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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Xeljanz® / Jakvinus® / Tofacitinib (CP-690, 550)

PROTOCOL NO.: A3921045

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

Study Centers: A total of 94 centers participated in the study and randomized subjects: 7 in Brazil, 5 in Bulgaria, 3 in Chile, 2 each in Colombia, Poland, and the Russian Federation, 9 in the Czech Republic, 1 in the Dominican Republic, 6 in Germany, 10 in India, 4 each in Malaysia, Mexico, and the Philippines, 5 in the Ukraine, and 30 in the United States (US).

Study Initiation and Final Completion Dates: 09 February 2009 to 23 June 2010

Phase of Development: Phase 3

Study Objectives:

Primary Objectives:

- To compare the efficacy of tofacitinib monotherapy 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 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) 20 response rates at Month 3. (ACR20 = calculated ≥20% improvement in tender and swollen joint counts, and a ≥20% improvement in 3 of the 5 remaining ACR core set measures).

- To compare physical function status of subjects with active RA after administration of tofacitinib monotherapy in doses of 5 mg BID and 10 mg BID vs placebo, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) response at Month 3.

- To compare the rate of achieving Disease Activity Score (DAS)28-4 Erythrocyte Sedimentation Rate (ESR) <2.6 at Month 3, in subjects with active RA after administration of tofacitinib monotherapy in doses of 5 mg BID and 10 mg BID vs placebo.

- To compare the safety of 2 doses of tofacitinib monotherapy vs placebo monotherapy in subjects with RA.

Secondary Objectives:

- To compare the incidence of DAS 28 remission and low disease activity state at each visit.

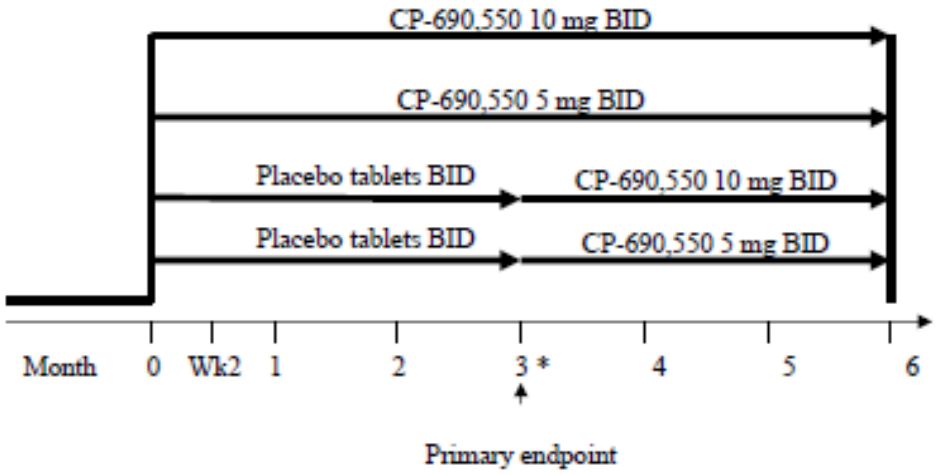
- To compare effects on all health outcome measures in the study at each visit, as appropriate for the specific outcome, compared to Baseline.

METHODS

Study Design: This was a Phase 3, double-blind, randomized, placebo-controlled, parallel-group, 6 month, multicenter study to evaluate efficacy and safety of tofacitinib in subjects with RA.

Eligible subjects were randomized (4:4:1:1 ratio) to receive 1 of the 4 parallel treatment sequences (Figure 1). The duration of study treatment was 24 weeks.

Figure 1. Schematic Study Design



All subjects randomized to treatment sequences 3 or 4 were advanced (→), at Month 3, to the second predetermined (ie, by the drug allocation system), double-blind treatment for the remainder of the 6 month study (Figure 1), because subjects were not receiving background treatment with methotrexate.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Activity		Screening[a]	Visits							
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
			Baseline Day 0	2 Weeks	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month or ET
Informed consent		X								
RA diagnosis, family and medical history[b]		X								
Concomitant medications		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	
Vital signs, temperature		X	X	X	X	X	X	X	X	X
QuantiFERON-Gold®™ or PPD/radiograph of chest		X								
12-lead electrocardiogram		X								X
Blood/Urine	Hematology[d], urinalysis	X	X		X	X	X	X	X	X
	Lipid profile (fasting)[e]		X		X		X			X
	Chemistry 1[f]	X	X							X
	Chemistry 2[g]				X	X	X	X	X	
	Urine pregnancy test (HCG)[h]	X	X	X	X	X	X	X	X	X
	HIV, HBsAg, HCV Ab	X								
	Rheumatoid factor/anti CCP antibodies		X							X
	Stool examination for parasites (Brazil only)	X								
	Molecular profiling[i]		X	X	X		X			X
ACR/DAS	C-Reactive protein (CRP)	X	X	X	X	X	X	X	X	X
	Erythrocyte sedimentation rate (ESR)[j]	X	X				X			X
	Tender/painful joint count, swollen joint count	X	X	X	X	X	X	X	X	X
	Subject assessment of arthritis pain		X	X	X	X	X	X	X	X
	Subject global assessment of arthritis		X	X	X	X	X	X	X	X
	Physician global assessment of arthritis		X	X	X	X	X	X	X	X
	Health assessment questionnaire – disability index		X	X	X	X	X	X	X	X
PRO scales[k]			X				X			X
Randomization			X							
2 week IVRS diary instruction (United States only)[l]			X							
Drug dispensing			X				X			
Drug accountability				X	X	X	X	X	X	X
Adverse event reporting			X	X	X	X	X	X	X	X
Review entry criteria for A3921024/A3921029									X	X

Table 1. Schedule of Activities

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CCP = cyclic citrullinated peptide; ESR = erythrocyte sedimentation rate; EQ-5D = A self-report questionnaire (a quality of life instrument) developed by the European quality of life (EuroQoL) group; ET = Early termination; EuroQoL = European quality of life; FACIT = functional assessment of chronic illness therapy; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropic; HCV Ab = hepatitis C virus antibody; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; IVRS = Interactive Voice Response System; LDL = low-density lipoprotein; MOS = medical outcomes study; PPD = purified protein derivative; PRO = patient reported outcome; RA = rheumatoid arthritis; RBC = red blood cell; SF-36 = short form-36 (questionnaire); WBC = white blood cell.

a. Screening Visit occurs within 1 month (+10 days), prior to the Baseline Visit.
b. Medical history included smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD).
c. Targeted physical exam consist of weight, examination of heart, lungs, abdomen and lymph nodes.
d. Hematology included CBC (RBC count, WBC with differential, hemoglobin, hematocrit and platelet count).
e. Lipid profile included fasting total cholesterol, LDL, HDL, and triglycerides. Additional lipoprotein tests, potentially including apolipoprotein A1, apolipoprotein B and particle size measurements were performed at Baseline, Month 3 and Month 6/Early termination.
f. Chemistry 1 (full serum chemistry) included blood urea nitrogen (BUN) & creatinine, glucose (fasting), calcium++, sodium+, potassium+, chloride, total carbon dioxide, AST, ALT, total bilirubin, alkaline phosphatase, albumin, gamma glutamyl transferase and creatine kinase.
g. Chemistry 2 included serum hepatic function testing (AST/ALT/total bilirubin/gamma glutamyl transferase /Alkaline phosphatase/albumin), and serum creatinine and creatine kinase.
h. Urinary pregnancy testing (HCG) was required only for women who were of childbearing potential; may be repeated more frequently if required by local practices, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected.
i. Molecular profiling (pharmacogenomic) research component was optional and conducted only at participating sites.
j. All ESR tests performed after screening must be done at a local lab that had the capability of reporting directly to the central lab, keeping the results blinded from the site personnel. If ESR cannot be performed in a blinded manner, the site should not perform ESR after screening.
k. SF-36 (Version 2, Acute), MOS-Sleep, FACIT-Fatigue Scale, EuroQol EQ-5D, Work Limitations Questionnaire, and RA Healthcare Resource Utilization Questionnaire.
l. Subjects in US were reported daily via IVRS for 2 weeks both the subject's assessment of arthritis pain and the subject's global assessment of arthritis.

Number of Subjects (Planned and Analyzed): In total, 500 subjects were planned to be enrolled in this study (200 each in Sequences 1 and 2, and 50 each in Sequences 3 and 4). A total of 611 subjects were randomized to treatment, and 610 received at least 1 dose of study medication; 83 in Brazil, 30 in Bulgaria, 10 in Chile, 28 in Colombia, 72 in the Czech Republic, 10 in the Dominican Republic, 30 in Germany, 49 in India, 17 in Malaysia, 35 in Mexico, 20 in the Philippines, 15 in Poland, 7 in the Russian Federation, 53 in the Ukraine, and 151 in the US.

Diagnosis and Main Criteria for Inclusion: Male and female subjects, ≥18 years of age, with a diagnosis of RA as per ACR, active RA at the time of the study (based on tender and/or swollen joint counts), with inadequate response to ≥1 DMARD (traditional or biologic) due to lack of efficacy or toxicity, with either ESR >28 mm as per local laboratory or CRP >7 mg/L as per central laboratory, no evidence of active, latent, or history of inadequately treated infection with *Mycobacterium tuberculosis*.

For DMARDs other than antimalarial medications, biologic response modifiers, and other concomitant medications, requirements were specified for washout periods and discontinuation prior to study entry.

Study Treatment: Tofacitinib was provided as 5 mg tablets with matching placebo. Subjects randomized to tofacitinib 10 mg were taking 2 active tablets BID, while subjects randomized to tofacitinib 5 mg took 1 active and 1 placebo tablet BID, and subjects randomized to placebo took 2 placebo tablets BID.

Subjects were randomized to 1 of the following 4 treatment sequences:

- Treatment Sequence 1 = tofacitinib 5 mg BID.
- Treatment Sequence 2 = tofacitinib 10 mg BID.
- Treatment Sequence 3 = placebo BID → tofacitinib 5 mg BID.
- Treatment Sequence 4 = placebo BID → tofacitinib 10 mg BID.

Study drug was allowed to be taken with or without food, other than on study visit days where fasting was required.

Efficacy Endpoints:

Primary Efficacy Endpoints:

- ACR20 responder rate vs placebo at the Month 3 visit.
- Change from Baseline in the HAQ-DI at the Month 3 visit.
- Rate of subjects achieving a DAS28-4 (ESR) <2.6 vs placebo at the Month 3 visit.

Secondary Efficacy Endpoints:

Signs and Symptoms:

- ACR20 responder rates analyzed at all timepoints other than Month 3.
- ACR50 and ACR70 responder rates (ie, ≥50% or ≥70% improvement, respectively) at all timepoints.
- DAS 28 at all timepoints.

Physical Function and Patient Reported Outcomes, assessed at all timepoints:

- HAQ-DI.
- Subject Assessment of Arthritis Pain.
- Subject Global Assessment of Arthritis.
- Physician Global Assessment of Arthritis.

Physical Function and Patient Reported Outcomes, assessed at Months 1, 3, and 6 or Early Termination:

- Short Form-36 (SF-36) (Version 2, Acute).
- Medical Outcome Study Sleep Scale (MOS-SS).
- Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue Scale.
- Self-report questionnaire (quality of life instrument) developed by the European Quality of Life (EuroQoL) Group (EQ-5D).
- RA Healthcare Resource Utilization (HCRU) Questionnaire.
- Work Limitations Questionnaire (WLQ).

Safety Evaluations: Safety was assessed as adverse events (AEs), physical examinations, vital signs, 12-lead electrocardiogram, and clinical laboratory values (hematology, biochemistry, and urinalysis).

Statistical Methods: The following analysis populations were defined for this study:

- The full analysis set (FAS) included all subjects who were randomized to the study and received at least 1 dose of the randomized study drug (tofacitinib) or placebo. The primary analysis population for this study was defined by the FAS.

- The Per Protocol analysis set included all FAS subjects who had no protocol deviation thought to affect the efficacy analysis.

- The safety analysis set included all subjects who received at least 1 dose of the study drug (tofacitinib or placebo).

The proposed sequence of primary endpoints was signs and symptoms as measured by ACR20 response rate at Month 3, physical function as measured by the mean change from Baseline in HAQ-DI at Month 3, and the rate of subjects achieving DAS28-4(ESR) <2.6 at Month 3. The normal approximation for the difference in binomial proportions was used to test the superiority of each dose of tofacitinib to placebo with respect to rates of subjects achieving ACR20 and DAS28-4(ESR) <2.6.

The ACR50 and ACR70 response variables, as well as all ACR20 responses for other time points, were analyzed in a similar manner as described for the ACR20 in the primary analysis. An analysis that used last observation carried forward (LOCF) rather than nonresponder imputation (NRI) was also performed to support the robustness of the results.

The HAQ-DI was expressed as a change from Baseline. The analysis was done using a mixed-effect repeated-measure model that included the fixed effects of treatment, visit (Week 2, Month 1, Month 2, and Month 3), treatment by visit interaction, baseline value, and geographic region. Subjects were a random effect and compound symmetry was assumed.

Additional analyses of the HAQ-DI included a responder analysis, where subjects with a change of 0.22, 0.3, or 0.5 were considered responders and an analysis where subjects who dropped from the study were considered nonresponsive (NRI approach). The normal approximation for the difference in binomial proportions was used to test the superiority of each dose of tofacitinib to placebo with respect to HAQ-DI response rates.

Number of days to the first ">1 day consecutive sequential decrease in pain" was analyzed using a Kaplan-Meier approach for each of the Subject Assessment of Arthritis Pain and Subject Global Assessment of Arthritis endpoints for study centers in the US only. Results were tabulated and displayed graphically.

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

- Incidence and severity of AEs.

- Serious infections and treated infections (serious infections were defined as any infection [viral, bacterial, or fungal] requiring hospitalization or parenteral antimicrobials).

- Incidence and severity of clinical laboratory abnormalities.

- Summary of changes in physical examination compared to Baseline.

- Mean change from Baseline in vital signs (blood pressure, heart rate, and oral, temporal or tympanic temperature preferred) measurements.

RESULTS

Subject Disposition and Demography: The subject disposition and analysis sets are summarized in Table 2. A total of 954 subjects were screened, 611 subjects were randomized, 610 subjects received at least 1 dose of study drug, and 555 (91.0%) subjects completed the study. The tofacitinib 5 mg sequence had the highest rate of completion (95.1%), and the placebo → tofacitinib 10 mg sequence had the highest rate of subjects who discontinued (16.4%). A total of 17 (2.8%) subjects withdrew due to AEs (12 subjects due to AEs considered related to study drug by the Investigator, and 5 subjects due to AEs not considered related by the Investigator). One subject (on tofacitinib 10 mg) died due to cardiac arrest and hyperkalemia.

Table 2. Subject Disposition

Number (%) of Subjects	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo → Tofacitinib 5 mg BID	Placebo → Tofacitinib 10 mg BID
Screened: 954				
Assigned to study treatment	244	245	61	61
Treated	243[a]	245	61	61
Completed	232 (95.1)	218 (89.0)	54 (88.5)	51 (83.6)
Discontinued	11 (4.5)	27 (11.0)	7 (11.5)	10 (16.4)
Subject died	0	1 (0.4)[b]	0	0
Related to study drug	4 (1.6)	7 (2.9)	5 (8.2)	5 (8.2)
Adverse event	3 (1.2)	6 (2.4)	2 (3.3)	1 (1.6)
Lack of efficacy	1 (0.4)	1 (0.4)	3 (4.9)	4 (6.6)
Not related to study drug	7 (2.9)	19 (7.8)	2 (3.3)	5 (8.2)
Adverse event	0	3 (1.2)	1 (1.6)	1 (1.6)
Other	3 (1.2)	10 (4.1)	1 (1.6)	2 (3.3)
Subject no longer willing to participate in study	4 (1.6)	6 (2.4)	0	2 (3.3)
Analyzed for efficacy:				
Full analysis Set	241 (98.8)	243 (99.2)	61 (100.0)	61 (100.0)
Per protocol analysis Set	205 (84.0)	201 (82.0)	50 (82.0)	45 (73.8)
Analyzed for safety:				
Adverse events	243 (99.6)	245 (100.0)	61 (100.0)	61 (100.0)
Laboratory data	243 (99.6)	245 (100.0)	60 (98.4)[c]	61 (100.0)

BID = twice daily.
a. This subject was randomized but not treated; the subject was no longer willing to participate in the study.
b. This subject was not included as discontinued due to an adverse event.
c. One subject had no postbaseline laboratory data and, therefore, was not included in the analysis of laboratory data.

The demographic characteristics of the treatment sequences were similar to one another and to the overall study population (Table 3). The majority of the treated subjects were female (528/610, 86.6%) and white (409/610, 67.0%). The mean age of all subjects was 51.8 years (range 21 to 81 years) and the mean weight was 72.1 kg (range 30.5 to 157.0 kg). The mean time from diagnosis of RA to enrollment in the study ranged from 7.3 to 8.6 years across the 4 treatment sequences; the overall duration of RA since diagnosis for all subjects ranged from 0.2 to 49.0 years.

Table 3. Demographic Characteristics

	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Placebo → Tofacitinib 5 mg BID			Placebo → Tofacitinib 10 mg BID			Total		
	M N=36	F N=207	Total N=243	M N=29	F N=216	Total N=245	M N=7	F N=54	Total N=61	M N=10	F N=51	Total N=61	M N=82	F N=528	Total N=610
Age (years), n (%)															
18-44	7 (19.4)	48 (23.2)	55 (22.6)	3 (10.3)	60 (27.8)	63 (25.7)	2 (28.6)	16 (29.6)	18 (29.5)	4 (40.0)	16 (31.4)	20 (32.8)	16 (19.5)	140 (26.5)	156 (25.6)
45-64	21 (58.3)	136 (65.7)	157 (64.6)	23 (79.3)	119 (55.1)	142 (58.0)	5 (71.4)	30 (55.6)	35 (57.4)	5 (50.0)	31 (60.8)	36 (59.0)	54 (65.9)	316 (59.8)	370 (60.7)
≥65	8 (22.2)	23 (11.1)	31 (12.8)	3 (10.3)	37 (17.1)	40 (16.3)	0	8 (14.8)	8 (13.1)	1 (10.0)	4 (7.8)	5 (8.2)	12 (14.6)	72 (13.6)	84 (13.8)
Mean (SD)	54.4 (12.9)	51.9 (11.3)	52.2 (11.5)	54.3 (8.4)	52.1 (12.0)	52.4 (11.7)	47.9 (9.3)	51.1 (13.2)	50.7 (12.8)	46.3 (13.4)	49.3 (11.7)	48.8 (11.9)	52.8 (11.5)	51.6 (11.8)	51.8 (11.8)
Range	22-76	21-81	21-81	34-70	22-78	22-78	37-62	24-77	24-77	24-65	25-75	24-75	22-76	21-81	21-81
Race, n (%)															
White	28 (77.8)	125 (60.4)	153 (63.0)	20 (69.0)	148 (68.5)	168 (68.6)	3 (42.9)	43 (79.6)	46 (75.4)	7 (70.0)	35 (68.6)	42 (68.9)	58 (70.7)	351 (66.5)	409 (67.0)
Black	2 (5.6)	10 (4.8)	12 (4.9)	3 (10.3)	7 (3.2)	10 (4.1)	2 (28.6)	1 (1.9)	3 (4.9)	1 (10.0)	2 (3.9)	3 (4.9)	8 (9.8)	20 (3.8)	28 (4.6)
Asian	1 (2.8)	40 (19.3)	41 (16.9)	3 (10.3)	29 (13.4)	32 (13.1)	1 (14.3)	6 (11.1)	7 (11.5)	1 (10.0)	7 (13.7)	8 (13.1)	6 (7.3)	82 (15.5)	88 (14.4)
Other	5 (13.9)	32 (15.5)	37 (15.2)	3 (10.3)	32 (14.8)	35 (14.3)	1 (14.3)	4 (7.4)	5 (8.2)	1 (10.0)	7 (13.7)	8 (13.1)	10 (12.2)	75 (14.2)	85 (13.9)
Weight (kg)															
Mean (SD)	89.8 (20.0)	69.2 (18.7)	72.2 (20.2)	81.4 (17.4)	70.3 (19.6)	71.6 (19.6)	67.8 (15.9)	70.0 (15.1)	69.8 (15.1)	85.6 (23.2)	73.2 (20.9)	75.3 (21.6)	84.4 (19.9)	70.1 (18.9)	72.1 (19.7)
Range	55.0-157.0	38.4-135.2	38.4-157.0	40.0-130.0	32.4-142.6	32.4-142.6	46.2-92.0	45.0-112.0	45.0-112.0	39.0-121.6	30.5-117.0	30.5-121.6	39.0-157.0	30.5-142.6	30.5-157.0
Body mass index (kg/m^2)															
Mean (SD)	28.8 (6.2)	26.9 (6.6)	27.2 (6.5)	27.0 (4.9)	27.6 (7.0)	27.5 (6.8)	22.7 (4.3)	27.5 (5.6)	26.9 (5.7)	27.9 (7.1)	28.7 (7.6)	28.6 (7.5)	27.5 (5.9)	27.4 (6.8)	27.4 (6.6)
Range	19.0-52.8	16.3-52.8	16.3-52.8	18.5-40.0	14.4-55.6	14.4-55.6	17.0-29.0	17.4-41.1	17.0-41.1	15.4-37.6	14.6-45.9	14.6-45.9	15.4-52.8	14.4-55.6	14.4-55.6
Height (cm)															
Mean (SD)	176.5 (6.5)	160.1 (7.3)	162.5 (9.2)	173.0 (7.6)	159.4 (7.9)	161.0 (9.0)	172.5 (7.9)	159.6 (6.7)	161.1 (7.9)	174.4 (7.9)	159.3 (7.5)	161.8 (9.4)	174.6 (7.2)	159.7 (7.5)	161.7 (9.1)
Range	161.8-192.0	140.0-178.0	140.0-192.0	147.0-184.0	125.3-185.0	125.3-185.0	163.2-183.0	146.0-172.0	146.0-183.0	159.0-184.0	136.0-174.0	136.0-184.0	147.0-192.0	125.3-185.0	125.3-192.0

Body Mass Index computed as Weight/$(Height/100)^2$.
BID = twice daily; F = femal; M = male, N = number of subjects; n = number of subjects meeting prespecified criteria; SD = standard deviation.

Efficacy Results:

Primary Endpoint Results:

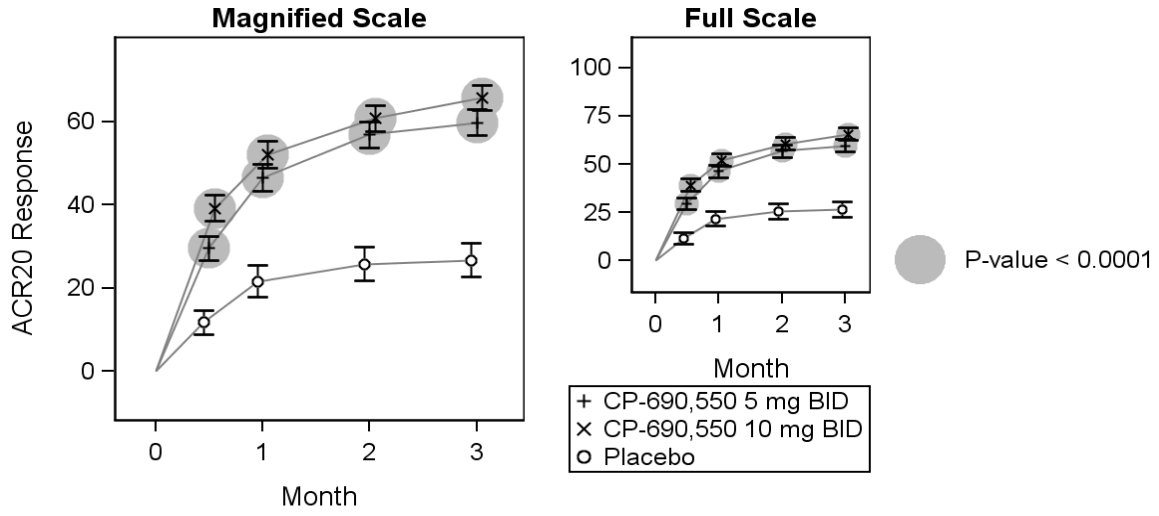
ACR20 Response Rates at Month 3: Both tofacitinib doses demonstrated statistically significant (p-value <0.0001 for both doses) and clinically meaningful reductions in signs and symptoms of RA over placebo as measured by the ACR20 at Month 3 (Table 4). Response rates for the tofacitinib 5 mg and 10 mg doses were superior to placebo at 2 weeks and throughout the study period (Figure 2).

Table 4. Normal Approximation to ACR20 Response Rates at Month 3 (FAS, NRI, Difference From Placebo)

Treatment	N	n	%	Difference From Placebo			
				Difference	95% CI for Difference		p-Value
					Lower	Upper	
Tofacitinib 5 mg BID	241	144	59.75	33.08	23.04	43.13	<0.0001
Tofacitinib 10 mg BID	242	159	65.70	39.04	29.12	48.95	<0.0001
Placebo	120	32	26.67				

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; N = number of subjects; n = number of subjects meeting prespecified criteria; NRI = nonresponder imputation.

Figure 2. ACR20 Response Rates (%) (±SE) Through Month 3 (FAS, NRI, Comparisons to Placebo)



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; NRI = nonresponder imputation; SE = standard error.

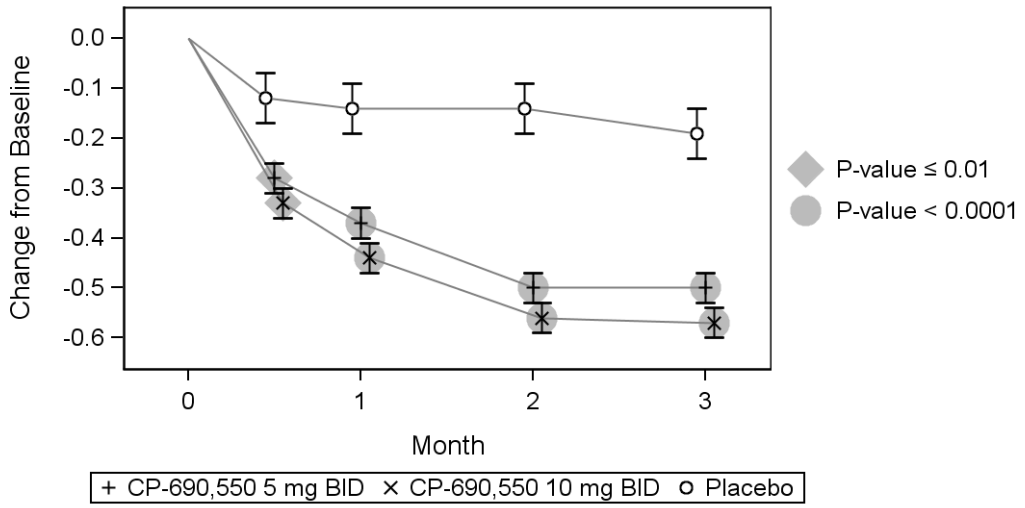
Changes From Baseline in HAQ-DI at Month 3: Both tofacitinib doses demonstrated statistically significant and clinically meaningful improvements in physical function over placebo as measured by the HAQ-DI at Month 3 (Table 5). Responses for the tofacitinib 5 mg and 10 mg doses were superior to placebo at 2 weeks and throughout the study period (Figure 3).

Table 5. Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Differences From Placebo)

Treatment	N	LS Mean	Differences From Placebo			
			Difference	95% CI for Difference		p-Value
				Lower	Upper	
Tofacitinib 5 mg BID	237	-0.50	-0.31	-0.43	-0.20	<0.0001
Tofacitinib 10 mg BID	227	-0.57	-0.38	-0.50	-0.27	<0.0001
Placebo	109	-0.19		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.

Figure 3. LS Mean Changes (±SE) From Baseline in HAQ-DI Through Month 3 (FAS, Comparisons to Placebo)



BID = twice daily; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-Disability Index; LS mean = least squares mean; SE = standard error.

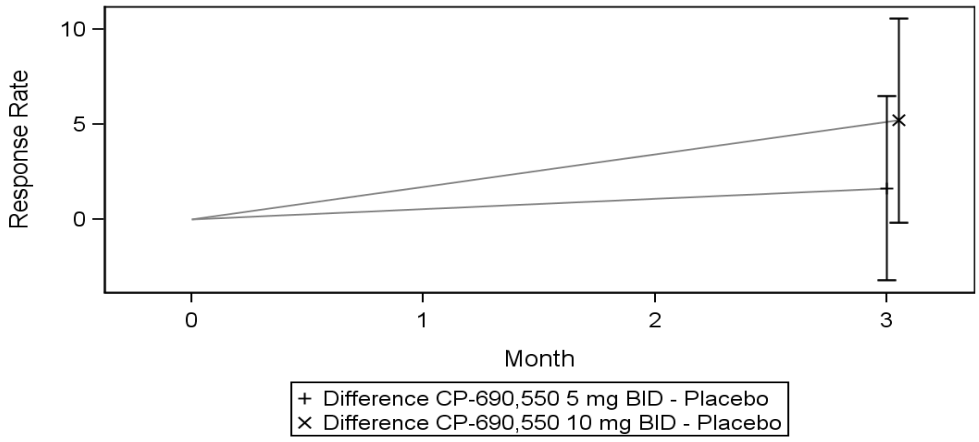
Rate of Subjects Achieving DAS28-4(ESR) <2.6 vs Placebo at Month 3: The rate of subjects achieving DAS28-4(ESR) <2.6 at Month 3 for tofacitinib 5 mg BID (14 [6.11%] subjects) was not statistically significantly different from placebo (p-value = 0.6193) Table 6, Figure 4.

Table 6. Summary of Subjects Achieving DAS28-4(ESR) <2.6 at Month 3 (FAS, No Imputation, Comparisons to Placebo)

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		p-Value
					Lower	Upper	
Tofacitinib 5 mg BID	229	14	6.11	1.31	-3.85	6.46	0.6193
Tofacitinib 10 mg BID	219	22	10.05	5.24	-0.49	10.96	0.0728
Placebo	104	5	4.81	Not applicable			

BID = twice daily; CI = confidence interval; DAS = disease activity score; ESR = erythrocyte sedimentation rate; FAS = full analysis set; N = number of subjects; n = number of subjects meeting prespecified criteria.

Figure 4. Differences From Placebo in Rates of Subjects Achieving DAS28-4(ESR) <2.6 Through Month 3 With 95% Confidence Intervals (FAS, NRI)



BID = twice daily; DAS = disease activity score; ESR = erythrocyte sedimentation rate; FAS = full analysis set; NRI = nonresponder imputation.

Secondary Endpoint Results:

ACR20 Response Rates at All Timepoints (Table 7): ACR20 response rates were higher for subjects in the tofacitinib 5 mg and 10 mg sequences at Month 3 compared with subjects in the placebo → tofacitinib 5 mg and placebo → tofacitinib 10 mg sequences at Month 3. By Month 6, response rates for subjects in the tofacitinib 5 mg and 10 mg sequences were 69.3% and 71.1%, respectively, compared with 58.3% and 56.7% for subjects in the placebo → tofacitinib 5 mg and placebo → tofacitinib 10 mg sequences, respectively. The tofacitinib 10 mg treatment sequence had higher response rates than the tofacitinib 5 mg treatment sequence. Subjects randomized to placebo showed clear improvements in ACR20 response rates after switching to tofacitinib treatment at Month 3.

Table 7. Normal Approximation to ACR 20 Response Rates Per Visit (FAS, NRI), Comparisons Within Sequence

		N	n	%	SE	Z Value	95% CI		p-Value
							Lower	Upper	
Week 2(NRI)	Tofacitinib 5 mg BID	240	71	29.58	2.95	10.04	23.81	35.36	<0.0001
	Tofacitinib 10 mg BID	240	94	39.17	3.15	12.43	32.99	45.34	<0.0001
	Placebo → 5 mg BID	59	8	13.56	4.46	3.04	4.82	22.30	0.0023
	Placebo → 10 mg BID	60	6	10.00	3.87	2.58	2.41	17.59	0.0098
Month 1(NRI)	Tofacitinib 5 mg BID	241	112	46.47	3.21	14.47	40.18	52.77	<0.0001
	Tofacitinib 10 mg BID	242	126	52.07	3.21	16.21	45.77	58.36	<0.0001
	Placebo → 5 mg BID	60	12	20.00	5.16	3.87	9.88	30.12	0.0001
	Placebo → 10 mg BID	60	14	23.33	5.46	4.27	12.63	34.04	<0.0001
Month 2(NRI)	Tofacitinib 5 mg BID	241	137	56.85	3.19	17.82	50.59	63.10	<0.0001
	Tofacitinib 10 mg BID	242	147	60.74	3.14	19.35	54.59	66.90	<0.0001
	Placebo → 5 mg BID	60	18	30.00	5.92	5.07	18.40	41.60	<0.0001
	Placebo → 10 mg BID	60	13	21.67	5.32	4.07	11.24	32.09	<0.0001
Month 4(NRI)	Tofacitinib 5 mg BID	241	167	69.29	2.97	23.32	63.47	75.12	<0.0001
	Tofacitinib 10 mg BID	242	167	69.01	2.97	23.21	63.18	74.83	<0.0001
	Placebo → 5 mg BID	60	31	51.67	6.45	8.01	39.02	64.31	<0.0001
	Placebo → 10 mg BID	60	37	61.67	6.28	9.82	49.36	73.97	<0.0001
Month 5(NRI)	Tofacitinib 5 mg BID	241	165	68.46	2.99	22.87	62.60	74.33	<0.0001
	Tofacitinib 10 mg BID	242	169	69.83	2.95	23.67	64.05	75.62	<0.0001
	Placebo → 5 mg BID	60	37	61.67	6.28	9.82	49.36	73.97	<0.0001
	Placebo → 10 mg BID	60	38	63.33	6.22	10.18	51.14	75.53	<0.0001
Month 6(NRI)	Tofacitinib 5 mg BID	241	167	69.29	2.97	23.32	63.47	75.12	<0.0001
	Tofacitinib 10 mg BID	242	172	71.07	2.91	24.39	65.36	76.79	<0.0001
	Placebo → 5 mg BID	60	35	58.33	6.36	9.17	45.86	70.81	<0.0001
	Placebo → 10 mg BID	60	34	56.67	6.40	8.86	44.13	69.21	<0.0001

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; N = number of subjects; n = number of subjects meeting prespecified criteria; NRI = nonresponder imputation; SE = standard error.

ACR50 Response Rates at All Timepoints: The differences for tofacitinib treatment from placebo in response rate were statistically significant (based on an unadjusted p-value) for tofacitinib at all timepoints beginning at Week 2 for the tofacitinib 10 mg dose, and were statistically significant beginning at Month 1 for the tofacitinib 5 mg dose (Table 8). The response rate was higher in the tofacitinib 10 mg dose than the tofacitinib 5 mg dose. Subjects randomized to placebo showed clear improvements in ACR50 response rates after switching to tofacitinib treatment at Month 3.

Table 8. Normal Approximation to ACR 50 Response Rates Per Visit (FAS, NRI), Comparisons Within Sequence

		N	n	%	SE	Z Value	95% CI		p-Value
							Lower	Upper	
Week 2(NRI)	Tofacitinib 5 mg BID	240	14	5.83	1.51	3.86	2.87	8.80	0.0001
	Tofacitinib 10 mg BID	240	31	12.92	2.16	5.97	8.67	17.16	<0.0001
	Placebo → 5 mg BID	59	3	5.08	2.86	1.78	-0.52	10.69	0.0754
	Placebo → 10 mg BID	60	2	3.33	2.32	1.44	-1.21	7.88	0.1503
Month 1(NRI)	Tofacitinib 5 mg BID	241	42	17.43	2.44	7.13	12.64	22.22	<0.0001
	Tofacitinib 10 mg BID	242	58	23.97	2.74	8.73	18.59	29.35	<0.0001
	Placebo → 5 mg BID	60	3	5.00	2.81	1.78	-0.51	10.51	0.0756
	Placebo → 10 mg BID	60	2	3.33	2.32	1.44	-1.21	7.88	0.1503
Month 2(NRI)	Tofacitinib 5 mg BID	241	63	26.14	2.83	9.24	20.59	31.69	<0.0001
	Tofacitinib 10 mg BID	242	82	33.88	3.04	11.14	27.92	39.85	<0.0001
	Placebo → 5 mg BID	60	5	8.33	3.57	2.34	1.34	15.33	0.0195
	Placebo → 10 mg BID	60	2	3.33	2.32	1.44	-1.21	7.88	0.1503
Month 3(NRI)	Tofacitinib 5 mg BID	241	75	31.12	2.98	10.43	25.27	36.97	<0.0001
	Tofacitinib 10 mg BID	242	89	36.78	3.10	11.86	30.70	42.85	<0.0001
	Placebo → 5 mg BID	60	9	15.00	4.61	3.25	5.96	24.04	0.0011
	Placebo → 10 mg BID	60	6	10.00	3.87	2.58	2.41	17.59	0.0098
Month 4(NRI)	Tofacitinib 5 mg BID	241	90	37.34	3.12	11.99	31.24	43.45	<0.0001
	Tofacitinib 10 mg BID	242	104	42.98	3.18	13.50	36.74	49.21	<0.0001
	Placebo → 5 mg BID	60	17	28.33	5.82	4.87	16.93	39.74	<0.0001
	Placebo → 10 mg BID	60	17	28.33	5.82	4.87	16.93	39.74	<0.0001
Month 5(NRI)	Tofacitinib 5 mg BID	241	95	39.42	3.15	12.52	33.25	45.59	<0.0001
	Tofacitinib 10 mg BID	242	110	45.45	3.20	14.20	39.18	51.73	<0.0001
	Placebo → 5 mg BID	60	22	36.67	6.22	5.89	24.47	48.86	<0.0001
	Placebo → 10 mg BID	60	21	35.00	6.16	5.68	22.93	47.07	<0.0001
Month 6(NRI)	Tofacitinib 5 mg BID	241	101	41.91	3.18	13.19	35.68	48.14	<0.0001
	Tofacitinib 10 mg BID	242	113	46.69	3.21	14.56	40.41	52.98	<0.0001
	Placebo → 5 mg BID	60	20	33.33	6.09	5.48	21.41	45.26	<0.0001
	Placebo → 10 mg BID	60	20	33.33	6.09	5.48	21.41	45.26	<0.0001

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; CI = confidence interval; FAS = full analysis set; N = number of subjects; n = number of subjects meeting prespecified criteria; NRI = nonresponder imputation; SE = standard error.

ACR70 Response Rates at All Timepoints: The percentage of subjects who achieved ACR70 by Month 3 for subjects treated with tofacitinib 10 mg and 5 mg was statistically significant compared with placebo (Table 9). The response rate was higher for subjects who received tofacitinib 10 mg than for those who received tofacitinib 5 mg. Response rates for the placebo → tofacitinib treatment sequences remained relatively low through Month 3; after Month 3 (ie, after advancing to tofacitinib), there was an increase.

Table 9. Normal Approximation to ACR 70 Response Rates Per Visit (FAS, NRI), Comparisons Within Sequence

		N	n	%	SE	Z Value	95% CI		p-Value
							Lower	Upper	
Week 2(NRI)	Tofacitinib 5 mg BID	240	5	2.08	0.92	2.26	0.28	3.89	0.0238
	Tofacitinib 10 mg BID	240	11	4.58	1.35	3.40	1.94	7.23	0.0007
	Placebo → 5 mg BID	59	0	0.00					
	Placebo → 10 mg BID	60	0	0.00					
Month 1(NRI)	Tofacitinib 5 mg BID	241	12	4.98	1.40	3.55	2.23	7.73	0.0004
	Tofacitinib 10 mg BID	242	22	9.09	1.85	4.92	5.47	12.71	<0.0001
	Placebo → 5 mg BID	60	1	1.67	1.65	1.01	-1.57	4.91	0.3132
	Placebo → 10 mg BID	60	1	1.67	1.65	1.01	-1.57	4.91	0.3132
Month 2(NRI)	Tofacitinib 5 mg BID	241	24	9.96	1.93	5.16	6.18	13.74	<0.0001
	Tofacitinib 10 mg BID	242	46	19.01	2.52	7.54	14.06	23.95	<0.0001
	Placebo → 5 mg BID	60	3	5.00	2.81	1.78	-0.51	10.51	0.0756
	Placebo → 10 mg BID	60	1	1.67	1.65	1.01	-1.57	4.91	0.3132
Month 3(NRI)	Tofacitinib 5 mg BID	241	37	15.35	2.32	6.61	10.80	19.90	<0.0001
	Tofacitinib 10 mg BID	242	49	20.25	2.58	7.84	15.18	25.31	<0.0001
	Placebo → 5 mg BID	60	4	6.67	3.22	2.07	0.35	12.98	0.0384
	Placebo → 10 mg BID	60	3	5.00	2.81	1.78	-0.51	10.51	0.0756
Month 4(NRI)	Tofacitinib 5 mg BID	241	48	19.92	2.57	7.74	14.87	24.96	<0.0001
	Tofacitinib 10 mg BID	242	63	26.03	2.82	9.23	20.50	31.56	<0.0001
	Placebo → 5 mg BID	60	8	13.33	4.39	3.04	4.73	21.93	0.0024
	Placebo → 10 mg BID	60	9	15.00	4.61	3.25	5.96	24.04	0.0011
Month 5(NRI)	Tofacitinib 5 mg BID	241	51	21.16	2.63	8.04	16.00	26.32	<0.0001
	Tofacitinib 10 mg BID	242	69	28.51	2.90	9.82	22.82	34.20	<0.0001
	Placebo → 5 mg BID	60	11	18.33	5.00	3.67	8.54	28.12	0.0002
	Placebo → 10 mg BID	60	11	18.33	5.00	3.67	8.54	28.12	0.0002
Month 6(NRI)	Tofacitinib 5 mg BID	241	53	21.99	2.67	8.24	16.76	27.22	<0.0001
	Tofacitinib 10 mg BID	242	71	29.34	2.93	10.02	23.60	35.08	<0.0001
	Placebo → 5 mg BID	60	12	20.00	5.16	3.87	9.88	30.12	0.0001
	Placebo → 10 mg BID	60	13	21.67	5.32	4.07	11.24	32.09	<0.0001

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; CI = confidence interval; FAS = full analysis set; N = number of subjects; n = number of subjects meeting prespecified criteria; NRI = nonresponder imputation; SE = standard error.

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

The percentage of subjects who achieved DAS28-4(ESR) ≤3.2 by Month 3 for subjects treated with tofacitinib 5 mg was statistically significant compared with placebo. The percentage of subjects who achieved DAS28-4(ESR) by Month 3 for subjects treated with tofacitinib 10 mg was also statistically significant compared with placebo; the response rates were relatively stable at Month 6. A smaller proportion of subjects in the placebo → tofacitinib treatment sequences achieved DAS28-4(ESR) ≤3.2 by Month 3.

The rates of subjects achieving DAS28-4(ESR) <2.6 at Month 3 for subjects who received tofacitinib were not statistically significantly different from placebo. The rates of subjects achieving DAS28-4(ESR) <2.6 at Months 3 and 6 were similar at both timepoints for all 4 treatment sequences.

For DAS28-4(ESR), proportion of subjects in the tofacitinib 5 mg treatment sequence with 0 active joints (ie, tender or swollen) increased from 6 at Month 3 to 12 at Month 6; the number of subjects in the tofacitinib 10 mg treatment sequence with 0 active joints increased from 11 at Month 3 to 21 Month 6. Treatment with tofacitinib (5 and 10 mg) resulted in statistically significantly greater response rates (ie, good or moderate) compared to placebo at Month 3.

Approximately three-fourths of subjects in the tofacitinib treatment sequences had achieved a 'good' or 'moderate' DAS28-4(ESR) response by Month 3; the response rates were relatively stable at Month 6. A smaller proportion of subjects in the placebo → tofacitinib treatment sequences achieved DAS28-4(ESR) response by Month 3.

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

Table 10. Descriptive Statistics of DAS28-4(ESR) per Visit, Comparisons to Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5 mg BID	236	6.71	0.93	3.83	6.11	6.77	7.31	8.83
	Tofacitinib 10 mg BID	234	6.7	0.94	4.43	5.99	6.77	7.41	8.81
	Placebo → 5 mg BID	58	6.61	0.87	4.66	6.09	6.72	7.23	8.46
	Placebo → 10 mg BID	57	6.69	1	4.42	6.02	6.8	7.21	8.94
Month 3	Tofacitinib 5 mg BID	229	4.78	1.37	1.37	3.78	4.79	5.74	8.7
	Tofacitinib 10 mg BID	219	4.55	1.39	0.51	3.58	4.51	5.66	7.32
	Placebo → 5 mg BID	54	5.48	1.5	1.17	4.34	5.58	6.47	8.32
	Placebo → 10 mg BID	50	5.6	1.43	1.9	4.68	5.54	6.72	8.86
Month 6	Tofacitinib 5 mg BID	221	4.33	1.39	1.24	3.31	4.25	5.32	7.92
	Tofacitinib 10 mg BID	209	4.01	1.38	0.83	2.9	3.93	5.04	8.06
	Placebo → 5 mg BID	52	4.31	1.34	1.08	3.26	4.32	5.37	7.55
	Placebo → 10 mg BID	47	3.98	1.5	1.01	2.82	3.81	4.87	7.32

BID = twice daily; DAS = disease activity score; ESR = erythrocyte sedimentation rate; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

DAS28-3(CRP): Subjects who received tofacitinib had statistically significant LS mean decreases from Baseline in DAS28-3(CRP) compared to placebo by Week 2 that continued through Month 3 (Table 11). Changes from Baseline were greater for subjects who received tofacitinib 10 mg compared with tofacitinib 5 mg.

The percentage of subjects who achieved DAS28-3(CRP) ≤3.2 by Month 3 for subjects treated with tofacitinib 5 mg (28.2%) was statistically significant compared with placebo (6.7%) (p-value <0.0001). The percentage of subjects who achieved DAS28-3(CRP) ≤3.2 by Month 3 for subjects treated with tofacitinib 10 mg (36.8%) was also statistically significant compared with placebo (p–value <0.0001); 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 3 (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.

The percentages of subjects in the tofacitinib treatment sequences who achieved DAS28-3(CRP) <2.6 increased at each timepoint through Month 6. 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 Month 3 (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.

Table 11. Descriptive Statistics of DAS28-3(CRP) Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5 mg BID	239	5.68	0.9	3.21	4.98	5.63	6.34	7.9
	Tofacitinib 10 mg BID	242	5.6	0.91	3.22	4.91	5.55	6.31	7.75
	Placebo → 5 mg BID	61	5.57	0.76	4.01	4.9	5.67	6.15	7.38
	Placebo → 10 mg BID	60	5.56	0.94	3.11	4.92	5.64	6.05	7.91
Week 2	Tofacitinib 5 mg BID	234	4.79	1.12	1.22	4.15	4.77	5.52	7.88
	Tofacitinib 10 mg BID	231	4.42	1.11	1.36	3.73	4.45	5.16	7
	Placebo → 5 mg BID	58	5.3	1.09	1.4	4.71	5.29	6.08	7.77
	Placebo → 10 mg BID	60	5.3	1.18	1.51	4.67	5.52	6.04	7.72
Month 1	Tofacitinib 5 mg BID	237	4.41	1.12	1.24	3.8	4.48	5.18	6.92
	Tofacitinib 10 mg BID	236	3.99	1.26	1.26	3.14	4.05	4.87	6.78
	Placebo → 5 mg BID	59	5.09	1.19	2.24	4.23	5.31	5.9	7.64
	Placebo → 10 mg BID	56	4.87	1.32	1.32	3.96	4.95	5.82	7.97
Month 2	Tofacitinib 5 mg BID	238	4.02	1.26	1.22	3.15	4.04	4.8	7.65
	Tofacitinib 10 mg BID	233	3.64	1.27	1.26	2.7	3.58	4.66	6.96
	Placebo → 5 mg BID	57	4.77	1.37	1.4	3.77	4.78	5.79	7.16
	Placebo → 10 mg BID	52	4.94	1.36	1.34	4.24	5.08	5.81	7.51
Month 3	Tofacitinib 5 mg BID	238	3.89	1.27	1.22	2.94	3.94	4.71	7.68
	Tofacitinib 10 mg BID	229	3.59	1.27	1.22	2.67	3.54	4.62	6.27
	Placebo → 5 mg BID	56	4.68	1.28	1.57	3.81	4.68	5.75	7.21
	Placebo → 10 mg BID	53	4.69	1.27	1.45	3.81	4.75	5.53	7.07
Month 4	Tofacitinib 5 mg BID	235	3.65	1.24	1.22	2.73	3.64	4.5	7.84
	Tofacitinib 10 mg BID	222	3.26	1.22	1.22	2.3	3.16	4.2	6.16
	Placebo → 5 mg BID	54	3.89	1.19	1.22	2.87	3.96	4.73	6.15
	Placebo → 10 mg BID	48	3.5	1.28	1.27	2.5	3.7	4.27	7.1
Month 5	Tofacitinib 5 mg BID	231	3.54	1.26	1.22	2.53	3.48	4.44	6.67
	Tofacitinib 10 mg BID	219	3.12	1.24	1.22	2.17	2.94	4.13	7.39
	Placebo → 5 mg BID	55	3.53	1.25	1.22	2.75	3.41	4.47	7.07
	Placebo → 10 mg BID	50	3.34	1.26	1.32	2.23	3.41	4.26	6.96
Month 6	Tofacitinib 5 mg BID	228	3.48	1.23	1.22	2.56	3.36	4.38	6.85
	Tofacitinib 10 mg BID	215	3.11	1.26	1.22	2.05	2.96	3.96	6.62
	Placebo → 5 mg BID	53	3.56	1.32	1.22	2.62	3.36	4.33	7.03
	Placebo → 10 mg BID	50	3.12	1.34	1.22	1.95	2.9	4.11	5.82

BID = twice daily; CRP = C-reactive protein; DAS = disease activity score; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

Health Assessment Questionnaire – Disability Index (HAQ-DI): Decreases from Baseline in HAQ-DI scores were noted in the tofacitinib treatment sequences as early as Week 2, and continued through Month 6 (Table 12). The subjects who received tofacitinib 5 mg and 10 mg demonstrated statistically significantly decreased LS mean HAQ-DI scores at Month 3 compared to placebo; subjects who received tofacitinib 10 mg experienced greater improvement compared with tofacitinib 5 mg.

Table 12. Descriptive Statistics of HAQ-DI Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5 mg BID	240	1.53	0.66	0	1.1	1.6	2	3
	Tofacitinib 10 mg BID	241	1.5	0.64	0	1.1	1.5	2	3
	Placebo → 5 mg BID	61	1.48	0.61	0.1	1	1.5	1.9	2.8
	Placebo → 10 mg BID	61	1.58	0.69	0	1	1.6	2.1	3
Week 2	Tofacitinib 5 mg BID	240	1.27	0.62	0	0.9	1.3	1.6	3
	Tofacitinib 10 mg BID	239	1.21	0.65	0	0.8	1.1	1.8	3
	Placebo → 5 mg BID	59	1.33	0.61	0	1	1.4	1.9	2.8
	Placebo → 10 mg BID	60	1.52	0.67	0	1.1	1.5	2	3
Month 1	Tofacitinib 5 mg BID	237	1.18	0.68	0	0.6	1.3	1.6	2.8
	Tofacitinib 10 mg BID	240	1.09	0.66	0	0.6	1.1	1.6	3
	Placebo → 5 mg BID	60	1.36	0.65	0	0.9	1.3	1.8	2.9
	Placebo → 10 mg BID	56	1.44	0.63	0.3	1	1.4	1.8	3
Month 2	Tofacitinib 5 mg BID	240	1.05	0.66	0	0.5	1	1.5	2.8
	Tofacitinib 10 mg BID	233	0.97	0.68	0	0.4	1	1.5	2.9
	Placebo → 5 mg BID	57	1.36	0.7	0	0.9	1.3	1.8	3
	Placebo → 10 mg BID	53	1.44	0.67	0.1	1	1.4	2	3
Month 3	Tofacitinib 5 mg BID	238	1.05	0.7	0	0.5	1	1.5	2.8
	Tofacitinib 10 mg BID	229	0.97	0.69	0	0.4	1	1.4	2.9
	Placebo → 5 mg BID	56	1.3	0.77	0	0.8	1.3	2	2.6
	Placebo → 10 mg BID	53	1.39	0.7	0.1	1	1.4	1.9	2.9
Month 4	Tofacitinib 5 mg BID	235	0.97	0.66	0	0.4	1	1.5	2.6
	Tofacitinib 10 mg BID	223	0.88	0.68	0	0.3	0.9	1.4	3
	Placebo → 5 mg BID	55	1.08	0.7	0	0.5	1	1.6	2.5
	Placebo → 10 mg BID	49	1.09	0.65	0	0.5	1.3	1.5	2.9
Month 5	Tofacitinib 5 mg BID	231	0.95	0.69	0	0.4	0.9	1.5	2.8
	Tofacitinib 10 mg BID	221	0.87	0.69	0	0.3	0.9	1.4	3
	Placebo → 5 mg BID	55	1.04	0.59	0	0.6	1	1.5	2.4
	Placebo → 10 mg BID	50	1.03	0.64	0	0.5	1.1	1.5	2.9
Month 6	Tofacitinib 5 mg BID	229	0.94	0.68	0	0.4	0.9	1.4	2.8
	Tofacitinib 10 mg BID	216	0.86	0.67	0	0.3	0.8	1.3	3
	Placebo → 5 mg BID	54	1.05	0.63	0	0.6	1.1	1.4	2.4
	Placebo → 10 mg BID	50	1	0.66	0	0.5	1	1.5	2.9

BID = twice daily; HAQ-DI = health assessment questionnaire-disability index; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

Pain (Visual Analog Scale [VAS]): Treatment with tofacitinib (5 and 10 mg) resulted in statistically significant LS mean decreases in pain from Baseline compared to placebo at Week 2 through Month 3. 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 approximately Month 4 and stabilized through Month 6 (Table 13).

Table 13. Descriptive Statistics of Pain VAS Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5 mg BID	241	61.35	22.27	3	49	64	76	100
	Tofacitinib 10 mg BID	243	62.03	23.63	3	47.9	60	81	100
	Placebo → 5 mg BID	61	60.56	20.73	3	46	64	74	100
	Placebo → 10 mg BID	61	63.02	21.9	3	51	65	79	99
Week 2	Tofacitinib 5 mg BID	239	45.92	22.87	0	30	48	60	100
	Tofacitinib 10 mg BID	239	42.13	25.06	0	21	41	60	100
	Placebo → 5 mg BID	59	51.59	23	7	33	50	70	96
	Placebo → 10 mg BID	60	59.55	23.76	5	46.5	61	79	100
Month 1	Tofacitinib 5 mg BID	237	40.68	23.04	1	24	40	57	100
	Tofacitinib 10 mg BID	240	36.86	24.46	0	16.5	37	53	99
	Placebo → 5 mg BID	60	51.57	24.1	4	35	52	67.5	96
	Placebo → 10 mg BID	56	53.43	25.28	5	28.5	53.5	73	99
Month 2	Tofacitinib 5 mg BID	240	36.39	23.29	0	20	32.5	54.5	98
	Tofacitinib 10 mg BID	233	31.66	24.38	0	11	27	49	95
	Placebo → 5 mg BID	57	48.74	25.88	3	30	47	66	97
	Placebo → 10 mg BID	53	56.3	25.99	3	36	57	81	99
Month 3	Tofacitinib 5 mg BID	237	34.93	23.73	0	14	32	50	98
	Tofacitinib 10 mg BID	228	31.37	24.35	0	10.9	26	48	100
	Placebo → 5 mg BID	56	47	25.91	0	28	48.5	65	95
	Placebo → 10 mg BID	52	52.9	24.08	6	34.5	51	73	100
Month 4	Tofacitinib 5 mg BID	235	33.18	23.02	0	12	32	51	97
	Tofacitinib 10 mg BID	223	29.7	23.21	0	10	23	46	94
	Placebo → 5 mg BID	55	34.27	24.53	1	14	31	49	94
	Placebo → 10 mg BID	49	35.47	25.28	1	17	31	53	100
Month 5	Tofacitinib 5 mg BID	231	32.63	23.07	0	12	31	50	97
	Tofacitinib 10 mg BID	221	29.1	22.24	0	10	25	42	97
	Placebo → 5 mg BID	55	34.05	23.48	0	14	31	47	93
	Placebo → 10 mg BID	50	35.06	24.82	2	11	33	53	99
Month 6	Tofacitinib 5 mg BID	228	32.6	23.55	0	12	28	50.5	93
	Tofacitinib 10 mg BID	216	27.89	23.17	0	7	22	44	92
	Placebo → 5 mg BID	54	33.96	24.62	1	13	30	52	88
	Placebo → 10 mg BID	50	32.28	23.79	3	12	28	47	100

BID = twice daily; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation; VAS = visual analog scale.

Subject Global Assessment of Arthritis: Treatment with tofacitinib (5 and 10 mg) resulted in statistically significant LS mean decreases from Baseline in Subject Global Assessment of Arthritis compared to placebo at Week 2 through Month 3. 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 approximately Month 4 and stabilized through Month 6 (Table 14).

Table 14. Descriptive Statistics of Subject Global Assessment Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5 mg BID	240	61.66	22	4	48	64	76.5	100
	Tofacitinib 10 mg BID	243	63.46	23.23	4	48	66	80	100
	Placebo → 5 mg BID	61	63.3	21.64	6	50	68	79	98
	Placebo → 10 mg BID	61	61.95	22.34	3	50	64	78	99
Week 2	Tofacitinib 5 mg BID	240	46.34	22.36	1	30	48	62.5	100
	Tofacitinib 10 mg BID	239	41.32	24.9	0	21	42	58	100
	Placebo → 5 mg BID	59	51.35	23.23	0	37	50	71	96
	Placebo → 10 mg BID	60	60.48	23.65	5	46.5	59	81.5	100
Month 1	Tofacitinib 5 mg BID	237	39.63	22.36	1	23	40	55	100
	Tofacitinib 10 mg BID	240	37.69	23.94	0	18	38.5	53.5	100
	Placebo → 5 mg BID	60	51.74	23.54	0	36.8	49	70.5	98
	Placebo → 10 mg BID	56	54.82	24.62	4.2	35.5	57.5	75	99
Month 2	Tofacitinib 5 mg BID	240	36.29	22.2	0	17.4	35.5	52.5	97
	Tofacitinib 10 mg BID	233	32.56	23.47	0	13	28	48	99
	Placebo → 5 mg BID	57	49.76	25.39	0	31	50	67	97
	Placebo → 10 mg BID	53	56.58	26.5	3	37	57	83	99
Month 3	Tofacitinib 5 mg BID	238	35.9	23.61	0	15	34.7	51	98
	Tofacitinib 10 mg BID	229	32.78	23.75	0	13	30	50	98
	Placebo → 5 mg BID	56	48.69	26.21	0	29.5	48.5	70	94
	Placebo → 10 mg BID	52	52.42	25.52	6	32.5	48	72	100
Month 4	Tofacitinib 5 mg BID	235	33.59	22.44	0	14	33	49	98
	Tofacitinib 10 mg BID	223	29.69	22.25	0	10	25	47	95
	Placebo → 5 mg BID	55	35.27	23.77	0	15	36	52	94
	Placebo → 10 mg BID	49	36.45	25.92	2	16	29	52	100
Month 5	Tofacitinib 5 mg BID	231	34.59	23.37	0	13	33	51	96
	Tofacitinib 10 mg BID	221	29.37	22.13	0	10	27	45	95
	Placebo → 5 mg BID	55	32.88	21.43	0	19	31	45	91
	Placebo → 10 mg BID	50	33.96	25.02	2	10	30	54	100
Month 6	Tofacitinib 5 mg BID	228	32.56	23.09	0	12.5	29	50.5	93
	Tofacitinib 10 mg BID	216	29.52	22.89	0	10	23.5	48	96
	Placebo → 5 mg BID	54	33.51	24	1	14	27.5	51	91
	Placebo → 10 mg BID	50	32.89	23.78	3	12	30	48	99

BID = twice daily; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

Physician Global Assessment of Arthritis: Treatment with tofacitinib (5 and 10 mg) resulted in statistically significant LS mean decreases from Baseline in Physician Global Assessment of Arthritis compared to placebo at Week 2 through Month 3. 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 approximately Month 4 and stabilized through Month 6 (Table 15).

Table 15. Descriptive Statistics of Physician Global Assessment Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5 mg BID	241	61.46	16.93	13	51	62	73	96
	Tofacitinib 10 mg BID	243	60.84	16.84	20	49	61	73	96
	Placebo → 5 mg BID	61	62.32	14.29	21	52	60	73	94
	Placebo → 10 mg BID	61	62.13	19.19	10	53	63	75	97
Week 2	Tofacitinib 5 mg BID	239	43.43	17.69	0	31	44	55	84
	Tofacitinib 10 mg BID	240	40.47	19.73	0	26	41	55	82
	Placebo → 5 mg BID	59	48.57	16.35	7	40	49	59	93
	Placebo → 10 mg BID	60	55.66	21.27	0	43	55	67	100
Month 1	Tofacitinib 5 mg BID	237	35.89	18.91	0	23	36	48	89
	Tofacitinib 10 mg BID	240	33.99	20.37	0	18	33	46	87
	Placebo → 5 mg BID	60	46.03	21.46	5	30.5	43	62	95
	Placebo → 10 mg BID	56	47.98	23.31	3.1	30	51	62	90
Month 2	Tofacitinib 5 mg BID	240	32.06	20.81	0	15	31	44.5	89
	Tofacitinib 10 mg BID	232	26.75	19.23	0	12	25	39	93
	Placebo → 5 mg BID	57	42.77	23.3	0	25	41	56	93
	Placebo → 10 mg BID	53	46.26	24.05	0	29	51	64	96
Month 3	Tofacitinib 5 mg BID	238	29.2	19.98	0	12	27	43	97
	Tofacitinib 10 mg BID	229	24.47	18.42	0	9	20	36	84
	Placebo → 5 mg BID	56	38.59	21.9	0	23	35	55.5	83
	Placebo → 10 mg BID	53	45.71	24.93	0	25	45	64	87
Month 4	Tofacitinib 5 mg BID	235	25.3	18.56	0	11	22.9	35	96
	Tofacitinib 10 mg BID	221	21.21	16.46	0	7	19	30	81
	Placebo → 5 mg BID	54	27.48	19.8	0	8	27.5	45	69
	Placebo → 10 mg BID	49	25.86	20.32	2	7	22	37	81
Month 5	Tofacitinib 5 mg BID	231	23.6	17.63	0	9	21	34	77
	Tofacitinib 10 mg BID	221	20.99	16.13	0	7	18.8	33	79
	Placebo → 5 mg BID	55	24.74	17.93	0	7	22	38	72
	Placebo → 10 mg BID	50	25.9	19.85	1	8	21	42	76
Month 6	Tofacitinib 5 mg BID	229	23.26	18.12	0	8	21	32	90
	Tofacitinib 10 mg BID	216	20.61	16.27	0	7	17.4	31	81
	Placebo → 5 mg BID	54	26.16	19.55	0	8	24.5	32	87
	Placebo → 10 mg BID	50	21.54	17.51	0	5	22.5	33	64

BID = twice daily; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

SF-36 (Version 2, Acute): Treatment with tofacitinib (5 and 10 mg) resulted in statistically significant LS mean improvements (increases) from Baseline in all SF-36 domains and component summary scores compared to placebo at Month 3 (Table 16). Score improvements for subjects who received tofacitinib 10 mg were greater than for those who received tofacitinib 5 mg.

Subjects in both tofacitinib treatment sequences demonstrated increases (improvements) from Baseline in each of the SF-36 domain scores at Month 3; the increases continued or remained stable through Month 6. 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 3; after Month 3 (ie, after advancing to tofacitinib), there was a continued increase.

Increases (improvments) 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 3; the greatest improvement was noted in the placebo → tofacitinib 10 mg sequence at Month 6. Increases (improvements) were also noted in the SF-36 physical component scores in each of the treatment sequences at Month 3 and Month 6, with larger increases in the tofacitinib treatment sequences compared to the placebo → tofacitinib sequences.

Table 16. Descriptive Statistics of SF-36 - Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Physical Functioning									
Baseline	Tofacitinib 5 mg BID	239	30.09	9.31	16.2	22.3	28.5	34.6	57.1
	Tofacitinib 10 mg BID	243	30.51	8.76	16.2	24.4	30.5	36.6	55.1
	Placebo → 5 mg BID	61	31.98	9.65	16.2	24.4	34.6	38.7	55.1
	Placebo → 10 mg BID	61	30.84	9.71	16.2	22.3	30.5	38.7	51
Month 3	Tofacitinib 5 mg BID	235	36.13	10.44	16.2	28.5	36.6	42.8	57.1
	Tofacitinib 10 mg BID	224	37.05	10.58	16.2	28.5	36.6	44.8	57.1
	Placebo → 5 mg BID	56	33.58	10.97	16.2	24.4	32.6	42.8	55.1
	Placebo → 10 mg BID	52	32.24	10.3	16.2	24.4	31.5	38.7	53
Month 6	Tofacitinib 5 mg BID	229	36.99	10.07	16.2	28.5	36.6	44.8	57.1
	Tofacitinib 10 mg BID	216	38.43	10.67	16.2	30.5	38.7	46.9	57.1
	Placebo → 5 mg BID	54	35.74	10.23	16.2	28.5	36.6	42.8	57.1
	Placebo → 10 mg BID	50	35.26	9.98	18.2	28.5	34.6	40.7	57.1
Role Physical									
Baseline	Tofacitinib 5 mg BID	239	32.84	8.87	18.4	28	32.8	37.5	56.6
	Tofacitinib 10 mg BID	243	33.45	8.69	18.4	28	35.1	37.5	56.6
	Placebo → 5 mg BID	61	34.21	8.92	18.4	28	35.1	37.5	56.6
	Placebo → 10 mg BID	61	32.45	9	18.4	23.2	35.1	37.5	51.9
Month 3	Tofacitinib 5 mg BID	233	38.9	9.41	18.4	32.8	37.5	44.7	56.6
	Tofacitinib 10 mg BID	224	40.45	9.9	18.4	35.1	37.5	47.1	56.6
	Placebo → 5 mg BID	55	35.15	9.08	18.4	28	35.1	39.9	56.6
	Placebo → 10 mg BID	52	35.24	10.45	18.4	28	36.3	41.1	56.6
Month 6	Tofacitinib 5 mg BID	229	39.85	9.57	18.4	35.1	37.5	47.1	56.6
	Tofacitinib 10 mg BID	215	40.93	9.5	18.4	35.1	39.9	47.1	56.6
	Placebo → 5 mg BID	53	38.25	9.73	18.4	30.4	37.5	44.7	56.6
	Placebo → 10 mg BID	50	38.97	9.06	18.4	35.1	39.9	42.3	56.6
Social Functioning									
Baseline	Tofacitinib 5 mg BID	239	36.78	11.04	13.4	29.5	34.9	45.6	56.4
	Tofacitinib 10 mg BID	243	36.07	11.27	13.4	29.5	34.9	40.3	56.4
	Placebo → 5 mg BID	61	35.95	9.61	13.4	29.5	34.9	40.3	56.4
	Placebo → 10 mg BID	61	34.36	11.05	13.4	24.1	34.9	40.3	56.4
Month 3	Tofacitinib 5 mg BID	235	41.62	10.9	13.4	34.9	40.3	51	56.4
	Tofacitinib 10 mg BID	224	43.25	9.95	13.4	34.9	40.3	51	56.4
	Placebo → 5 mg BID	56	35.37	9.63	13.4	29.5	34.9	40.3	56.4
	Placebo → 10 mg BID	52	36.96	10.5	13.4	29.5	34.9	45.6	56.4
Month 6	Tofacitinib 5 mg BID	229	42.36	10.6	13.4	34.9	40.3	51	56.4
	Tofacitinib 10 mg BID	216	42.98	10.15	18.8	34.9	45.6	51	56.4
	Placebo → 5 mg BID	54	39.57	11.45	13.4	34.9	40.3	51	56.4
	Placebo → 10 mg BID	50	43.39	9.78	24.1	34.9	45.6	51	56.4
Bodily Pain									
Baseline	Tofacitinib 5 mg BID	239	32.41	7.57	19.2	28.4	32.1	36.3	60.9
	Tofacitinib 10 mg BID	243	32.74	7.55	19.2	28.4	32.1	36.3	60.9
	Placebo → 5 mg BID	61	33.36	7.24	19.2	28.4	32.6	36.3	50.1
	Placebo → 10 mg BID	61	32.19	8.09	19.2	28.4	32.1	36.3	50.1
Month 3	Tofacitinib 5 mg BID	235	40.56	9.38	19.2	36.3	40.5	45.1	60.9
	Tofacitinib 10 mg BID	224	43.08	9.5	19.2	36.3	40.9	50.1	60.9
	Placebo → 5 mg BID	56	35.98	8.53	19.2	28.4	34.4	40.9	55.9
	Placebo → 10 mg BID	52	36.75	9.17	19.2	28.4	36.3	45.1	60.9
Month 6	Tofacitinib 5 mg BID	229	41.8	9.55	19.2	36.3	40.9	50.1	60.9
	Tofacitinib 10 mg BID	216	43.67	9.54	24.2	36.3	45.1	50.1	60.9
	Placebo → 5 mg BID	54	40.8	9.36	19.2	36.3	40.7	45.9	60.9
	Placebo → 10 mg BID	50	42.19	9.46	28.4	36.3	36.3	50.1	60.9

Table 16. Descriptive Statistics of SF-36 - Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Mental Health									
Baseline	Tofacitinib 5 mg BID	239	40.05	11.49	8	33	41.3	46.8	63.4
	Tofacitinib 10 mg BID	243	40.5	12.57	10.8	33	41.3	49.6	63.4
	Placebo → 5 mg BID	61	37.45	12.93	8	30.2	35.7	46.8	63.4
	Placebo → 10 mg BID	61	39.41	11.79	8	33	41.3	49.6	63.4
Month 3	Tofacitinib 5 mg BID	235	44.33	11.5	10.8	35.7	44	52.3	63.4
	Tofacitinib 10 mg BID	224	45.13	11.25	16.3	35.7	44	52.3	63.4
	Placebo → 5 mg BID	56	38.65	10.11	16.3	31.6	38.5	46.8	63.4
	Placebo → 10 mg BID	52	42.97	11.02	16.3	35.7	44	51	63.4
Month 6	Tofacitinib 5 mg BID	229	43.98	12.18	8	35.7	44	52.3	63.4
	Tofacitinib 10 mg BID	216	45.05	11.01	13.6	35.7	46.8	55.1	63.4
	Placebo → 5 mg BID	54	42.14	11.9	19.1	35.7	41.3	52.3	63.4
	Placebo → 10 mg BID	50	47.03	10.62	24.6	38.5	49.6	55.1	63.4
Role Emotional									
Baseline	Tofacitinib 5 mg BID	239	34.26	12.63	10.2	25.4	33	44.3	55.7
	Tofacitinib 10 mg BID	243	36.7	13.03	10.2	25.4	36.7	44.3	55.7
	Placebo → 5 mg BID	61	33.96	11.97	10.2	25.4	33	44.3	55.7
	Placebo → 10 mg BID	61	36.38	14.16	10.2	25.4	36.7	48.1	55.7
Month 3	Tofacitinib 5 mg BID	233	38.76	12.13	10.2	33	36.7	48.1	55.7
	Tofacitinib 10 mg BID	224	40.84	11.57	10.2	33	40.5	53.8	55.7
	Placebo → 5 mg BID	55	33.51	11.85	10.2	25.4	33	44.3	55.7
	Placebo → 10 mg BID	52	38.79	13.04	10.2	33	38.6	48.1	55.7
Month 6	Tofacitinib 5 mg BID	229	40.37	11.32	10.2	33	40.5	48.1	55.7
	Tofacitinib 10 mg BID	214	41.03	11.47	10.2	33	40.5	51.9	55.7
	Placebo → 5 mg BID	53	39.04	12.93	10.2	29.2	40.5	51.9	55.7
	Placebo → 10 mg BID	50	42.66	12.1	10.2	33	42.4	55.7	55.7
Vitality									
Baseline	Tofacitinib 5 mg BID	239	41.22	10.06	22	34	43	49	63.9
	Tofacitinib 10 mg BID	243	41.04	10.27	22	34	40	49	66.9
	Placebo → 5 mg BID	61	40.03	9.86	22	34	40	46	63.9
	Placebo → 10 mg BID	61	40.23	9.86	22	34	40	46	66.9
Month 3	Tofacitinib 5 mg BID	235	47.36	10.69	22	40	46	54.9	69.9
	Tofacitinib 10 mg BID	224	49.03	9.86	22	43	49	54.9	69.9
	Placebo → 5 mg BID	56	41.69	8.84	22	34	41.5	49	60.9
	Placebo → 10 mg BID	52	42.8	10.69	25	32.5	44.5	52	63.9
Month 6	Tofacitinib 5 mg BID	229	47.47	10.58	22	40	46	54.9	69.9
	Tofacitinib 10 mg BID	216	48.89	10.29	22	43	49	56.4	69.9
	Placebo → 5 mg BID	54	45.08	9.5	28	37	44.5	52	66.9
	Placebo → 10 mg BID	50	47.88	9.19	31	40	49	54.9	69.9
General Health Perception									
Baseline	Tofacitinib 5 mg BID	239	34.86	8.72	16.8	28.5	33.2	40.2	57.6
	Tofacitinib 10 mg BID	243	35.71	8.86	16.8	28.5	35.5	41.2	60
	Placebo → 5 mg BID	61	33.62	8.11	16.8	28.5	33.2	37.9	55.3
	Placebo → 10 mg BID	61	35.77	9.76	19.1	28.5	35.5	41.2	57.6
Month 3	Tofacitinib 5 mg BID	235	39.52	9.37	19.1	33.2	37.9	45.9	62.3
	Tofacitinib 10 mg BID	224	41.5	9.78	21.4	33.2	40.2	48.2	63.7
	Placebo → 5 mg BID	56	37.19	8.22	21.4	30.8	37.2	41.2	56.7
	Placebo → 10 mg BID	52	37.25	9.37	21.4	30.1	35.5	45.4	57.6
Month 6	Tofacitinib 5 mg BID	229	41.05	9.24	21.4	35.5	40.2	48.2	63.7
	Tofacitinib 10 mg BID	215	42.58	9.84	22.4	34.1	41.2	50.6	63.7
	Placebo → 5 mg BID	54	38.99	8.73	19.1	31.8	37.9	44.9	59
	Placebo → 10 mg BID	50	40.42	10.83	19.1	33.2	39.5	48.2	63.7

Table 16. Descriptive Statistics of SF-36 - Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Mental Component									
Baseline	Tofacitinib 5 mg BID	239	41.36	11.68	8.9	33.3	40.7	48.9	66.3
	Tofacitinib 10 mg BID	243	42.19	12.44	11.8	33.6	42.8	50.6	69.9
	Placebo → 5 mg BID	61	38.79	11.51	14.9	31.4	40	44.5	63.6
	Placebo → 10 mg BID	61	40.96	11.72	13.9	33.4	41.5	49.6	67.4
Month 3	Tofacitinib 5 mg BID	233	45.21	11.65	9.8	37.4	45.8	54.8	69.6
	Tofacitinib 10 mg BID	224	46.58	10.81	16.2	39.2	46.1	55.2	68.5
	Placebo → 5 mg BID	55	38.5	10.21	13	31.2	37.8	45.7	60.5
	Placebo → 10 mg BID	52	43.92	11	16.7	36.4	43.2	51	66.9
Month 6	Tofacitinib 5 mg BID	229	45.43	11.58	12.3	37.7	46.1	54.5	68.4
	Tofacitinib 10 mg BID	213	46.08	10.44	16.2	38.2	45.6	53.7	65.9
	Placebo → 5 mg BID	53	43.29	12.37	14.8	34.2	42.4	52.3	70.8
	Placebo → 10 mg BID	50	48.76	11.06	25.4	41.7	49.4	57	70.3
Physical Component									
Baseline	Tofacitinib 5 mg BID	239	31.23	8.03	8.1	26	30.6	35.9	56
	Tofacitinib 10 mg BID	243	31.37	7.39	8.6	26.4	31.7	36.2	49.9
	Placebo → 5 mg BID	61	33.11	7.9	16.1	28	34.4	39.8	46.1
	Placebo → 10 mg BID	61	31.3	8.75	11.3	26.3	30.7	37.6	51.1
Month 3	Tofacitinib 5 mg BID	233	38.03	9.18	13.5	32.4	37.9	43.4	60.4
	Tofacitinib 10 mg BID	224	39.69	9.31	14.5	33.1	39.5	46.4	63.3
	Placebo → 5 mg BID	55	35.6	8.42	22.4	28.7	34.4	41.6	53.4
	Placebo → 10 mg BID	52	33.49	9.42	10.4	25	33.4	40.1	55.5
Month 6	Tofacitinib 5 mg BID	229	39.24	8.42	11.9	34.6	39.2	43.8	60.3
	Tofacitinib 10 mg BID	213	40.89	9.04	16.7	33.9	41.2	47.7	60.1
	Placebo → 5 mg BID	53	37.89	9.56	9.5	32	39	45.6	56.9
	Placebo → 10 mg BID	50	37.06	9.14	19.1	29	37	42.5	58.7

BID = twice daily; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation; SF = short form.

MOS Sleep Scale (MOS-SS): Treatment with tofacitinib 10 mg resulted in statistically significant LS mean improvements from Baseline compared to placebo in the Overall Sleep Problems, Sleep Problems Index, Somnolence, awaken short of breadth, and Adequacy subscales at Month 3 (Table 17). Treatment with tofacitinib 10 mg resulted in statistically significant improvement from Baseline compared to placebo in the Adequacy subscale at Month 3 (p-value =0.0048).

In the tofacitinib treatment sequences, improvement was most marked at Month 3 and scores remained stable at Month 6. The placebo → tofacitinib treatment sequences showed the most improvement from Months 3 to 6.

The percentages of subjects who received tofacitinib who achieved optimal sleep on the MOS-SS Optimal Sleep subscale were not statistically significantly different compared to placebo at Month 3. The proportions of subjects in each treatment sequence achieving optimal sleep were stable from Month 3 to Month 6.

Table 17. Descriptive Statistics of Medical Outcome Study(MOS) Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Overall Sleep Problem Score									
Baseline	Tofacitinib 5 mg BID	238	42.45	18.38	2.2	29.4	40.8	55	86.7
	Tofacitinib 10 mg BID	242	43.09	20.41	0	29.4	40.8	57.2	95.6
	Placebo → 5 mg BID	61	46.84	22.07	2.2	29.4	50	64.4	92.8
	Placebo → 10 mg BID	61	47.81	20.56	0	32.2	52.2	62.2	88.9
Month 3	Tofacitinib 5 mg BID	236	35.53	19.3	0	22.8	33.9	48.1	86.7
	Tofacitinib 10 mg BID	228	33.29	19.96	0	18.3	31.7	45	86.7
	Placebo → 5 mg BID	56	40.8	21.18	2.2	25.8	33.9	58.1	88.9
	Placebo → 10 mg BID	53	41.47	21.64	4.4	24.4	41.1	63.3	86.7
Month 6	Tofacitinib 5 mg BID	228	35.68	18.8	0	21.7	33.9	48.9	86.7
	Tofacitinib 10 mg BID	213	33.33	19.19	0	20	32.2	45	91.1
	Placebo → 5 mg BID	54	37.29	19.26	0	20.6	39.2	52.8	75
	Placebo → 10 mg BID	50	35.64	21.2	6.7	17.8	33.9	50	82.2
Sleep Problem Summary									
Baseline	Tofacitinib 5 mg BID	239	40.59	18.98	0	26.7	40	53.3	86.7
	Tofacitinib 10 mg BID	242	42.38	21.01	0	30	40	56.7	93.3
	Placebo → 5 mg BID	61	46.01	22.34	0	26.7	46.7	63.3	96.7
	Placebo → 10 mg BID	61	45.96	21.53	0	30	46.7	63.3	83.3
Month 3	Tofacitinib 5 mg BID	236	34.46	19.89	0	20	33.3	46.7	86.7
	Tofacitinib 10 mg BID	228	33.25	20.16	0	16.7	33.3	46.7	90
	Placebo → 5 mg BID	56	39.88	21.42	3.3	23.3	35	55	86.7
	Placebo → 10 mg BID	53	41.26	22.83	3.3	20	40	60	86.7
Month 6	Tofacitinib 5 mg BID	229	35.17	18.81	0	20	36.7	46.7	93.3
	Tofacitinib 10 mg BID	213	33.33	19.66	0	20	33.3	46.7	86.7
	Placebo → 5 mg BID	54	37.41	20.3	0	20	40	53.3	76.7
	Placebo → 10 mg BID	50	35.87	20.8	3.3	16.7	35	50	80
Somnolence									
Baseline	Tofacitinib 5 mg BID	239	37.21	22.47	0	20	33.3	53.3	100
	Tofacitinib 10 mg BID	243	37.64	21.76	0	20	33.3	53.3	100
	Placebo → 5 mg BID	61	36.61	19.23	0	20	40	53.3	86.7
	Placebo → 10 mg BID	61	36.5	23.34	0	20	33.3	46.7	93.3
Month 3	Tofacitinib 5 mg BID	236	30.28	21.28	0	13.3	26.7	40	93.3
	Tofacitinib 10 mg BID	229	30.45	21.26	0	13.3	26.7	40	100
	Placebo → 5 mg BID	56	34.64	22.61	0	20	30	46.7	93.3
	Placebo → 10 mg BID	53	36.73	23.59	0	20	33.3	46.7	93.3
Month 6	Tofacitinib 5 mg BID	228	30.26	21.01	0	13.3	26.7	40	100
	Tofacitinib 10 mg BID	213	29.42	20.64	0	13.3	26.7	40	100
	Placebo → 5 mg BID	54	31.36	19.75	0	20	30	46.7	80
	Placebo → 10 mg BID	50	29.6	21.56	0	13.3	26.7	40	100
Snoring									
Baseline	Tofacitinib 5 mg BID	238	35.71	31.07	0	0	40	60	100
	Tofacitinib 10 mg BID	243	30.29	30.5	0	0	20	40	100
	Placebo → 5 mg BID	61	31.48	33.76	0	0	20	60	100
	Placebo → 10 mg BID	60	29	29.09	0	0	20	40	100
Month 3	Tofacitinib 5 mg BID	236	32.63	29.61	0	0	20	40	100
	Tofacitinib 10 mg BID	229	25.85	27.57	0	0	20	40	100
	Placebo → 5 mg BID	56	27.14	32.46	0	0	20	40	100
	Placebo → 10 mg BID	53	27.92	26.99	0	0	20	40	100
Month 6	Tofacitinib 5 mg BID	229	35.28	31.04	0	20	20	40	100
	Tofacitinib 10 mg BID	213	27.79	28.24	0	0	20	40	100
	Placebo → 5 mg BID	54	26.3	28.5	0	0	20	40	100
	Placebo → 10 mg BID	50	29.2	27.47	0	0	20	40	100

Table 17. Descriptive Statistics of Medical Outcome Study(MOS) Per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Quantity									
Baseline	Tofacitinib 5 mg BID	240	6.53	1.56	2	6	6	7	12
	Tofacitinib 10 mg BID	243	6.38	1.63	1	5	6	8	11
	Placebo → 5 mg BID	61	6.25	1.73	3	5	6	8	10
	Placebo → 10 mg BID	61	6.49	1.77	3	5	6	8	12
Month 3	Tofacitinib 5 mg BID	237	6.77	1.63	2	6	7	8	16
	Tofacitinib 10 mg BID	228	6.89	1.45	2	6	7	8	11
	Placebo → 5 mg BID	56	6.84	1.39	3	6	7	8	10
	Placebo → 10 mg BID	53	6.72	1.57	4	6	7	8	10
Month 6	Tofacitinib 5 mg BID	229	6.64	1.45	2	6	7	8	12
	Tofacitinib 10 mg BID	213	6.87	1.71	1	6	7	8	18
	Placebo → 5 mg BID	54	6.65	1.52	2	6	6.5	8	9
	Placebo → 10 mg BID	50	6.64	1.27	4	6	7	8	10
Sleep Disturbance									
Baseline	Tofacitinib 5 mg BID	238	44.44	24.11	0	25	42.5	62.5	100
	Tofacitinib 10 mg BID	242	43.33	26.18	0	25	41.3	62.5	100
	Placebo → 5 mg BID	61	49.9	27.03	0	25	52.5	75	95
	Placebo → 10 mg BID	61	52.64	24.84	0	36.3	55	72.5	100
Month 3	Tofacitinib 5 mg BID	236	36.58	24.67	0	16.3	31.3	52.5	100
	Tofacitinib 10 mg BID	229	32.58	24.27	0	15	30	46.3	100
	Placebo → 5 mg BID	56	41.09	28.01	0	20	36.3	62.5	100
	Placebo → 10 mg BID	53	41.23	27	0	21.3	37.5	60	95
Month 6	Tofacitinib 5 mg BID	229	35.75	25.11	0	15	31.3	53.8	100
	Tofacitinib 10 mg BID	214	33.38	23.91	0	15	31.3	46.3	100
	Placebo → 5 mg BID	54	37.8	23.96	0	20	36.3	57.5	88.8
	Placebo → 10 mg BID	50	33.8	25.83	0	11.3	31.3	52.5	95
Awaken Short of Breath									
Baseline	Tofacitinib 5 mg BID	239	18.16	23.76	0	0	0	40	100
	Tofacitinib 10 mg BID	243	20.91	25.47	0	0	20	40	100
	Placebo → 5 mg BID	61	28.2	31.28	0	0	20	40	100
	Placebo → 10 mg BID	61	21.64	27.15	0	0	20	40	100
Month 3	Tofacitinib 5 mg BID	236	15.93	21.29	0	0	0	20	100
	Tofacitinib 10 mg BID	228	16.23	21.69	0	0	0	20	100
	Placebo → 5 mg BID	56	23.21	25.23	0	0	20	40	100
	Placebo → 10 mg BID	53	21.13	24.94	0	0	20	40	100
Month 6	Tofacitinib 5 mg BID	229	15.55	21.67	0	0	0	20	100
	Tofacitinib 10 mg BID	214	15.7	21.41	0	0	0	20	100
	Placebo → 5 mg BID	54	21.11	21.43	0	0	20	40	60
	Placebo → 10 mg BID	50	23.2	25.67	0	0	20	40	100
Adequacy									
Baseline	Tofacitinib 5 mg BID	239	45.44	27.25	0	20	40	60	100
	Tofacitinib 10 mg BID	243	42.63	27.37	0	20	40	60	100
	Placebo → 5 mg BID	61	42.13	28.93	0	20	40	60	100
	Placebo → 10 mg BID	61	38.03	27.86	0	20	40	50	100
Month 3	Tofacitinib 5 mg BID	236	51.69	28.77	0	30	50	80	100
	Tofacitinib 10 mg BID	229	52.93	27.75	0	30	50	80	100
	Placebo → 5 mg BID	56	45.89	28.14	0	20	40	70	100
	Placebo → 10 mg BID	53	42.83	27.34	0	20	40	70	100
Month 6	Tofacitinib 5 mg BID	229	48.52	27.41	0	30	50	70	100
	Tofacitinib 10 mg BID	214	53.04	29.14	0	30	50	80	100
	Placebo → 5 mg BID	54	49.44	29.36	0	20	45	80	100
	Placebo → 10 mg BID	50	49	27.94	0	20	40	80	100

BID = twice daily; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

FACIT Fatigue Scale: All 4 treatment sequences had greater changes from Baseline at Month 6 compared to Month 3; changes from Baseline were greater in the tofacitinib 10 mg treatment sequence compared with the tofacitinib 5 mg sequence (Table 18).

Table 18. Descriptive Statistics of FACIT - Fatigue Scale per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5 mg BID	240	27.9	10.7	3	20	28	37	49
	Tofacitinib 10 mg BID	243	27.72	11.15	0	19	28	36	52
	Placebo → 5 mg BID	61	26.66	10.48	4	21	27	34	48
	Placebo → 10 mg BID	61	27.69	11.33	2	20	27	36	51
Month 3	Tofacitinib 5 mg BID	237	34.4	10.65	4	27	35	43	52
	Tofacitinib 10 mg BID	227	35.42	9.75	4	30	36	43	52
	Placebo → 5 mg BID	56	30.07	10.12	4	23.5	31	35	50
	Placebo → 10 mg BID	53	30.04	11.7	4	21	32	39	48
Month 6	Tofacitinib 5 mg BID	229	34.58	10.69	3	28	36	43	52
	Tofacitinib 10 mg BID	216	36.3	10.1	3	30	37	44	52
	Placebo → 5 mg BID	54	33.63	9.29	12	27	33	41	51
	Placebo → 10 mg BID	50	36.46	9.27	15	30	36.4	44	51

BID = twice daily; FACIT = functional assessment of chronic illness therapy; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

EuroQoL EQ-5D: The tofacitinib treatment sequences had numerically greater improvements from Baseline at Month 3 compared with placebo; the increases were maintained through Month 6 for the tofacitinib treatment sequences (Table 19).

Table 19. Descriptive Statistics of EuroQol EQ-5D Health State Profile-Utility Score per Visit, Comparisons Within Sequence

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5 mg BID	240	0.41	0.32	-0.3	0.1	0.5	0.6	1
	Tofacitinib 10 mg BID	243	0.39	0.32	-0.5	0.1	0.5	0.6	1
	Placebo → 5 mg BID	61	0.39	0.32	-0.3	0.1	0.6	0.6	0.8
	Placebo → 10 mg BID	61	0.45	0.3	-0.3	0.5	0.6	0.7	0.8
Month 3	Tofacitinib 5 mg BID	237	0.6	0.25	-0.3	0.5	0.6	0.7	1
	Tofacitinib 10 mg BID	227	0.66	0.23	-0.2	0.5	0.7	0.8	1
	Placebo → 5 mg BID	55	0.47	0.33	-0.2	0.2	0.6	0.7	1
	Placebo → 10 mg BID	53	0.54	0.29	-0.3	0.5	0.6	0.7	1
Month 6	Tofacitinib 5 mg BID	227	0.63	0.23	-0.2	0.5	0.6	0.8	1
	Tofacitinib 10 mg BID	214	0.68	0.22	-0.1	0.6	0.7	0.8	1
	Placebo → 5 mg BID	54	0.58	0.29	-0.1	0.5	0.6	0.8	1
	Placebo → 10 mg BID	49	0.65	0.21	0	0.5	0.7	0.8	1

BID = twice daily; EuroQol = European quality of life; EQ-5D = A self-report questionnaire (a quality of life instrument) developed by the EuroQol group; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

Results of the RA-HCRU Questionnaire are summarized in Table 20.

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Seen any doctor/healthcare professional in past 3 months	Baseline	Tofacitinib 5 mg BID	236	1.19	0.39	1	1	1	1	2
		Tofacitinib 10 mg BID	239	1.15	0.36	1	1	1	1	2
		Placebo	119	1.17	0.38	1	1	1	1	2
	Month 3	Tofacitinib 5 mg BID	235	1.42	0.49	1	1	1	2	2
		Tofacitinib 10 mg BID	228	1.41	0.49	1	1	1	2	2
		Placebo	109	1.39	0.49	1	1	1	2	2
Total visits to doctor/healthcare professional in past 3 months	Baseline	Tofacitinib 5 mg BID	193	4.38	4.5	1	2	3	5	31
		Tofacitinib 10 mg BID	204	3.85	4.07	1	2	3	5	32
		Placebo	102	3.56	2.73	1	1	3	5	12
	Month 3	Tofacitinib 5 mg BID	141	3.6	2.4	0	2	3	5	12
		Tofacitinib 10 mg BID	137	3.64	3.44	0	1	3	4	27
		Placebo	66	4	3.12	1	2	3	5	19
RA related	Baseline	Tofacitinib 5 mg BID	192	1.26	0.81	0	1	1	1	6
		Tofacitinib 10 mg BID	205	1.18	0.85	0	1	1	1	6
		Placebo	100	1.33	0.89	0	1	1	2	7
	Month 3	Tofacitinib 5 mg BID	142	0.83	0.67	0	0	1	1	4
		Tofacitinib 10 mg BID	138	0.81	0.81	0	0	1	1	5
		Placebo	66	0.92	0.81	0	0	1	1	4
Treated in a hospital emergency room in past 3 months	Baseline	Tofacitinib 5 mg BID	236	1.94	0.23	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.92	0.26	1	2	2	2	2
		Placebo	120	1.92	0.28	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	236	1.94	0.24	1	2	2	2	2
		Tofacitinib 10 mg BID	229	1.94	0.24	1	2	2	2	2
		Placebo	109	1.93	0.26	1	2	2	2	2
Number of visits to hospital ER in past 3 months	Baseline	Tofacitinib 5 mg BID	13	1.15	0.38	1	1	1	1	2
		Tofacitinib 10 mg BID	18	1.61	1.29	1	1	1	2	5
		Placebo	10	1.4	0.7	1	1	1	2	3
	Month 3	Tofacitinib 5 mg BID	14	1.21	0.8	1	1	1	1	4
		Tofacitinib 10 mg BID	14	1.29	0.47	1	1	1	2	2
		Placebo	8	1.5	0.76	1	1	1	2	3
Admitted for overnight stay	Baseline	Tofacitinib 5 mg BID	13	0.15	0.55	0	0	0	0	2
		Tofacitinib 10 mg BID	18	0.17	0.51	0	0	0	0	2
		Placebo	10	0.2	0.63	0	0	0	0	2
	Month 3	Tofacitinib 5 mg BID	14	0.29	0.61	0	0	0	0	2
		Tofacitinib 10 mg BID	14	0.43	0.65	0	0	0	1	2
		Placebo	8	0.5	0.93	0	0	0	1	2

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
ER visit RA related	Baseline	Tofacitinib 5 mg BID	12	0.75	0.75	0	0	1	1	2
		Tofacitinib 10 mg BID	18	0.5	0.62	0	0	0	1	2
		Placebo	10	0.8	0.92	0	0	0.5	2	2
	Month 3	Tofacitinib 5 mg BID	14	0.14	0.53	0	0	0	0	2
		Tofacitinib 10 mg BID	13	0.15	0.55	0	0	0	0	2
		Placebo	8	0.25	0.46	0	0	0	0.5	1
Hospitalized in past 3 months	Baseline	Tofacitinib 5 mg BID	236	1.94	0.24	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.92	0.27	1	2	2	2	2
		Placebo	120	1.94	0.24	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	236	1.99	0.09	1	2	2	2	2
		Tofacitinib 10 mg BID	228	1.97	0.16	1	2	2	2	2
		Placebo	109	1.98	0.13	1	2	2	2	2
Number of visits hospitalized in past 3 months	Baseline	Tofacitinib 5 mg BID	14	1.07	0.27	1	1	1	1	2
		Tofacitinib 10 mg BID	19	1.11	0.32	1	1	1	1	2
		Placebo	7	1	0	1	1	1	1	1
	Month 3	Tofacitinib 5 mg BID	2	1	0	1	1	1	1	1
		Tofacitinib 10 mg BID	6	1.17	0.41	1	1	1	1	2
		Placebo	2	1	0	1	1	1	1	1
Hospitalized length of stay	Baseline	Tofacitinib 5 mg BID	14	15.43	12.33	2	6	13	17	42
		Tofacitinib 10 mg BID	19	9.63	7.27	1	4	9	14	32
		Placebo	7	4.29	2.81	1	2	3	8	8
	Month 3	Tofacitinib 5 mg BID	2	7.5	6.36	3	3	7.5	12	12
		Tofacitinib 10 mg BID	6	6.33	7.12	1	2	3.5	8	20
		Placebo	2	12	2.83	10	10	12	14	14
Hospitalized RA related	Baseline	Tofacitinib 5 mg BID	14	1	0.55	0	1	1	1	2
		Tofacitinib 10 mg BID	19	0.84	0.6	0	0	1	1	2
		Placebo	8	0.88	0.64	0	0.5	1	1	2
	Month 3	Tofacitinib 5 mg BID	2	0.5	0.71	0	0	0.5	1	1
		Tofacitinib 10 mg BID	7	0	0	0	0	0	0	0
		Placebo	2	0	0	0	0	0	0	0
Had any outpatient surgeries in past 3 months	Baseline	Tofacitinib 5 mg BID	236	1.97	0.16	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.95	0.21	1	2	2	2	2
		Placebo	120	1.98	0.16	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	236	1.97	0.17	1	2	2	2	2
		Tofacitinib 10 mg BID	229	1.98	0.15	1	2	2	2	2
		Placebo	109	1.98	0.13	1	2	2	2	2

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Number of outpatient surgeries in past 3 months	Baseline	Tofacitinib 5 mg BID	6	1	0	1	1	1	1	1
		Tofacitinib 10 mg BID	11	1	0	1	1	1	1	1
		Placebo	2	1	0	1	1	1	1	1
	Month 3	Tofacitinib 5 mg BID	7	1.14	0.38	1	1	1	1	2
		Tofacitinib 10 mg BID	5	1.6	0.89	1	1	1	2	3
		Placebo	2	1	0	1	1	1	1	1
Outpatient surgery RA related	Baseline	Tofacitinib 5 mg BID	6	0	0	0	0	0	0	0
		Tofacitinib 10 mg BID	11	0.55	0.82	0	0	0	1	2
		Placebo	3	0	0	0	0	0	0	0
	Month 3	Tofacitinib 5 mg BID	7	0.29	0.76	0	0	0	0	2
		Tofacitinib 10 mg BID	5	0	0	0	0	0	0	0
		Placebo	2	1	1.41	0	0	1	2	2
Had any non-study diagnostic tests in past 3 months	Baseline	Tofacitinib 5 mg BID	235	1.83	0.38	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.78	0.41	1	2	2	2	2
		Placebo	120	1.83	0.37	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	236	1.87	0.33	1	2	2	2	2
		Tofacitinib 10 mg BID	228	1.88	0.32	1	2	2	2	2
		Placebo	109	1.87	0.34	1	2	2	2	2
Number of non-study diagnostic tests	Baseline	Tofacitinib 5 mg BID	39	1.69	1.22	1	1	1	2	7
		Tofacitinib 10 mg BID	51	1.94	1.22	1	1	1	3	5
		Placebo	17	1.59	1.06	1	1	1	2	5
	Month 3	Tofacitinib 5 mg BID	27	1.26	0.81	1	1	1	1	5
		Tofacitinib 10 mg BID	25	1.6	0.82	1	1	1	2	3
		Placebo	13	1.54	0.78	1	1	1	2	3
Diagnostic tests RA related	Baseline	Tofacitinib 5 mg BID	41	0.61	0.67	0	0	1	1	2
		Tofacitinib 10 mg BID	52	0.83	0.94	0	0	1	1	4
		Placebo	19	0.95	0.97	0	0	1	1	4
	Month 3	Tofacitinib 5 mg BID	30	0.13	0.35	0	0	0	0	1
		Tofacitinib 10 mg BID	26	0.15	0.37	0	0	0	0	1
		Placebo	14	0.21	0.43	0	0	0	0	1
Subject in a nursing home in past 3 months	Baseline	Tofacitinib 5 mg BID	236	1.98	0.13	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.99	0.09	1	2	2	2	2
		Placebo	120	1.99	0.09	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	236	2	0	2	2	2	2	2
		Tofacitinib 10 mg BID	229	2	0.07	1	2	2	2	2
		Placebo	109	1.99	0.1	1	2	2	2	2

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Number of days in nursing home in past 3 months	Baseline	Tofacitinib 5 mg BID	4	23.25	2.63	21	21	23	25.5	26
		Tofacitinib 10 mg BID	2	16.5	6.36	12	12	16.5	21	21
		Placebo	1	10		10	10	10	10	10
	Month 3	Tofacitinib 10 mg BID	1	2		2	2	2	2	2
		Placebo	1	10		10	10	10	10	10
Used home healthcare services in past 3 months	Baseline	Tofacitinib 5 mg BID	235	1.99	0.09	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.98	0.13	1	2	2	2	2
		Placebo	119	1.99	0.09	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	236	1.99	0.09	1	2	2	2	2
		Tofacitinib 10 mg BID	228	2	0	2	2	2	2	2
		Placebo	108	1.99	0.1	1	2	2	2	2
Home healthcare services hours per day	Baseline	Tofacitinib 5 mg BID	1	2		2	2	2	2	2
		Tofacitinib 10 mg BID	4	3.75	5.5	1	1	1	6.5	12
		Placebo	1	1		1	1	1	1	1
	Month 3	Tofacitinib 5 mg BID	2	2.5	2.12	1	1	2.5	4	4
		Placebo	1	1		1	1	1	1	1
Home healthcare services RA related	Baseline	Tofacitinib 5 mg BID	2	1.5	0.71	1	1	1.5	2	2
		Tofacitinib 10 mg BID	4	2.25	2.5	1	1	1	3.5	6
		Placebo	1	1		1	1	1	1	1
	Month 3	Tofacitinib 5 mg BID	2	0.5	0.71	0	0	0.5	1	1
		Placebo	1	0		0	0	0	0	0
Required aids/devices for daily functioning in past 3 months	Baseline	Tofacitinib 5 mg BID	236	1.84	0.37	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.87	0.34	1	2	2	2	2
		Placebo	119	1.83	0.38	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	235	1.89	0.32	1	2	2	2	2
		Tofacitinib 10 mg BID	228	1.91	0.28	1	2	2	2	2
		Placebo	109	1.87	0.34	1	2	2	2	2
Aids or devices used days	Baseline	Tofacitinib 5 mg BID	37	118.95	134.74	1	15	90	180	455
		Tofacitinib 10 mg BID	31	85.52	95.38	1	9	48	180	390
		Placebo	20	55.9	56.66	1	7	40	90	185
	Month 3	Tofacitinib 5 mg BID	27	109.93	107.85	3	15	90	170	450
		Tofacitinib 10 mg BID	20	89.5	89.98	8	19.5	90	90	360
		Placebo	14	94.86	111.05	2	10	31	180	290

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Aids or devices RA related	Baseline	Tofacitinib 5 mg BID	38	2.21	1.47	0	1	2	3	5
		Tofacitinib 10 mg BID	31	1.9	1.33	0	1	2	2	6
		Placebo	20	1.45	0.69	1	1	1	2	3
	Month 3	Tofacitinib 5 mg BID	27	1.81	1.36	0	1	1	2	6
		Tofacitinib 10 mg BID	20	1.5	0.95	0	1	1	2	4
		Placebo	14	1.93	1.21	1	1	1.5	3	5
Seen any non-medical practitioners in past 3 months	Baseline	Tofacitinib 5 mg BID	236	1.97	0.18	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.99	0.09	1	2	2	2	2
		Placebo	120	1.98	0.13	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	236	1.98	0.13	1	2	2	2	2
		Tofacitinib 10 mg BID	229	2	0.07	1	2	2	2	2
		Placebo	109	2	0	2	2	2	2	2
Non-medical practitioner visits	Baseline	Tofacitinib 5 mg BID	8	12	12.99	1	1.5	8	20	36
		Tofacitinib 10 mg BID	2	7	7.07	2	2	7	12	12
		Placebo	2	1	0	1	1	1	1	1
	Month 3	Tofacitinib 5 mg BID	4	10.75	6.99	2	6	11	15.5	19
		Tofacitinib 10 mg BID	1	7		7	7	7	7	7
Non-medical practitioner RA related	Baseline	Tofacitinib 5 mg BID	8	1.13	0.64	0	1	1	1.5	2
		Tofacitinib 10 mg BID	2	1.5	0.71	1	1	1.5	2	2
		Placebo	2	0.5	0.71	0	0	0.5	1	1
	Month 3	Tofacitinib 5 mg BID	4	0.25	0.5	0	0	0	0.5	1
		Tofacitinib 10 mg BID	1	2		2	2	2	2	2
Are you currently employed	Baseline	Tofacitinib 5 mg BID	236	1.69	0.46	1	1	2	2	2
		Tofacitinib 10 mg BID	239	1.64	0.48	1	1	2	2	2
		Placebo	120	1.64	0.48	1	1	2	2	2
	Month 3	Tofacitinib 5 mg BID	236	1.71	0.45	1	1	2	2	2
		Tofacitinib 10 mg BID	228	1.65	0.48	1	1	2	2	2
		Placebo	109	1.62	0.49	1	1	2	2	2
Hours of work per day	Baseline	Tofacitinib 5 mg BID	71	7.66	1.87	4	7	8	8	12
		Tofacitinib 10 mg BID	85	8.6	6.12	4	6	8	8	50
		Placebo	43	8.95	5.2	4	8	8	9	40
	Month 3	Tofacitinib 5 mg BID	66	8.2	7.28	2	7	8	8	65
		Tofacitinib 10 mg BID	79	7.68	2.37	2	6	8	8	16
		Placebo	41	8.85	5.34	3	8	8	8	40

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Days of work per week	Baseline	Tofacitinib 5 mg BID	72	5.08	1.04	1	5	5	6	7
		Tofacitinib 10 mg BID	84	4.92	1.17	1	5	5	5	8
		Placebo	43	5.02	0.96	2	5	5	5	7
	Month 3	Tofacitinib 5 mg BID	68	5	0.93	1	5	5	5	7
		Tofacitinib 10 mg BID	79	5.05	1.19	1	5	5	6	8
		Placebo	41	4.88	1.17	2	5	5	5	7
Feel well enough to work if job were available	Baseline	Tofacitinib 5 mg BID	111	1.86	0.35	1	2	2	2	2
		Tofacitinib 10 mg BID	90	1.83	0.37	1	2	2	2	2
		Placebo	57	1.86	0.35	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	108	1.72	0.45	1	1	2	2	2
		Tofacitinib 10 mg BID	93	1.69	0.47	1	1	2	2	2
		Placebo	50	1.86	0.35	1	2	2	2	2
Unable to work due to RA	Baseline	Tofacitinib 5 mg BID	111	1.37	0.48	1	1	1	2	2
		Tofacitinib 10 mg BID	93	1.29	0.46	1	1	1	2	2
		Placebo	59	1.41	0.5	1	1	1	2	2
	Month 3	Tofacitinib 5 mg BID	107	1.51	0.5	1	1	2	2	2
		Tofacitinib 10 mg BID	98	1.48	0.5	1	1	1	2	2
		Placebo	52	1.35	0.48	1	1	1	2	2
Lost job or retired early due to RA	Baseline	Tofacitinib 5 mg BID	110	1.61	0.49	1	1	2	2	2
		Tofacitinib 10 mg BID	92	1.55	0.5	1	1	2	2	2
		Placebo	58	1.55	0.5	1	1	2	2	2
	Month 3	Tofacitinib 5 mg BID	107	1.68	0.47	1	1	2	2	2
		Tofacitinib 10 mg BID	92	1.7	0.46	1	1	2	2	2
		Placebo	49	1.59	0.5	1	1	2	2	2
Work disabled due to RA	Baseline	Tofacitinib 5 mg BID	111	1.54	0.5	1	1	2	2	2
		Tofacitinib 10 mg BID	91	1.48	0.5	1	1	1	2	2
		Placebo	58	1.52	0.5	1	1	2	2	2
	Month 3	Tofacitinib 5 mg BID	109	1.57	0.5	1	1	2	2	2
		Tofacitinib 10 mg BID	92	1.62	0.49	1	1	2	2	2
		Placebo	49	1.47	0.5	1	1	1	2	2
I am retired	Baseline	Tofacitinib 5 mg BID	116	1.57	0.5	1	1	2	2	2
		Tofacitinib 10 mg BID	99	1.57	0.5	1	1	2	2	2
		Placebo	59	1.49	0.5	1	1	1	2	2
	Month 3	Tofacitinib 5 mg BID	115	1.52	0.5	1	1	2	2	2
		Tofacitinib 10 mg BID	107	1.51	0.5	1	1	2	2	2
		Placebo	51	1.53	0.5	1	1	2	2	2

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Sick leave in past 3 months from work due to RA	Baseline	Tofacitinib 5 mg BID	191	1.82	0.38	1	2	2	2	2
		Tofacitinib 10 mg BID	202	1.83	0.38	1	2	2	2	2
		Placebo	99	1.74	0.44	1	1	2	2	2
	Month 3	Tofacitinib 5 mg BID	180	1.93	0.26	1	2	2	2	2
		Tofacitinib 10 mg BID	183	1.91	0.29	1	2	2	2	2
		Placebo	88	1.89	0.32	1	2	2	2	2
No of days on sick leave due to RA	Baseline	Tofacitinib 5 mg BID	33	25.12	33.23	1	4	10	30	90
		Tofacitinib 10 mg BID	34	10.91	18.15	1	3	4	8	90
		Placebo	25	22.4	29.72	1	2	8	30	90
	Month 3	Tofacitinib 5 mg BID	13	15	23.59	1	4	6	20	90
		Tofacitinib 10 mg BID	17	14.82	23.32	1	2	5	20	90
		Placebo	10	19.6	27.68	3	5	7.5	15	90
Performed part time work in past 3 months due to RA	Baseline	Tofacitinib 5 mg BID	192	1.89	0.31	1	2	2	2	2
		Tofacitinib 10 mg BID	202	1.87	0.34	1	2	2	2	2
		Placebo	98	1.88	0.33	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	181	1.94	0.23	1	2	2	2	2
		Tofacitinib 10 mg BID	180	1.94	0.24	1	2	2	2	2
		Placebo	88	1.9	0.3	1	2	2	2	2
No of days performed part time work due to RA	Baseline	Tofacitinib 5 mg BID	20	15.65	22.74	0	3	6	20	90
		Tofacitinib 10 mg BID	25	20.44	26.71	1	4	7	20	90
		Placebo	12	12.42	10.57	2	4.5	7.5	20	35
	Month 3	Tofacitinib 5 mg BID	10	12.7	20.97	1	1	5	10	70
		Tofacitinib 10 mg BID	11	19.09	25.07	5	5	7	22	90
		Placebo	9	6.22	5.7	2	3	5	5	20
Average hrs of missed work per day due to RA	Baseline	Tofacitinib 5 mg BID	19	3.47	2.67	0	2	3	4	12
		Tofacitinib 10 mg BID	25	10.84	24.54	0	2	3	5	92
		Placebo	12	6.17	12.29	0	2	2.5	4	45
	Month 3	Tofacitinib 5 mg BID	10	2.2	1.55	0	1	2	4	4
		Tofacitinib 10 mg BID	9	3.67	1.41	1	3	4	5	5
		Placebo	9	9.56	19.04	0	2	3	4	60
Performed paid work in past 3 months while bothered by RA	Baseline	Tofacitinib 5 mg BID	191	1.64	0.48	1	1	2	2	2
		Tofacitinib 10 mg BID	204	1.66	0.48	1	1	2	2	2
		Placebo	99	1.62	0.49	1	1	2	2	2
	Month 3	Tofacitinib 5 mg BID	179	1.75	0.44	1	1	2	2	2
		Tofacitinib 10 mg BID	184	1.76	0.43	1	2	2	2	2
		Placebo	88	1.65	0.48	1	1	2	2	2

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
No of days performed paid work while bothered by RA	Baseline	Tofacitinib 5 mg BID	69	33.87	31.01	1	10	20	60	120
		Tofacitinib 10 mg BID	68	28.15	29.06	1	5	15	46.5	90
		Placebo	37	38.3	27.52	3	12	30	60	90
	Month 3	Tofacitinib 5 mg BID	44	21.7	26.22	2	4.5	10	30	90
		Tofacitinib 10 mg BID	44	19.39	23.1	1	5	10	27	90
		Placebo	30	26.5	27.03	1	7	15	45	90
Work performance in past 3 months on days bothered	Baseline	Tofacitinib 5 mg BID	146	5.59	3.17	0	3	6	8	10
		Tofacitinib 10 mg BID	174	5.61	6.42	0	3	5	8	80
		Placebo	79	5.41	2.94	0	3	6	8	10
	Month 3	Tofacitinib 5 mg BID	138	3.39	2.85	0	1	3	5	10
		Tofacitinib 10 mg BID	148	3.43	2.88	0	1	3	5	10
		Placebo	75	4.57	2.94	0	3	5	7	10
Unable to complete chores in past 3 months due to RA	Baseline	Tofacitinib 5 mg BID	235	1.36	0.48	1	1	1	2	2
		Tofacitinib 10 mg BID	238	1.32	0.47	1	1	1	2	2
		Placebo	118	1.3	0.46	1	1	1	2	2
	Month 3	Tofacitinib 5 mg BID	231	1.6	0.49	1	1	2	2	2
		Tofacitinib 10 mg BID	227	1.63	0.49	1	1	2	2	2
		Placebo	107	1.39	0.49	1	1	1	2	2
Chores carried out by housekeeper due to RA	Baseline	Tofacitinib 5 mg BID	235	1.86	0.35	1	2	2	2	2
		Tofacitinib 10 mg BID	239	1.82	0.39	1	2	2	2	2
		Placebo	119	1.81	0.4	1	2	2	2	2
	Month 3	Tofacitinib 5 mg BID	235	1.88	0.32	1	2	2	2	2
		Tofacitinib 10 mg BID	229	1.92	0.28	1	2	2	2	2
		Placebo	108	1.79	0.41	1	2	2	2	2
Hours per day chores done by housekeeper	Baseline	Tofacitinib 5 mg BID	33	5.64	4.06	2	3	4	7	20
		Tofacitinib 10 mg BID	43	4.67	2.07	1	3	5	6	11
		Placebo	22	5.86	3.06	1	4	6	8	12
	Month 3	Tofacitinib 5 mg BID	27	5.74	4.7	1	3	4	8	24
		Tofacitinib 10 mg BID	19	5.21	4.89	2	3	4	6	24
		Placebo	23	5.91	4.75	2	3	5	8	24
No of days chores done by housekeeper	Baseline	Tofacitinib 5 mg BID	33	17.3	24.67	1	4	10	20	91
		Tofacitinib 10 mg BID	43	16.63	25.99	1	2	6	12	90
		Placebo	22	14.55	22.32	1	3	5.5	14	90
	Month 3	Tofacitinib 5 mg BID	26	7.73	8.43	1	2	4	12	30
		Tofacitinib 10 mg BID	19	6.32	5.73	1	2	6	8	20
		Placebo	23	18.13	25.19	1	3	6	30	90

Table 20. Descriptive Statistics of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) per Visit, Comparisons to Placebo

		Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Chores carried out by family/friends due to RA	Baseline	Tofacitinib 5 mg BID	235	1.4	0.49	1	1	1	2	2
		Tofacitinib 10 mg BID	239	1.44	0.5	1	1	1	2	2
		Placebo	118	1.29	0.45	1	1	1	2	2
	Month 3	Tofacitinib 5 mg BID	234	1.65	0.48	1	1	2	2	2
		Tofacitinib 10 mg BID	229	1.64	0.48	1	1	2	2	2
		Placebo	108	1.49	0.5	1	1	1	2	2
Hours per day chores done by family/friends	Baseline	Tofacitinib 5 mg BID	139	3.99	4.02	1	2	3	4	24
		Tofacitinib 10 mg BID	131	3.32	2.89	0	2	3	4	24
		Placebo	82	4.85	6.88	1	2	3	5	48
	Month 3	Tofacitinib 5 mg BID	79	3.09	1.96	1	2	2	4	12
		Tofacitinib 10 mg BID	82	3.82	6.91	1	2	2	4	60
		Placebo	54	3.69	3.82	1	2	2	4	24
No of days chores done by family/friends	Baseline	Tofacitinib 5 mg BID	139	29.54	31.72	1	6	15	45	92
		Tofacitinib 10 mg BID	131	27.85	34.8	1	5	10	40	200
		Placebo	84	22.12	27.36	1	5	10	26	90
	Month 3	Tofacitinib 5 mg BID	81	25.72	31.12	1	5	10	30	90
		Tofacitinib 10 mg BID	82	27.29	33.02	1	4	10	35	120
		Placebo	55	27	30.37	1	5	12	40	90

BID = twice daily; HCRU = healthcare resource utilization; Max = maximum; Min = minimum; N = number of subjects; Q = question; RA = rheumatoid arthritis; SD = standard deviation.

Work Limitations Questionnaire: There were no statistically significant differences between treatment with tofacitinib and placebo at Month 3 for any of the subscales of the Work Limitations Questionnaire. There were, however, statistically significant LS mean improvements over time within the tofacitinib 5 mg BID and tofacitinib 10 mg BID sequences at Months 3 and 6 for the Time Management Scale, Mental/Interpersonal Demands Scale, Output Demands Scale, and Work Loss Index (Table 21).

Table 21. Descriptive Statistics of Work Limitation Questionnaire

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Time Management									
Baseline	Tofacitinib 5 mg BID	118	50.84	26.52	0	30	50	75	100
	Tofacitinib 10 mg BID	119	48.98	27.17	0	30	50	70	100
	Placebo → 5 mg BID	28	46.06	25.64	0	27.5	41.9	63.8	100
	Placebo → 10 mg BID	34	50.96	27.25	0	35	47.5	68.8	100
Month 3	Tofacitinib 5 mg BID	94	37.65	29.03	0	10	35	60	100
	Tofacitinib 10 mg BID	89	34.63	29.91	0	10	30	55	100
	Placebo → 5 mg BID	21	45.36	22.78	5	25	45	60	87.5
	Placebo → 10 mg BID	24	37.8	23.61	0	20	35	52.5	95
Month 6	Tofacitinib 5 mg BID	80	36.27	29.22	0	12.5	25	55	100
	Tofacitinib 10 mg BID	81	30.42	28.39	0	10	25	50	100
	Placebo → 5 mg BID	25	34.4	25.59	0	10	35	55	75
	Placebo → 10 mg BID	23	39.86	30.64	0	10	30	65	100
Physical Demands									
Baseline	Tofacitinib 5 mg BID	117	51.84	22.44	0	33.3	50	66.7	100
	Tofacitinib 10 mg BID	119	49.24	27.51	0	25	50	66.7	100
	Placebo → 5 mg BID	30	53.35	22.63	15	40	52.1	70.8	91.7
	Placebo → 10 mg BID	36	49.42	27.58	0	29.2	47.9	65	100
Month 3	Tofacitinib 5 mg BID	98	51.89	29.32	0	29.2	55.2	75	100
	Tofacitinib 10 mg BID	90	46.48	30.71	0	25	44.4	70	100
	Placebo → 5 mg BID	21	47.46	24.05	4.2	25	50	62.5	87.5
	Placebo → 10 mg BID	25	46.08	25.86	4.2	25	41.7	70.8	87.5
Month 6	Tofacitinib 5 mg BID	85	45.37	29.86	0	20.8	45.8	66.7	100
	Tofacitinib 10 mg BID	81	45.17	34.14	0	12.5	43.8	75	100
	Placebo → 5 mg BID	26	57.16	27.63	5	31.3	58.3	75	100
	Placebo → 10 mg BID	25	50.33	31.74	0	25	55	70.8	100
Mental Demands									
Baseline	Tofacitinib 5 mg BID	119	31.04	24.05	0	11.1	27.8	50	93.8
	Tofacitinib 10 mg BID	120	36.14	28.41	0	8.3	34.7	56.9	100
	Placebo → 5 mg BID	30	36.99	25.29	0	14.3	39.8	58.3	88.9
	Placebo → 10 mg BID	36	40.11	29.94	0	14.3	36.1	65.3	100
Month 3	Tofacitinib 5 mg BID	100	24.64	27.02	0	2.8	19.7	36.1	100
	Tofacitinib 10 mg BID	93	24.62	29.12	0	0	16.7	36.1	100
	Placebo → 5 mg BID	20	32.6	29.72	0	9.7	28	43.1	94.4
	Placebo → 10 mg BID	27	25.53	23.78	0	2.8	19.4	44.4	75
Month 6	Tofacitinib 5 mg BID	81	22.66	25.71	0	2.8	11.1	33.3	100
	Tofacitinib 10 mg BID	82	21.61	29.09	0	0	8.3	25	97.2
	Placebo → 5 mg BID	25	25.84	24.54	0	5.6	19.4	41.7	81.3
	Placebo → 10 mg BID	26	29.77	29.64	0	8.3	20.8	47.2	100
Output Demands									
Baseline	Tofacitinib 5 mg BID	114	39.7	24.76	0	25	40	55	95
	Tofacitinib 10 mg BID	116	44.85	30.23	0	25	40	70	100
	Placebo → 5 mg BID	29	42.7	28.98	5	25	40	60	100
	Placebo → 10 mg BID	34	47.51	27.58	0	25	46.9	70	100
Month 3	Tofacitinib 5 mg BID	96	27.03	24.44	0	5	25	45	100
	Tofacitinib 10 mg BID	90	28.31	29.37	0	0	25	45	100
	Placebo → 5 mg BID	21	37.74	24.6	0	20	35	60	90
	Placebo → 10 mg BID	24	29.62	21.87	0	11.3	32.3	45	75
Month 6	Tofacitinib 5 mg BID	80	25.04	24.29	0	0	20	40	90
	Tofacitinib 10 mg BID	81	26.3	29.4	0	0	20	40	100
	Placebo → 5 mg BID	26	28.65	23.9	0	10	25	45	85

Table 21. Descriptive Statistics of Work Limitation Questionnaire

	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
	Placebo → 10 mg BID	23	35.05	29.32	0	5	30	58.3	100
Work Loss Index									
Baseline	Tofacitinib 5 mg BID	124	10.82	5.21	0	7.3	10.4	14.2	23.2
	Tofacitinib 10 mg BID	122	11.95	6.2	0	7.2	11.6	16.7	26
	Placebo → 5 mg BID	30	11.91	5.52	3.5	7.4	11.1	14.5	23.2
	Placebo → 10 mg BID	37	12.35	6.3	1.9	7.5	11.7	17.1	25
Month 3	Tofacitinib 5 mg BID	102	8.48	5.6	0	4	8.3	11.2	22.9
	Tofacitinib 10 mg BID	98	8.05	6.63	0	3.3	6.4	11.1	26
	Placebo → 5 mg BID	22	10.38	5.77	0.5	6.3	9.3	14.7	22.1
	Placebo → 10 mg BID	27	8.4	5.51	0	4.1	8.6	12.6	19.7
Month 6	Tofacitinib 5 mg BID	85	7.85	5.64	0	3.8	6.6	10.2	23.6
	Tofacitinib 10 mg BID	85	7.6	6.49	0	3.6	5.5	10	24.9
	Placebo → 5 mg BID	26	9.07	5.22	0.9	5.2	9.1	12	21.2
	Placebo → 10 mg BID	27	9.23	6.26	0	4.1	9	12.8	25

BID = twice daily; Max = maximum; Min = minimum; N = number of subjects; Q = question; SD = standard deviation.

Safety Results:

All-causality AEs (including treatment-related, as judged by the Investigator), summarized by treatment group, are presented in Table 22.

Table 22. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in >4% of Subjects

System Organ Class	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Placebo		
Preferred Term	n[a] (%)	n1[b]	n2[c]	n[a] (%)	n1[b]	n2[c]	n[a] (%)	n1[b]	n2[c]
Number (%) of subjects:									
Evaluable for AEs	243			245			122		
With AEs	88 (36.2)			97 (39.6)			49 (40.2)		
Blood and lymphatic system disorders	7 (2.9)	7	5	11 (4.5)	12	6	4 (3.3)	4	3
Anaemia	7 (2.9)	7	5	11 (4.5)	12	6	4 (3.3)	4	3
Gastrointestinal disorders	27 (11.1)	33	19	25 (10.2)	31	15	14 (11.5)	15	7
Diarrhoea	12 (4.9)	12	6	12 (4.9)	13	3	6 (4.9)	6	2
Dyspepsia	8 (3.3)	10	8	6 (2.4)	7	5	5 (4.1)	5	1
Nausea	9 (3.7)	11	5	11 (4.5)	11	7	4 (3.3)	4	4
General disorders and administration site conditions	8 (3.3)	8	3	9 (3.7)	10	3	6 (4.9)	6	0
Oedema peripheral	8 (3.3)	8	3	9 (3.7)	10	3	6 (4.9)	6	0
Infections and infestations	35 (14.4)	42	16	43 (17.6)	54	20	24 (19.7)	27	8
Influenza	6 (2.5)	7	2	7 (2.9)	7	3	7 (5.7)	8	2
Nasopharyngitis	6 (2.5)	6	3	10 (4.1)	11	3	2 (1.6)	2	0
Upper respiratory tract infection	19 (7.8)	24	9	13 (5.3)	15	7	10 (8.2)	11	5
Urinary tract infection	5 (2.1)	5	2	18 (7.3)	21	7	6 (4.9)	6	1
Investigations	5 (2.1)	5	4	12 (4.9)	12	12	4 (3.3)	4	3
Blood creatine phosphokinase increased	5 (2.1)	5	4	12 (4.9)	12	12	4 (3.3)	4	3
Musculoskeletal and connective tissue disorders	11 (4.5)	13	2	16 (6.5)	17	0	8 (6.6)	14	2
Arthralgia	5 (2.1)	7	1	5 (2.0)	5	0	5 (4.1)	11	2
Back pain	6 (2.5)	6	1	12 (4.9)	12	0	3 (2.5)	3	0
Nervous system disorders	21 (8.6)	23	12	14 (5.7)	17	10	6 (4.9)	8	5
Headache	21 (8.6)	23	12	14 (5.7)	17	10	6 (4.9)	8	5
Vascular disorders	5 (2.1)	5	1	12 (4.9)	12	6	5 (4.1)	5	2
Hypertension	5 (2.1)	5	1	12 (4.9)	12	6	5 (4.1)	5	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 (version 13.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

a. The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
b. The number of occurrences of treatment emergent all causalities adverse events.
c. The number of occurrences of treatment emergent causally related to treatment adverse events.

All-causality SAEs (including treatment-related, as judged by the Investigator), summarized by treatment group, are presented in Table 23.

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Placebo		
	n[a] (%)	n1[b]	n2[c]	n[a] (%)	n1[b]	n2[c]	n[a] (%)	n1[b]	n2[c]
Number (%) of subjects:									
Evaluable for AEs	243			245			122		
With AEs	6 (2.5)			10 (4.1)			6 (4.9)		
Blood and lymphatic system disorders	1 (0.4)	1	1	0	0	0	0	0	0
Thrombocytopenia	1 (0.4)	1	1	0	0	0	0	0	0
Cardiac disorders	0	0	0	3 (1.2)	6	0	0	0	0
Atrial fibrillation	0	0	0	1 (0.4)	1	0	0	0	0
Cardiac arrest	0	0	0	1 (0.4)	1	0	0	0	0
Cardiac failure congestive	0	0	0	2 (0.8)	3	0	0	0	0
Myocardial infarction	0	0	0	1 (0.4)	1	0	0	0	0
Ear and labyrinth disorders	0	0	0	1 (0.4)	1	0	0	0	0
Vertigo	0	0	0	1 (0.4)	1	0	0	0	0
Gastrointestinal disorders	0	0	0	1 (0.4)	1	0	0	0	0
Vomiting	0	0	0	1 (0.4)	1	0	0	0	0
General disorders and administration site conditions	0	0	0	1 (0.4)	2	0	0	0	0
Asthenia	0	0	0	1 (0.4)	1	0	0	0	0
Multi-organ failure	0	0	0	1 (0.4)	1	0	0	0	0
Hepatobiliary disorders	0	0	0	1 (0.4)	1	0	0	0	0
Cholecystitis acute	0	0	0	1 (0.4)	1	0	0	0	0
Infections and infestations	1 (0.4)	1	0	4 (1.6)	4	2	1 (0.8)	1	0
Bronchitis	0	0	0	1 (0.4)	1	0	0	0	0
Cellulitis	1 (0.4)	1	0	0	0	0	1 (0.8)	1	0
Liver abscess	0	0	0	1 (0.4)	1	1	0	0	0
Pyelonephritis	0	0	0	1 (0.4)	1	0	0	0	0
Tuberculous pleurisy	0	0	0	1 (0.4)	1	1	0	0	0
Injury, poisoning and procedural complications	2 (0.8)	3	0	0	0	0	0	0	0
Humerus fracture	1 (0.4)	1	0	0	0	0	0	0	0
Lower limb fracture	1 (0.4)	1	0	0	0	0	0	0	0
Patella fracture	1 (0.4)	1	0	0	0	0	0	0	0
Metabolism and nutrition disorders	1 (0.4)	1	0	3 (1.2)	3	0	0	0	0
Diabetes mellitus	0	0	0	1 (0.4)	1	0	0	0	0
Hyperkalaemia	0	0	0	1 (0.4)	1	0	0	0	0
Hypoglycaemia	1 (0.4)	1	0	0	0	0	0	0	0
Hyponatraemia	0	0	0	1 (0.4)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	1 (0.8)	1	0
Rheumatoid arthritis	0	0	0	0	0	0	1 (0.8)	1	0

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Placebo		
	n[a] (%)	n1[b]	n2[c]	n[a] (%)	n1[b]	n2[c]	n[a] (%)	n1[b]	n2[c]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	1 (0.4)	1	0	1 (0.8)	1	0
Non-small cell lung cancer	0	0	0	1 (0.4)	1	0	0	0	0
Uterine leiomyoma	0	0	0	0	0	0	1 (0.8)	1	0
Nervous system disorders	0	0	0	0	0	0	2 (1.6)	2	0
Grand mal convulsion	0	0	0	0	0	0	1 (0.8)	1	0
Transient ischaemic attack	0	0	0	0	0	0	1 (0.8)	1	0
Reproductive system and breast disorders	0	0	0	0	0	0	1 (0.8)	1	0
Uterine polyp	0	0	0	0	0	0	1 (0.8)	1	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1	0	3 (1.2)	3	0	2 (1.6)	2	0
Chronic obstructive pulmonary disease	1 (0.4)	1	0	2 (0.8)	2	0	0	0	0
Pulmonary embolism	0	0	0	0	0	0	1 (0.8)	1	0
Pulmonary fibrosis	0	0	0	1 (0.4)	1	0	0	0	0
Sleep apnoea syndrome	0	0	0	0	0	0	1 (0.8)	1	0
Surgical and medical procedures	0	0	0	1 (0.4)	2	0	0	0	0
Abdominoplasty	0	0	0	1 (0.4)	1	0	0	0	0
Breast prosthesis implantation	0	0	0	1 (0.4)	1	0	0	0	0
Vascular disorders	0	0	0	0	0	0	1 (0.8)	1	0
Deep vein thrombosis	0	0	0	0	0	0	1 (0.8)	1	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 (version 13.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

a. The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
b. The number of occurrences of treatment emergent all causalities adverse events.
c. The number of occurrences of treatment emergent causally related to treatment adverse events.

Of the 17 subjects who discontinued the study due to AEs, 12 discontinued due to AEs considered related to study drug (9 during treatment with tofacitinib and 3 during treatment with placebo) (Table 24).

Table 24. Discontinuations Due to Treatment-Emergent Adverse Events

S.No	System Organ Class	Preferred Term	Severity/Outcome	Causality
Tofacitinib 5 mg BID				
1	Eye disorders	Dry eye	Mild/still present	Study drug
	Gastrointestinal disorders	Dry mouth	Mild/still present	Study drug
	Nervous system disorders	Neuropathy peripheral	Mild/still present	Disease under study
	Respiratory, thoracic, and mediastinal disorders	Dry throat	Mild/still present	Study drug
	Skin and subcutaneous tissue disorders	Alopecia	Mild/still present	Disease under study
2	Hepatobiliary disorders	Hepatotoxicity	Moderate/still present	Study drug
3	Blood and lymphatic system disorders	Thrombocytopenia[a]	Severe/still present	Study drug
Tofacitinib 10 mg BID				
4	Infections and infestations	Pneumonia	Moderate/resolved	Other illness-bacterial infection
5	Metabolism and nutrition disorders	Diabetes mellitus[a]	Severe/still present	Other illness-increased diabetes secondary to other illnesses
	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Non-small cell lung cancer[a]	Severe/still present	Other illness-pre-existing disease process
	Respiratory, thoracic and mediastinal disorders	Pulmonary fibrosis[a]	Severe/still present	Other illness-pulmonary fibrosis
6	Infections and infestations	Tuberculous pleurisy[a]	Severe/still present	Study drug
7	Gastrointestinal disorders	Constipation	Moderate/resolved	Study drug
8	Infections and infestations	Liver abscess[a]	Severe/resolved	Study drug
9	Blood and lymphatic system disorders	Anemia	Moderate/still present	Study drug
10[b]	Cardiac disorders	Cardiac arrest	Severe/resolved	Other illness-diarrhea
	Cardiac disorders	Cardiac failure congestive	Moderate/still present	Disease under study
	Gastrointestinal disorders	Diarrhea	Moderate/resolved	Other illness-probable viral infection
	General disorders and administration site conditions	Asthenia	Severe/still present	Other illness-diarrhea
	General disorders and administration site conditions	Multi-organ failure	Severe/still present	Other illness-diarrhea
	Metabolism and nutrition disorders	Dehydration	Severe/still present	Other illness-diarrhea
	Metabolism and nutrition disorders	Hyperkalemia	Severe/resolved	Other illness-diarrhea
	Renal and urinary disorders	Renal failure	Severe/still present	Other illness-diarrhea
11	Infections and infestations	Herpes zoster	Moderate/resolved	Study drug
12	Gastrointestinal disorders	Gastrointestinal hemorrhage	Moderate/resolved	Disease under study
13	Gastrointestinal disorders	Nausea	Moderate/still present	Study drug
Placebo Tofacitinib 5 mg BID				
14	Gastrointestinal disorders	Abdominal discomfort	Moderate/resolved	Study drug
15	Musculoskeletal and connective tissue disorders	Rheumatoid arthritis[c]	Severe/resolved	Disease under study
16	Investigations	Transaminases increased	Mild/resolved	Study drug
Placebo Tofacitinib 10 mg BID				
17	Gastrointestinal disorders	Glossodynia	Moderate/resolved	Study drug
18	Investigations	Hepatic enzyme increased	Moderate/resolved	Concomitant treatment-isoniazide, nimesulide

BID = twice daily; S.No = serial number.

a. Subject had not advanced from treatment with placebo to treatment with tofacitinib at the time of the onset of the event.
b. This subject's study status was recorded as subject died.
c. Serious adverse event, according to Investigator assessment.

Deaths: One subject a 79 year old female (tofacitinib 10 mg sequence) had an onset of diarrhea on Day 102; the Investigator considered the diarrhea as not related to study drug. Study drug was stopped on Day 102 due to this event. This subject died on Day 107 of treatment due to cardiac arrest and hyperkalemia; the Investigator considered these events as not related to study drug, but related to other illness (ie, diarrhea).

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 3.

- 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 2 weeks.

- Treatment with tofacitinib 5 mg BID or 10 mg BID did not result in statistically significantly greater rates of DAS28 <2.6 vs placebo; however, numerical improvements over placebo were observed.

- Subjects who received placebo for 3 months and then advanced to tofacitinib treatment (5 mg or 10 mg BID) for 3 months showed improvement 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 3.

- In general, treatment with tofacitinib (5 or 10 mg BID) resulted in improvements compared with placebo with sustained responses through Month 6 in self-reported measures of sleep (MOS-SS) and health status (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.

- Efficacy responses were sustained in the tofacitinib 5 and 10 mg BID sequences through Month 6.

- The most frequent MedDRA SOC of AEs was infections and infestations, and the frequencies were similar among treatments.

- The frequency of SAEs, including serious infections, was low.

- One subject (tofacitinib 10 mg sequence) died due to cardiac arrest and hyperkalemia.

- Changes in laboratory parameters were observed for tofacitinib 5 mg and 10 mg relative to placebo, including decreases in neutrophil counts, increases in HDL and LDL levels, and changes in hemoglobin levels.

- CK elevations were reported as AEs with tofacitinib 5 mg and 10 mg; the clinical significance of these elevations is unknown.