine aminotransferase increased was similar across treatment groups. Of the 54 subjects who discontinued the study due to AEs, 34 discontinued due to AEs considered related to study drug (14 during treatment with tofacitinib 5 mg and 20 during treatment with tofacitinib 10 mg) (Table 37)

Table 37 Discontinuations Due to Treatment-Emergent Adverse Events

System Organ Class	MedDRA Preferred Term	Treatment Phase	Severity/ Outcome	Causality
Tofacitinib 5 mg BID				
Investigations	International normalized ratio increased	Active	Mild/resolved	Study drug
	Transaminases increased	Active	Mild/resolved	Study drug
Infections and infestations	Herpes zoster disseminated[a]	Active	Severe/resolved	Study drug
Skin and subcutaneous tissue disorders	Angioedema[a]	Active	Severe/resolved	Concomitant treatment - lisinopril
Hepatobiliary disorders	Cholecystitis[a]	Active	Severe/resolved	Other illness-cholelithiasis
Nervous system disorders	Tremor	Active	Moderate/resolved	Other illness-intention tremors
Skin and subcutaneous tissue disorders	Drug eruption	Active	Mild/resolved	Study drug
Infections and infestations	Paronychia	Active	Severe/resolved	Study drug
Skin and subcutaneous tissue disorders	Decubitus ulcer	Active	Mild/still present	Concomitant treatment-left hip replacement revision
Gastrointestinal disorders	Diarrhoea	Active	Mild/still present	Study drug
Infections and infestations	Upper respiratory tract infection	Active	Mild/resolved	Study drug
Infections and infestations	Bronchitis[a]	Active	Moderate/still present	Study drug
Ear and labyrinth disorders	Vertigo	Active	Moderate/resolved	Study drug
Tofacitinib 5 mg BID				
Investigations	Alanine aminotransferase increased	Active	Severe/resolved	Study drug
	Aspartate aminotransferase	Active	Severe/resolved	Study drug
Investigations	Neutrophil count decreased	Active	Moderated/resolved	Study drug
	Platelet count decreased	Active	Moderated/resolved	Study drug
	White blood cell count decreased	Active	Moderated/resolved	Study drug
Investigations	Neutrophil count decreased	Active	Moderated/resolved	Study drug
	White blood cell count decreased	Active	Moderated/resolved	Study drug
Skin and subcutaneous tissue disorders	Dermatitis allergic	Active	Moderated/resolved	Study drug
Hepatobiliary disorders	Cholecystitis[a]	Active	Severe/Resolved	Study drug
Infections and infestations	Nasopharyngitis	Active	Mild/still present	Other illness- viral illness
Musculoskeletal and connective tissue disorders	Rheumatoid arthritis[a]	Active	Severe/still present	Other- the reason of rheumatoid arthritis worsening is unknown
Skin and subcutaneous tissue disorders	Rash	Active	Mild/resolved	Study drug

Table 37 Discontinuations Due to Treatment-Emergent Adverse Events

System Organ Class	MedDRA Preferred Term	Treatment Phase	Severity/ Outcome	Causality
Tofacitinib 10 mg BID				
Gastrointestinal disorders	Peritonitis[a]	Active	Severe/resolved	Study drug
Investigations	Gamma-glutamyltransferase increased	Active	Moderate/resolved	Study drug
Investigations	White blood cell count decreased	Active	Mild/still present	Background study drug-PI deemed methotrexate most likely caused a/e
Infections and infestations	Pneumonia[a]	Active	Moderate/resolved	Other illness-unknown cause
Investigations	Blood creatinine increased	Active	Moderate/resolved	Other illness-history of elevated creatine, worsening from Baseline
Infections and infestations	Aspergilloma	Active	Mild/still present	Study drug
Infections and infestations	Pneumonia[a]	Active	Severe/resolved	Study drug
Infections and infestations	Pneumonia cryptococcal[a]	Active	Severe/still present	Study drug
Gastrointestinal disorders	Epigastric discomfort	Active	Moderate/still present	Other illness-cholecystitis and gall stones
	Nausea	Active	Severe/still present	Other illness-cholecystitis and gall stones
	Vomiting	Active	Severe/resolved	Other illness-cholecystitis and gall stones
General disorders and administrations site conditions	Oedema	Active	Mild/still present	Study drug
Renal and urinary disorders	Dysuria	Active	Mild/still present	Study drug
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Active	Mild/still present	Other-unknown
Reproductive system and breast disorders	Amenorrhoea	Active	Moderate/resolved	Study drug
Investigations	Blood creatinine increased	Active	Mild/still present	Study drug
Nervous system disorders	Syncope[a]	Active	Severe/resolved	Other illness-orthostatic induced vasovagal syncope
Infections and infestations	Diabetic foot infection[a]	Active	Severe/resolved	Study drug
Gastrointestinal disorders	Constipation	Active	Mild/resolved	Study drug
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer[a]	Active	Moderate/still present	Study drug
Infections and infestations	Herpes zoster	Active	Moderate/still present	Study drug

Table 37 Discontinuations Due to Treatment-Emergent Adverse Events

System Organ Class	MedDRA Preferred Term	Treatment Phase	Severity/ Outcome	Causality
Investigations	Blood creatine phosphokinase increased	Active	Mild/resolved	Study drug
Investigations	White blood cell count decreased	Active	Mild/resolved	Study drug
Musculoskeletal and connective tissue disorders	Lupus-like syndrome	Active	Moderate/still present	Disease under study
Infections and infestations	Pulmonary tuberculosis[a]	Active	Severe/still present	Study drug
Infections and infestations	Sinusitis	Active	Moderate/resolved	Study drug
Infections and infestations	Bronchopneumonia	Active	Mild/resolved	Study drug
Musculoskeletal and connective tissue disorders	Synovitis	Active	Moderate/still present	Disease under study
Blood and lymphatic system disorders	Thrombocytopenia[a]	Active	Severe/resolved	Concomitant treatment-rifampicin, pyrazinamide induced thrombocytopenia
Infections and infestations	Pulmonary tuberculosis[a]	Active	Severe/still present	Study drug
Investigations	Alanine aminotransferase increased	Active	Severe/still present	Background study drug-diclofenac and methotrexate intake
	Alanine aminotransferase increased	Active	Severe/resolved	Background study drug-diclofenaci and methotrexate intake
	Gamma-glutamyltransferase increased	Active	Severe/still present	Background study drug-diclofenaci and methotrexate intake
Cardiac disorders	Tachyarrhythmia	Active	Moderate/still present	Other illness-anemia caused by neoplasm
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastasis[a]	Active	Severe/still present	Other-unknown
Investigations	Blood creatinine increased	Active	Moderate/resolved	Study drug
Ear and labyrinth disorders	Vertigo	Active	Moderate/resolved	Study drug
Gastrointestinal disorders	Diarrhoea	Active	Severe/resolved	Study drug
	Nausea	Active	Severe/resolved	Study drug
	Vomiting	Active	Severe/resolved	Study drug
Placebo				
Musculoskeletal and connective tissue disorders	Rheumatoid arthritis	Active	Moderate/still present	Disease under study

Table 37 Discontinuations Due to Treatment-Emergent Adverse Events

System Organ Class	MedDRA Preferred Term	Treatment Phase	Severity/ Outcome	Causality
Musculoskeletal and connective tissue disorders	Rheumatoid arthritis[a]	Active	Moderate/resolved	Disease under study
Injury, poisoning and procedural complications	Medication error	Active	Mild/resolved	Other–the subject took the wrong dose
Placebo Tofacitinib →10 mg BID				
Infections and Infestations	Genital Herpes	Active	Moderate/resolved	Other illness–herpes virus
Investigations	Blood creatinine increased	Active	Moderate/still present	Other illness–renal insufficiency

MedDRA (v13.1) coding dictionary applied. All events were treatment-emergent. Values in brackets were imputed from incomplete dates and time.
a. Serious adverse event, according to Investigator assessment.
BID = twice a day, MedDRA = Medical Dictionary for Regulatory Activities, v = version.

CONCLUSIONS:

- Treatment with tofacitinib (5 and 10 mg BID) was efficacious compared with placebo in reducing the signs and symptoms of RA in subjects with RA as measured by the co-primary endpoint, ACR20 response rate at Month 6 and demonstrated statistically significant differences from placebo as early as Week 2.

- Treatment with tofacitinib (5 and 10 mg BID) was efficacious compared with placebo in improving the physical function status of subjects with RA as measured by the co-primary endpoint, HAQ-DI response rate at Month 3, and demonstrated statistically significant differences from placebo as early as Week 2.

- The proportion of subjects treated with tofacitinib 5 mg BID or 10 mg BID achieving DAS28-4(ESR) <2.6 was greater than placebo at Month 6 and demonstrated statistically significant differences from placebo as early as Week 2.

- Subjects who received placebo for 3 to 6 months and then advanced to tofacitinib treatment (5 mg or 10 mg BID) showed improvement after advancement in all efficacy measures (ACR20, ACR50, ACR70, HAQ-DI, DAS28-3[CRP], and DAS28-4[ESR]).

- Treatment with tofacitinib (5 and 10 mg BID) was efficacious compared with placebo in improving secondary endpoints of signs and symptoms of RA in subjects with RA (DAS28-4[ESR] and DAS28-3[CRP]) through Month 6.

- In general, treatment with tofacitinib (5 or 10 mg BID) resulted in modest improvements compared with placebo through Month 6 in self-reported measures of sleep (MOS-SS) and statistically significant improvement in every domain of the SF-36.

- Subjects treated with tofacitinib 10 mg BID generally showed numerically greater ACR20/50/70 response rates, and improvements from Baseline in DAS28 and HAQ-DI, compared with those treated with tofacitinib 5 mg BID.

- Improvements in subjects treated with tofacitinib (5 or 10 mg BID) was consistent across all components of ACR assessments (joint counts, Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, CRP, and HAQ-DI scores).

- Efficacy responses were sustained in the tofacitinib 5 and 10 mg BID sequences through Month 12.

- Efficacy responses were consistent across treatment sequences.

- The most frequently reported AEs were those coding to the MedDRA SOC of infections and infestations and gastrointestinal disorders, and the frequencies were similar among treatments.

- There were more discontinuations due to AEs in the tofacitinib 5 mg and 10 mg groups compared with the placebo subjects.

- A total of 4 subjects died (2 each in the tofacitinib 5 and 10 mg BID groups); 2 of the deaths occurred while the subjects were still in the study and 2 occurred after the subject had already been withdrawn.

- The frequency of SAEs, including serious infections, was similar to the frequency observed in previous studies in RA subjects.

- Changes in mean laboratory parameters were observed for tofacitinib 5 mg and 10 mg relative to placebo, including small decreases in neutrophil counts, small increases in creatinine levels, and increases in high density lipoprotein, low density lipoprotein, and total cholesterol levels.

- In comparison to placebo, subjects treated with tofacitinib 5 mg showed an increase in mean hemoglobin levels; subjects treated with tofacitinib 10 mg exhibited mean hemoglobin levels similar to placebo.

- Creatine kinase (CK) elevations were reported as AEs and increases in CK values >3 x upper limit of normal occurred more frequently with tofacitinib 5 mg and 10 mg; the clinical significance of these elevations is unknown.

- Subjects treated with tofacitinib 5 and 10 mg showed increases in mean weight from Baseline and placebo-treated subjects also showed increases in mean weight after advancement to tofacitinib therapy; the clinical significance of these results is unknown.

- Changes in systolic and diastolic BP were small and variable across treatment groups with no clear dose-response relationship.

- The proportion of subjects meeting the seventh report of the joint national committee on prevention detection, evaluation, and treatment of high blood pressure (JNC7) criteria for Stage 1 or 2 hypertension remained relatively stable throughout the 12 months of therapy with no consistent change across dose groups.

- The safety profile was consistent across treatment sequences.

- The safety profile of tofacitinib 5 mg and 10 mg was similar to that seen in previous Phase 2 studies and the completed Phase 3 study (A3921045) of tofacitinib in subjects with active RA; no new safety signals were observed.