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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Xeljanz® / Tofacitinib

PROTOCOL NO.: A3921019

PROTOCOL TITLE:

A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Compare 3 Dose Levels of CP-690,550 Versus Placebo, Administered Orally Twice Daily (BID) for 6 Weeks, in the Treatment of the Signs and Symptoms of Subjects With Active Rheumatoid Arthritis

Study Centers:

Fifty-three (53) centers took part in the study and randomized subjects; 19 in the United States, 7 in Germany, 5 each in Mexico and Spain, 4 each in Brazil, Canada, and Slovakia, 3 in Italy and 1 each in Belgium and Austria.

Study Initiation and Final Completion Dates:

03 January 2005 to 22 June 2006

Phase of Development:

Phase 2

Study Objectives:

Primary Objective: To compare the efficacy of 3 dose levels of oral tofacitinib monotherapy (5 mg, 15 mg, and 30 mg BID[twice a day]) versus placebo, administered over 6 weeks, for the treatment of the signs and symptoms of subjects with active rheumatoid arthritis (RA).

Secondary Objectives:

- To evaluate the safety and tolerability over 12 weeks of tofacitinib administered for 6 weeks, plus 6 weeks post-dosing follow-up, to subjects with active RA;
- To evaluate the pharmacokinetics of tofacitinib and its correlation with clinical responses and with biomarkers of inflammation and immunosuppression;
- To evaluate health status and functional status.

METHODS

Study Design:

This was a Phase 2A, randomized, double-blind, placebo-controlled, parallel-group study in subjects with RA. After screening, eligible subjects were randomized in a 1:1:1:1 ratio to receive 1 of 3 doses of tofacitinib (dose levels of 5, 15, or 30 mg BID) or placebo. Subjects received study treatment as outpatients. Subjects returned to the study site for the Baseline Visit on Day 0 (the day of first dose of study medication), and at the End of Weeks 1, 2, 4, and 6 (end-of-treatment/early termination [ET]). A Follow-Up evaluation was conducted at Weeks 8 and 12 for subjects who completed 6 weeks of treatment. The duration of study was 12 weeks, with a 6-week Follow-Up period. The study plan is presented in Table 1.

Table 1. Timetable of Study Procedures/Evaluations

Schedule of Events[a]	Screening 1	Screening 2	Baseline	Week Visits			End-of-Treatment	Follow-Up	
	Day -28	Day -25	Day 0	1	2	4	Week 6/ET[b]	Week 8	Week 12
Informed consent	X								
Rheumatoid arthritis (RA) diagnosis	X								
Tender/painful joint count, swollen joint count, morning stiffness	X								
Physical examination (includes complete and targeted)	X		X		X	X	X	X	X
Medical history and current medication	X								
History of alcohol and drug abuse	X								
Mantoux PPD intradermal injection	X								
Mantoux PPD induration evaluation		X							
Chest x-ray		X							
American College of Rheumatology (ACR) assessments			X	X	X	X	X	X	
Vital signs and oral or tympanic temperature	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)		X		X	X	X	X		
Hematology tests (includes ESR at Screening visit only)	X		X	X	X	X	X	X	X
Stool examination for parasites[c] (Brazil only)	X								
Safety chemistry Panel 1	X		X				X		
Safety chemistry Panel 2				X	X	X		X	X
Rheumatoid factor		X							
C-reactive protein	X		X	X	X	X	X	X	
Serum pregnancy test		X						X	X
Follicle-stimulating hormone (FSH) (optional for post menopausal women)		X							
Urinalysis tests (includes drug screening at Screening 1 visit)	X		X	X	X	X	X	X	X
Urine pregnancy test	X		X	X	X	X	X		
Serology tests[c]		X							
Polymerase chain reaction (PCR): blood Epstein-Barr Virus (EBV) DNA		X	X	X	X	X	X	X	X
Fluorescence-activated cell sorting (FACS) analysis			X	X	X		X	X	X
Biomarkers gene expression (mRNA)			X[d]	X	X		X[d]	X	X
Pre dose pharmacokinetic (PK) sample (0 h)			X	X	X		X		
Postdose PK sample (1-3 h)			X	X	X		X		
Postdose PK sample (4-5 h)			X				X		
Retained urine and serum biomarker sample			X	X	X		X	X	X
Dosing			X	X	X	X	X		

Table 1. Timetable of Study Procedures/Evaluations

Schedule of Events[a]	Screening 1	Screening 2	Baseline	Week Visits			End-of-Treatment	Follow-Up	
	Day -28	Day -25	Day 0	1	2	4	Week 6/ET[b]	Week 8	Week 12
Adverse event (AE) assessment			X	X	X	X	X	X	X
Concomitant medication			X	X	X	X	X	X	X
SF-36			X				X		X
Drug dispensing			X		X	X			
Drug accountability					X	X	X		

DNA = deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; ET = early termination; HIV = human immunodeficiency virus; mRNA = messenger ribonucleic acid; PPD = purified derivative (of tuberculin).

a. Screening 1 (Day -28) visit to occur between 14-28 days prior to Baseline visit (Day 0). Screening 2 (Day -25) visit to occur 48-72 hours after Screening 1 visit. Visit window ±3 days.

b. All end-of-treatment procedures to be performed for any subject terminating early (ET visit).

c. Brazil only requires strongyloidiasis serology and stool testing; Canada only requires HIV serology during Screening 2 (Day -25).

d. mRNA samples to be taken at both pre and postdose on the Day 0 and Week 6 (end-of-treatment/ET) visits.

Number of Subjects (Planned and Analyzed):

Planned enrolment was 252 subjects. A total of 264 subjects were enrolled, treated and analyzed for safety, efficacy and pharmacokinetics.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male or female subjects ≥18 years of age with a diagnosis of RA (based upon the American College of Rheumatology [ACR] criteria) and continuing active disease, had a history of inadequate response to methotrexate, etanercept, infliximab, or adalimumab; had discontinued all disease-modifying anti-rheumatic drugs (DMARD) and immunosuppressive/immunomodulatory therapy for at least 4 weeks prior to the first dose of study treatment.

Main Exclusion Criteria: Subjects receiving parenteral or intra-articular corticosteroid injections and other DMARDs or biologic-response modifiers were excluded from the study.

Study Treatment:

Subjects were randomized to receive tofacitinib (5, 15, or 30 mg) or placebo tablets administered (with or without food) orally BID for 6 weeks.

Efficacy, Pharamcokinatic and Pharmacodynamic Endpoints:

Primary Endpoint: The 20% improvement in disease activity (ACR 20) responder rate at the Week 6 Visit.

Secondary Endpoints:

- ACR 20 responder rate at Week 1, 2, 4 and 8 Visits.
- The 50% improvement in disease activity (ACR 50) responder rate at Week 1, 2, 4, 6 and 8 Visits.
- The 70% improvement in disease activity (ACR 70) responder rate at Week 1, 2, 4, 6 and 8 Visits.
- Area under the ACR- n curve at Week 1, 2, 4, 6 and 8 Visits.
- Actual and change from Baseline of the 7 individual components of the ACR 20, 50, and 70 response criteria at Week 1, 2, 4, 6 and 8 Visits.
- Actual and change from Baseline in disease activity, assessed as the "Disease Activity Score (DAS) using C-Reactive Protein (CRP)" (DAS 28-3[CRP]) and the categorization of Disease Activity based on DAS at Week 1, 2, 4, 6 and 8 Visits.
- Actual and change from Baseline in the Health Assessment Questionnaire (HAQ) at Week 1, 2, 4, 6 and 8 Visits.

- Tofacitinib pharmacokinetics summarization and modelling at Week 1, 2, 4, 6 and 8 Visits.
- Tofacitinib pharmacodynamics summarization at Week 1, 2, 4, 6 and 8 Visits.
- Actual and change from Baseline in the SF-36 Health Questionnaire (version 2) (SF-36 v.2) at Baseline, Week 6 and Follow-Up Week 12.

Safety Evaluations:

Safety assessments included monitoring of adverse events (AEs), safety laboratory tests, vital signs, 12-lead electrocardiograms, and assessment of blood levels for the Epstein-Barr virus (EBV).

Statistical Methods:

Efficacy analyses were performed on 2 analysis populations: the full-analysis set (FAS), and the Week 6 set (W6S). The FAS included all subjects who were randomized to the study. The W6S was a subset of the FAS dataset as it only included subjects who had the Week 6 measurement of the primary efficacy variable.

Primary Efficacy Analyses: The primary efficacy variable was the proportion of ACR 20 responders in the FAS dataset at Week 6. A normal approximation to the difference in binomial random variables was performed in pairwise analyses (separate for each of the tofacitinib doses versus placebo) and the 1-sided p-values were generated.

Secondary Efficacy Analyses: Analyses of secondary endpoints included analyses using the FAS and W6S population dataset. Dichotomous variables (eg, ACR 20, ACR 50, etc) were analyzed at Each Visit using a normal approximation to the difference in binomial random variables in pairwise analyses (separate tables for each of the tofacitinib doses versus placebo) and the 1-sided p-values were generated.

RESULTS

Subject Disposition and Demography:

A total of 439 subjects were screened, of which 264 subjects were assigned, treated and evaluated for safety and efficacy measures. The percentage of subjects who completed the study was 95%, 87%, and 75% for the 5, 15, and 30 mg tofacitinib BID groups, respectively, compared to 74% in the placebo group. A higher number of subjects discontinued the study from the 30 mg tofacitinib BID group and placebo group (17 subjects each) than from the 5 and 15 mg tofacitinib BID groups (3 and 9 subjects, respectively). The primary reason for discontinuation was AE (7 subjects) in the 30 mg tofacitinib BID group and lack of efficacy (8 subjects) in the placebo group. Subject disposition is summarized in Table 2.

Table 2. Subject Disposition

	Tofacitinib			Placebo
	5 mg BID	15 mg BID	30 mg BID	
Screened: N=439				
Assigned to study treatment	61	69	69	65
Treated	61	69	69	65
Completed	58 (95.1)	60 (87.0)	52 (75.4)	48 (73.8)
Discontinued	3 (4.9)	9 (13.0)	17 (24.6)	17 (26.2)
Reason for discontinuation				
Related to study drug	2 (3.3)	4 (5.8)	7 (10.1)	9 (13.8)
Adverse event	1 (1.6)	3 (4.3)	5 (7.2)	1 (1.5)
Laboratory abnormality	0 (0)	0 (0)	1 (1.4)	0 (0)
Lack of efficacy	1 (1.6)	1 (1.4)	1 (1.4)	8 (12.3)
Not related to study drug	1 (1.6)	5 (7.2)	10 (14.5)	8 (12.3)
Adverse event	0 (0)	3 (4.3)	2 (2.9)	2 (3.1)
Laboratory abnormality	0 (0)	0 (0)	1 (1.4)	0 (0)
Other	1 (1.6)	1 (1.4)	3 (4.3)	3 (4.6)
Subject defaulted	0 (0)	1 (1.4)	4 (5.8)	3 (4.6)
Analyzed for efficacy (full-analysis set)	61 (100)	69 (100)	69 (100)	65 (100)
Analyzed for safety				
Adverse events	61 (100)	69 (100)	69 (100)	65 (100)
Laboratory data	61 (100)	69 (100)	69 (100)	63 (96.9)

BID = twice daily; N = total number of subjects.

Treatment groups were comparable with regard to demography and baseline characteristics. The demography characteristic details are represented in Table 3.

Table 3. Demographic Distributions of Age and Race by Sex and Treatment

	Tofacitinib									Placebo		
	5 mg BID			15 mg BID			30 mg BID					
	Male N =8	Female N =53	Total N =61	Male N =11	Female N =58	Total N =69	Male N =9	Female N =60	Total N =69	Male N =10	Female N =55	Total N =65
Age, years (%)												
18-44	3 (37.5)	17 (32.1)	20 (32.8)	2 (18.2)	21 (36.2)	23 (33.3)	0 (0)	16 (26.7)	16 (23.2)	0 (0)	18 (32.7)	18 (27.7)
45-64	4 (50.0)	36 (67.9)	40 (65.6)	6 (54.5)	26 (44.8)	32 (46.4)	5 (55.6)	38 (63.3)	43 (62.3)	9 (90.0)	31 (56.4)	40 (61.5)
≥65	1 (12.5)	0 (0)	1 (1.6)	3 (27.3)	11 (19.0)	14 (20.3)	4 (44.4)	6 (10.0)	10 (14.5)	1 (10.0)	6 (10.9)	7 (10.8)
Race												
White	6 (75.0)	36 (67.9)	42 (68.9)	9 (81.8)	38 (65.5)	47 (68.1)	8 (88.9)	36 (60.0)	44 (63.8)	9 (90.0)	38 (69.1)	47 (72.3)
Black	1 (12.5)	2 (3.8)	3 (4.9)	1 (9.1)	3 (5.2)	4 (5.8)	0 (0)	5 (8.3)	5 (7.2)	1 (10.0)	1 (1.8)	2 (3.1)
Asian	0 (0)	1 (1.9)	1 (1.6)	1 (9.1)	1 (1.7)	2 (2.9)	0 (0)	2 (3.3)	2 (2.9)	0 (0)	0 (0)	0 (0)
Hispanic	1 (12.5)	14 (26.4)	15 (24.6)	0 (0)	14 (24.1)	14 (20.3)	1 (11.1)	17 (28.3)	18 (26.1)	0 (0)	15 (27.3)	15 (23.1)
Other	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.4)	2 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)	1 (1.5)

BID = twice daily; N = number of subjects.

Efficacy, Pharmacokinetic and Pharmacodynamics Results:

All 3 tofacitinib doses were highly efficacious in the primary and secondary efficacy measures. A dose response was clearly evident in all 3 treatment groups (5, 15 and 30 mg tofacitinib), showing consistent highly significant differences from Baseline for most endpoints. For the primary endpoint (ACR 20 responder rates at the Week 6 visit), the percentage-point differences from placebo were 41%, 52%, and 48% in the 5, 15, and 30 mg tofacitinib BID groups, respectively and the results are summarized in Table 4.

Table 4. ACR 20 Response at Week 6, FAS

	N	n	%	Difference From Placebo				
				Difference	SE of Difference	80% Confidence		p-Value
						Lower	Upper	
Tofacitinib 5 mg BID	61	43	70.49	41.26	8.12	30.86	51.66	<0.0001
Tofacitinib 15 mg BID	69	56	81.16	51.93	7.35	42.52	61.34	<0.0001
Tofacitinib 30 mg BID	69	53	76.81	47.58	7.59	37.86	57.31	<0.0001
Placebo	65	19	29.23	--	--	--	--	--

ACR 20 = 20% improvement in disease activity; BID = twice daily; FAS = full-analysis set; N = total number of subjects; n = number of subjects; SE = standard error.

The ACR 20 response at Weeks 1, 2, 4 and 8 are summarized in Table 5.

Table 5. ACR 20 Response at Weeks 1, 2, 4 and 8, FAS

	N	n	%	SE	Difference From Placebo				
					Difference	SE of Difference	95% Confidence		p-Value
							Lower	Upper	
Week 1 (LOCF)									
Tofacitinib 5 mg BID	61	17	27.87	5.74	15.56	7.04	1.76	29.36	0.0271
Tofacitinib 15 mg BID	69	30	43.48	5.97	31.17	7.23	17.01	45.33	<0.0001
Tofacitinib 30 mg BID	69	39	56.52	5.97	44.21	7.23	30.05	58.38	<0.0001
Placebo	65	8	12.31	4.07	--	--	--	--	--
Week 2 (LOCF)									
Tofacitinib 5 mg BID	61	31	50.82	6.40	30.82	8.10	14.95	46.69	0.0001
Tofacitinib 15 mg BID	69	49	71.01	5.46	51.01	7.38	36.55	65.48	<0.0001
Tofacitinib 30 mg BID	69	47	68.12	5.61	48.12	7.49	33.44	62.80	<0.0001
Placebo	65	13	20.00	4.96	--	--	--	--	--
Week 4 (LOCF)									
Tofacitinib 5 mg BID	61	39	63.93	6.15	33.17	8.40	16.70	49.63	<0.0001
Tofacitinib 15 mg BID	69	52	75.36	5.19	44.59	7.73	29.45	59.73	<0.0001
Tofacitinib 30 mg BID	69	52	75.36	5.19	44.59	7.73	29.45	59.73	<0.0001
Placebo	65	20	30.77	5.72	--	--	--	--	--
Week 8									
Tofacitinib 5 mg BID	56	28	50.00	--	21.11	9.50	2.49	39.74	0.0263
Tofacitinib 15 mg BID	56	37	66.07	--	37.18	9.26	19.04	55.33	<0.0001
Tofacitinib 30 mg BID	51	36	70.59	--	41.70	9.29	23.49	59.91	<0.0001
Placebo	45	13	28.89	--	--	--	--	--	--

ACR 20= 20% improvement in disease activity; BID = twice daily; FAS = full analysis set; N = total number of subject; n = number of subjects; LOCF = last observation carried forward; SE = standard error.

All tofacitinib-treated groups had increased response rates relative to placebo at all time points. These differences were statistically significant as early as Week 1 in the 30 mg tofacitinib BID group, Week 2 in the 15 and 30 mg tofacitinib BID groups, and for all tofacitinib-treated groups at Weeks 4 and 6. The percentage-point differences from placebo

in the ACR 50 for the tofacitinib-treated groups at Weeks 1, 2, 4, 6 and 8 are listed in Table 6.

Table 6. ACR 50 Response at Weeks 1, 2, 4, 6 and 8, FAS

	N	n	%	SE	Difference From Placebo				
					Difference	SE of Difference	95% Confidence Lower	95% Confidence Upper	p-Value
Week 1 (LOCF)									
Tofacitinib 5 mg BID	61	4	6.56	3.17	3.48	3.83	-4.02	10.98	0.3629
Tofacitinib 15 mg BID	69	6	8.70	3.39	5.62	4.01	-2.24	13.48	0.1613
Tofacitinib 30 mg BID	69	13	18.84	4.71	15.76	5.17	5.63	25.90	0.0023
Placebo	65	2	3.08	2.14	--	--	--	--	--
Week 2 (LOCF)									
Tofacitinib 5 mg BID	61	6	9.84	3.81	6.76	4.37	-1.81	15.33	0.1222
Tofacitinib 15 mg BID	69	16	23.19	5.08	20.11	5.51	9.30	30.92	0.0003
Tofacitinib 30 mg BID	69	20	28.99	5.46	25.91	5.87	14.41	37.41	<0.0001
Placebo	65	2	3.08	2.14	--	--	--	--	--
Week 4 (LOCF)									
Tofacitinib 5 mg BID	61	20	32.79	6.01	26.63	6.71	13.48	39.78	<0.0001
Tofacitinib 15 mg BID	69	29	42.03	5.94	35.88	6.65	22.85	48.91	<0.0001
Tofacitinib 30 mg BID	69	29	42.03	5.94	35.88	6.65	22.85	48.91	<0.0001
Placebo	65	4	6.15	2.98	--	--	--	--	--
Week 6 (LOCF)									
Tofacitinib 5 mg BID	61	20	32.79	6.01	26.63	6.71	13.48	39.78	<0.0001
Tofacitinib 15 mg BID	69	37	53.62	6.00	47.47	6.70	34.33	60.61	<0.0001
Tofacitinib 30 mg BID	69	35	50.72	6.02	44.57	6.72	31.41	57.73	<0.0001
Placebo	65	4	6.15	2.98	--	--	--	--	--
Week 8									
Tofacitinib 5 mg BID	56	10	17.86	--	4.52	7.20	-9.59	18.64	0.5299
Tofacitinib 15 mg BID	56	17	30.36	--	17.02	7.96	1.41	32.63	0.0326
Tofacitinib 30 mg BID	51	23	45.10	--	31.76	8.62	14.88	48.65	0.0002
Placebo	45	6	13.33	--	--	--	--	--	--

ACR 50 = 50% improvement in disease activity; BID = twice daily; FAS = full-analysis set; LOCF = last observation carried forward; N = total number of subjects; n = number of subjects; SE = standard error.

The ACR 70 response at Weeks 1, 2, 4, and 6 of tofacitinib- treated groups had increased response rates relative to placebo. The differences were statistically significant by Week 2 in the 30 mg tofacitinib BID group, and for all tofacitinib-treated groups at Weeks 4 and 6 which are summarized in Table 7.

Table 7. ACR 70 Response at Weeks 1, 2, 4, 6 and 8, FAS

	N	n	%	SE	Difference From Placebo				
					Difference	SE of Difference	95% Confidence		p-Value
							Lower	Upper	
Week 1 (LOCF)									
Tofacitinib 5 mg BID	61	1	1.64	1.63	1.64	1.63	-1.55	4.83	0.3133
Tofacitinib 15 mg BID	69	3	4.35	2.46	4.35	2.46	-0.46	9.16	0.0766
Tofacitinib 30 mg BID	69	3	4.35	2.46	4.35	2.46	-0.46	9.16	0.0766
Placebo	65	0	0.00	0.00	--	--	--	--	--
Week 2 (LOCF)									
Tofacitinib 5 mg BID	61	3	4.92	2.77	3.38	3.16	-2.82	9.58	0.2851
Tofacitinib 15 mg BID	69	3	4.35	2.46	2.81	2.89	-2.86	8.48	0.3312
Tofacitinib 30 mg BID	69	7	10.14	3.63	8.61	3.94	0.88	16.33	0.0290
Placebo	65	1	1.54	1.53	--	--	--	--	--
Week 4 (LOCF)									
Tofacitinib 5 mg BID	61	6	9.84	3.81	8.30	4.11	0.25	16.35	0.0434
Tofacitinib 15 mg BID	69	12	17.39	4.56	15.85	4.81	6.42	25.28	0.0010
Tofacitinib 30 mg BID	69	15	21.74	4.97	20.20	5.19	10.02	30.38	0.0001
Placebo	65	1	1.54	1.53	--	--	--	--	--
Week 6 (LOCF)									
Tofacitinib 5 mg BID	61	8	13.11	4.32	10.04	4.82	0.58	19.49	0.0374
Tofacitinib 15 mg BID	69	15	21.74	4.97	18.66	5.41	8.06	29.26	0.0006
Tofacitinib 30 mg BID	69	19	27.54	5.38	24.46	5.79	13.11	35.80	<0.0001
Placebo	65	2	3.08	2.14	--	--	--	--	--
Week 8									
Tofacitinib 5 mg BID	56	5	8.93	--	0.04	5.70	-11.14	11.22	0.9944
Tofacitinib 15 mg BID	56	8	14.29	--	5.40	6.31	-6.98	17.77	0.3927
Tofacitinib 30 mg BID	51	14	27.45	--	18.56	7.55	3.76	33.37	0.0140
Placebo	45	4	8.89	--	--	--	--	--	--

ACR 70 = 70% improvement in disease activity;BID = twice daily; FAS = full-analysis set; LOCF = last observation carried forward; N = total number of subjects; n = number of subjects; SE = standard error.

The Mean area under the ACR-n curve showed highly significant (p<0.0001) differences (increases) from placebo for all tofacitinib-treated groups and the details were summarized in Table 8.

Table 8. Mean Area Under the ACR-n Curve, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Tofacitinib 5 mg BID	59	756.14	2.038	1351.9	4.503	751.97	1951.8	<0.0001
Tofacitinib 15 mg BID	69	1082.63	3.978	1678.4	3.548	1100	2256.7	<0.0001
Tofacitinib 30 mg BID	66	1150.93	9.810	1746.7	7.470	1160.6	2332.7	<0.0001
Placebo	62	-595.75	5.122	--	--	--	--	--

ACR-n = area under the ACRn curve; BID = twice daily; FAS = full-analysis set; N = total number of subject; SE = standard error.

The tender/painful joint count was assessed on 68 joints. The mean change from Baseline in tender-joint counts decreased (showed a greater improvement) in a dose-related manner for the 5, 15, and 30 mg tofacitinib groups. The mean change from Baseline in tender-joint counts at Weeks 1, 2, 4, 6 and 8 are represented in Table 9.

Table 9. Mean Change From Baseline in Tender-Joint Counts at Weeks 1, 2, 4, 6 and 8, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Week 1 (LOCF)								
Tofacitinib 5 mg BID	60	-7.06	1.435	-4.33	1.992	-8.24	-0.41	0.0303
Tofacitinib 15 mg BID	68	-11.70	1.338	-8.97	1.937	-12.77	-5.16	<0.0001
Tofacitinib 30 mg BID	65	-14.14	1.362	-11.40	1.949	-15.23	-7.57	<0.0001
Placebo	59	-2.74	1.417	--	--	--	--	--
Week 2 (LOCF)								
Tofacitinib 5 mg BID	57	-11.68	1.459	-6.55	2.008	-10.49	-2.60	0.0012
Tofacitinib 15 mg BID	66	-15.66	1.350	-10.53	1.944	-14.34	-6.71	<0.0001
Tofacitinib 30 mg BID	65	-15.78	1.365	-10.64	1.952	-14.48	-6.81	<0.0001
Placebo	60	-5.13	1.416	--	--	--	--	--
Week 4 (LOCF)								
Tofacitinib 5 mg BID	56	-15.23	1.465	-5.13	2.077	-9.21	-1.05	0.0138
Tofacitinib 15 mg BID	58	-18.33	1.403	-8.24	2.046	-12.26	-4.22	<0.0001
Tofacitinib 30 mg BID	58	-18.66	1.413	-8.56	2.050	-12.59	-4.54	<0.0001
Placebo	49	-10.09	1.508	--	--	--	--	--
Week 6 (LOCF)								
Tofacitinib 5 mg BID	56	-18.35	1.466	-8.66	2.070	-12.73	-4.60	<0.0001
Tofacitinib 15 mg BID	59	-19.81	1.398	-10.12	2.037	-14.12	-6.12	<0.0001
Tofacitinib 30 mg BID	52	-21.37	1.461	-11.69	2.078	-15.77	-7.60	<0.0001
Placebo	50	-9.69	1.500	--	--	--	--	--
Week 8								
Tofacitinib 5 mg BID	57	16.32	1.62	-4.05	2.34	-8.64	0.53	0.0832
Tofacitinib 15 mg BID	56	11.50	1.58	-8.87	2.32	-13.42	-4.32	0.0001
Tofacitinib 30 mg BID	52	11.21	1.62	-9.16	2.34	-13.76	-4.56	0.0001
Placebo	45	20.37	1.71	--	--	--	--	--

BID = twice daily; FAS = full-analysis set; LOCF = last observation carried forward; N = total number of subject; SE = standard error.

The Joints were assessed for swelling using scale: Present/absent/not done/not applicable (to be used for artificial joints). A total of 66 joints were assessed for swelling. Artificial joints were not assessed. The mean change from Baseline in swollen-joint counts decreased (showed a greater improvement) in a dose–related manner at all but 1 time point for the 5, 15, and 30 mg tofacitinib BID groups and the details of mean change from Baseline in swollen-joint counts at Weeks 1, 2, 4, 6 and 8 are presented in Table 10.

Table 10. Mean Change From Baseline in Swollen-Joint Counts at Weeks 1, 2, 4, 6 and 8, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Week 1 (LOCF)								
Tofacitinib 5 mg BID	60	-5.02	0.913	-1.83	1.267	-4.32	0.66	0.1487
Tofacitinib 15 mg BID	68	-8.20	0.855	-5.01	1.233	-7.44	-2.59	<0.0001
Tofacitinib 30 mg BID	65	-9.00	0.866	-5.81	1.238	-8.24	-3.38	<0.0001
Placebo	59	-3.19	0.900	--	--	--	--	--
Week 2 (LOCF)								
Tofacitinib 5 mg BID	57	-7.83	0.927	-2.60	1.276	-5.11	-0.09	0.0420
Tofacitinib 15 mg BID	66	-11.33	0.863	-6.10	1.237	-8.53	-3.67	<0.0001
Tofacitinib 30 mg BID	65	-11.11	0.868	-5.88	1.240	-8.32	-3.44	<0.0001
Placebo	60	-5.23	0.900	--	--	--	--	--
Week 4 (LOCF)								
Tofacitinib 5 mg BID	56	-11.03	0.930	-3.30	1.317	-5.89	-0.71	0.0126
Tofacitinib 15 mg BID	58	-12.10	0.894	-4.37	1.297	-6.92	-1.82	0.0008
Tofacitinib 30 mg BID	58	-12.58	0.897	-4.85	1.299	-7.40	-2.30	0.0002
Placebo	49	-7.73	0.954	--	--	--	--	--
Week 6 (LOCF)								
Tofacitinib 5 mg BID	56	-12.10	0.931	-4.04	1.313	-6.62	-1.46	0.0022
Tofacitinib 15 mg BID	59	-13.13	0.891	-5.07	1.292	-7.61	-2.53	<0.0001
Tofacitinib 30 mg BID	52	-13.91	0.925	-5.85	1.315	-8.43	-3.26	<0.0001
Placebo	50	-8.06	0.950	--	--	--	--	--
Week 8								
Tofacitinib 5 mg BID	57	10.31	1.07	-2.05	1.55	-5.09	0.99	0.1862
Tofacitinib 15 mg BID	56	6.02	1.05	-6.34	1.54	-9.35	-3.32	<0.0001
Tofacitinib 30 mg BID	52	6.77	1.08	-5.59	1.55	-8.64	-2.54	0.0003
Placebo	45	12.36	1.14	--	--	--	--	--

BID = twice daily; FAS = full-analysis set; LOCF = last observation carried forward; N = total number of subject; SE = standard error.

Subjects rated arthritic pain on a visual analog scale (VAS), from 0 = no pain to 100 = pain as bad as it could be. Decreases in pain from Baseline were statistically significant compared to placebo at all time points, with highly significant ($p<0.0001$) changes occurring in the 15 and 30 mg tofacitinib BID groups at all time points, and in the 5 mg tofacitinib BID group at Weeks 4 and 6 (Table 11).

Table 11. Mean Change From Baseline in Visual Analog Scores for Subject Pain Assessments at Weeks 1, 2, 4 and 6, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Week 1								
Tofacitinib 5 mg BID	57	-15.01	3.102	-11.71	4.291	-20.14	-3.28	0.0066
Tofacitinib 15 mg BID	67	-19.74	2.843	-16.44	4.127	-24.55	-8.33	<0.0001
Tofacitinib 30 mg BID	63	-29.66	2.932	-26.36	4.187	-34.58	-18.13	<0.0001
Placebo	58	-3.30	3.027	--	--	--	--	--
Week 2								
Tofacitinib 5 mg BID	55	-21.44	3.142	-16.65	4.317	-25.13	-8.17	0.0001
Tofacitinib 15 mg BID	65	-26.10	2.870	-21.31	4.147	-29.45	-13.16	<0.0001
Tofacitinib 30 mg BID	63	-35.85	2.936	-31.06	4.192	-39.29	-22.82	<0.0001
Placebo	53	-4.79	3.027	--	--	--	--	--
Week 4								
Tofacitinib 5 mg BID	55	-29.27	3.137	-20.87	4.467	-29.64	-12.10	<0.0001
Tofacitinib 15 mg BID	57	-35.47	2.996	-27.07	4.387	-35.68	-18.45	<0.0001
Tofacitinib 30 mg BID	56	-40.10	3.050	-31.69	4.424	-40.38	-23.01	<0.0001
Placebo	48	-8.40	3.242	--	--	--	--	--
Week 6								
Tofacitinib 5 mg BID	54	-31.42	3.159	-19.16	4.464	-27.93	-10.39	<0.0001
Tofacitinib 15 mg BID	58	-37.67	2.983	-25.41	4.367	-33.99	-16.84	<0.0001
Tofacitinib 30 mg BID	51	-42.89	3.144	-30.63	4.476	-39.42	-21.84	<0.0001
Placebo	49	-12.26	3.223	--	--	--	--	--

BID = twice daily; FAS = full-analysis set; N = total number of subject; SE = standard error.

Subjects global assessment of disease activity decreases from Baseline were statistically significant at all time points in all 3 treatment groups compared to placebo, with highly significant ($p<0.0001$) changes occurring in the 15 and 30 mg tofacitinib BID groups at all time points (Table 12).

Table 12. Mean Change From Baseline in Subject Global Assessments at Weeks 1, 2, 4 and 6, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Week 1								
Tofacitinib 5 mg BID	56	-17.98	3.121	-12.81	4.290	-21.24	-4.38	0.0030
Tofacitinib 15 mg BID	66	-21.56	2.859	-16.39	4.122	-24.49	-8.29	<0.0001
Tofacitinib 30 mg BID	62	-26.16	2.948	-20.99	4.178	-29.19	-12.78	<0.0001
Placebo	57	-5.18	3.022	--	--	--	--	--
Week 2								
Tofacitinib 5 mg BID	53	-22.06	3.184	-13.92	4.317	-22.40	-5.44	0.0013
Tofacitinib 15 mg BID	63	-25.71	2.900	-17.58	4.317	-25.71	-9.45	<0.0001
Tofacitinib 30 mg BID	60	-33.33	2.984	-25.19	4.192	-33.43	-16.96	<0.0001
Placebo	59	-8.14	2.998	--	--	--	--	--
Week 4								
Tofacitinib 5 mg BID	53	-30.23	3.176	-17.06	4.481	-25.86	-8.26	0.0002
Tofacitinib 15 mg BID	57	-37.35	3.001	-24.18	4.375	-32.78	-15.59	<0.0001
Tofacitinib 30 mg BID	55	-38.71	3.072	-25.54	4.419	-34.22	-16.87	<0.0001
Placebo	47	-13.17	3.238	--	--	--	--	--
Week 6								
Tofacitinib 5 mg BID	52	-31.64	3.203	-16.57	4.481	-25.37	-7.77	0.0002
Tofacitinib 15 mg BID	57	-37.78	3.005	-22.71	4.368	-31.29	-14.13	<0.0001
Tofacitinib 30 mg BID	49	-40.50	3.191	-25.44	4.489	-34.25	-16.63	<0.0001
Placebo	48	-15.06	3.219	--	--	--	--	--

BID = twice daily; FAS = full-analysis set; N = total number of subject; SE = standard error.

Decreases in the mean change from Baseline in the physician's global assessment of disease activity were statistically significant compared to placebo at all but 1 time point (5 mg tofacitinib BID group at Week 1), with highly significant ($p<0.0001$) changes occurring in the 15 and 30 mg tofacitinib BID groups at all time points (Table 13).

Table 13. Mean Change From Baseline in Physician Global Assessments at Weeks 1, 2, 4 and 6, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Week 1								
Tofacitinib 5 mg BID	59	-17.13	2.626	-4.88	3.671	-12.09	2.33	0.1841
Tofacitinib 15 mg BID	67	-28.25	2.445	-16.00	3.571	-23.01	-8.98	<0.0001
Tofacitinib 30 mg BID	62	-30.89	2.534	-18.64	3.628	-25.77	-11.52	<0.0001
Placebo	57	-12.25	2.636	--	--	--	--	--
Week 2								
Tofacitinib 5 mg BID	56	-25.43	2.675	-11.14	3.689	-18.39	-3.90	0.0026
Tofacitinib 15 mg BID	66	-36.60	2.456	-22.31	3.562	-29.31	-15.32	<0.0001
Tofacitinib 30 mg BID	63	-34.56	2.525	-20.28	3.607	-27.36	-13.19	<0.0001
Placebo	59	-14.29	2.611	--	--	--	--	--
Week 4								
Tofacitinib 5 mg BID	55	-33.29	2.686	-12.38	3.832	-19.90	-4.85	0.0013
Tofacitinib 15 mg BID	58	-38.44	2.563	-17.53	3.772	-24.94	-10.13	<0.0001
Tofacitinib 30 mg BID	56	-42.65	2.627	-21.74	3.812	-29.22	-14.25	<0.0001
Placebo	48	-20.91	2.803	--	--	--	--	--
Week 6								
Tofacitinib 5 mg BID	55	-35.97	2.690	-16.10	3.818	-23.60	-8.60	<0.0001
Tofacitinib 15 mg BID	58	-43.69	2.566	-23.82	3.763	-31.21	-16.43	<0.0001
Tofacitinib 30 mg BID	50	-46.70	2.730	-26.83	3.872	-34.43	-19.22	<0.0001
Placebo	49	-19.87	2.786	--	--	--	--	--

BID = twice daily; FAS = full-analysis set; N = total number of subjects; SE = standard error.

In this study, the DAS was based on the CRP and the 28-count subsets of tender/painful joints and swollen joints, ie, DAS28-3(CRP). The DAS 28 provides a number on a scale from 0 to 10 indicating the current activity of the subject's RA. A DAS 28 above 5.1 indicates high disease activity whereas a DAS 28 below 3.2 indicates low disease activity. DAS 28-3(CRP) scores decreased over time and with increased dose of tofacitinib (Table 14). Similarly, the mean change from Baseline in $\log_{10}$ CRP values decreased over time and also in a dose-responsive fashion, while on treatment (Table 15).

Table 14. DAS28-3 (CRP) at Baseline and Weeks 1, 2, 4, and 6 (FAS)

	Treatments	N	Mean	SD	Min/Max	Median
Baseline	Tofacitinib 5 mg BID	50	6.17	0.89	3.9/7.7	6.3
	Tofacitinib 15 mg BID	57	5.69	0.92	3.2/7.6	5.6
	Tofacitinib 30 mg BID	56	5.91	0.91	3.2/7.8	5.9
	Placebo	51	6.00	0.90	4.3/7.4	6.1
Week 1	Tofacitinib 5 mg BID	49	5.29	1.08	2.3/7.1	5.4
	Tofacitinib 15 mg BID	54	4.42	1.12	1.6/6.8	4.3
	Tofacitinib 30 mg BID	54	4.28	1.21	1.6/6.7	4.4
	Placebo	47	5.66	1.10	3.7/7.6	5.7
Week 2	Tofacitinib 5 mg BID	46	4.93	1.08	2.2/7.3	5.0
	Tofacitinib 15 mg BID	53	3.80	1.17	1.6/6.0	3.7
	Tofacitinib 30 mg BID	51	3.90	1.17	1.5/6.3	4.1
	Placebo	48	5.37	1.15	3.0/7.4	5.4
Week 4	Tofacitinib 5 mg BID	46	4.44	1.20	1.6/7.1	4.6
	Tofacitinib 15 mg BID	49	3.56	1.12	1.8/6.0	3.3
	Tofacitinib 30 mg BID	47	3.46	1.33	1.3/6.6	3.4
	Placebo	39	4.91	1.22	2.5/7.5	5.0
Week 6	Tofacitinib 5 mg BID	45	4.18	1.29	2.0/7.4	4.2
	Tofacitinib 15 mg BID	49	3.42	1.16	1.3/5.9	3.5
	Tofacitinib 30 mg BID	40	3.10	1.17	1.3/5.7	3.2
	Placebo	41	4.78	1.05	2.5/7.3	4.8

BID = twice daily; CRP = C-reactive protein; DAS = disease activity score; FAS = full-analysis set; min/max = minimum/maximum; N = total number of subjects; SD = standard deviation.

Table 15. Mean Change From Baseline in Log_{10} C-Reactive Protein at Weeks 1, 2, 4, and 6, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Week 1								
Tofacitinib 5 mg BID	50	0.63	1.156	0.61	1.225	0.41	0.91	0.0149
Tofacitinib 15 mg BID	54	0.25	1.148	0.25	1.220	0.17	0.36	<0.0001
Tofacitinib 30 mg BID	55	0.25	1.147	0.25	1.218	0.17	0.36	<0.0001
Placebo	48	1.03	1.157	--	--	--	--	--
Week 2								
Tofacitinib 5 mg BID	46	0.52	1.161	0.47	1.229	0.31	0.70	0.0002
Tofacitinib 15 mg BID	52	0.23	1.149	0.20	1.222	0.14	0.30	<0.0001
Tofacitinib 30 mg BID	53	0.17	1.149	0.15	1.221	0.10	0.22	<0.0001
Placebo	48	1.12	1.157	--	--	--	--	--
Week 4								
Tofacitinib 5 mg BID	46	0.48	1.160	0.52	1.238	0.34	0.79	0.0002
Tofacitinib 15 mg BID	49	0.20	1.153	0.22	1.233	0.14	0.33	<0.0001
Tofacitinib 30 mg BID	47	0.19	1.155	0.20	1.235	0.13	0.31	<0.0001
Placebo	39	0.92	1.169	--	--	--	--	--
Week 6								
Tofacitinib 5 mg BID	45	0.40	1.162	0.35	1.236	0.23	0.53	<0.0001
Tofacitinib 15 mg BID	49	0.19	1.153	0.17	1.231	0.11	0.25	<0.0001
Tofacitinib 30 mg BID	41	0.22	1.163	0.19	1.238	0.13	0.29	<0.0001
Placebo	41	1.15	1.166	--	--	--	--	--

BID = twice daily; FAS = full-analysis set; N = total number of subject; SE = standard error.

The HAQ disability index was significantly reduced (improved functional status) while on treatment with increased dose of tofacitinib when compared to placebo and the results (Table 16). All tofacitinib-treated groups had increased response rates relative to placebo at all time points for the ACR 50 and 70.

Table 16. Mean Change From Baseline in HAQ-DI at Weeks 1, 2, 4, and 6, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Week 1								
Tofacitinib 5 mg BID	59	-0.25	0.066	-0.20	0.093	-0.38	-0.02	0.0308
Tofacitinib 15 mg BID	68	-0.30	0.061	-0.24	0.090	-0.42	-0.07	0.0070
Tofacitinib 30 mg BID	64	-0.44	0.063	-0.39	0.092	-0.57	-0.21	<0.0001
Placebo	55	-0.05	0.067	--	--	--	--	--
Week 2								
Tofacitinib 5 mg BID	56	-0.39	0.067	-0.24	0.093	-0.42	-0.05	0.0111
Tofacitinib 15 mg BID	66	-0.50	0.062	-0.34	0.090	-0.52	-0.16	0.0002
Tofacitinib 30 mg BID	63	-0.56	0.063	-0.40	0.092	-0.58	-0.22	<0.0001
Placebo	57	-0.15	0.067	--	--	--	--	--
Week 4								
Tofacitinib 5 mg BID	56	-0.55	0.067	-0.42	0.096	-0.61	-0.23	<0.0001
Tofacitinib 15 mg BID	57	-0.60	0.064	-0.46	0.095	-0.65	-0.28	<0.0001
Tofacitinib 30 mg BID	57	-0.69	0.065	-0.55	0.096	-0.74	-0.37	<0.0001
Placebo	44	-0.13	0.071	--	--	--	--	--
Week 6								
Tofacitinib 5 mg BID	54	-0.60	0.068	-0.39	0.096	-0.58	-0.21	<0.0001
Tofacitinib 15 mg BID	59	-0.72	0.063	-0.52	0.094	-0.70	-0.33	<0.0001
Tofacitinib 30 mg BID	51	-0.74	0.067	-0.54	0.096	-0.73	-0.35	<0.0001
Placebo	47	-0.20	0.070	--	--	--	--	--

BID = twice daily; FAS = full-analysis set; HAQ-DI = Health Assessment Questionnaire Disability Index; N = total number of subject; SE = standard error.

The SF-36 measures 8 general health concepts: physical functioning, role physical, bodily pain, general health, vitality, social functioning, and role emotional, and mental health (also summarized as physical and mental component scores). Improvements from Baseline were statistically significant in all tofacitinib treatment groups for the domains of role-physical, bodily pain, general health, and the physical component summary. Treatment with 30 mg tofacitinib BID resulted in statistically significant improvement in all 8 domains and both summary scores of the SF-36 (Table 17).

Table 17. Mean Change From Baseline in SF-36 at Week 6 and 12, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence		p-Value
						Lower	Upper	
Physical Function								
Week 6								
Tofacitinib 5 mg BID	56	5.79	1.173	3.31	1.726	-0.08	6.71	0.0556
Tofacitinib 15 mg BID	56	6.57	1.157	4.09	1.731	0.69	7.50	0.0186
Tofacitinib 30 mg BID	52	8.58	1.201	6.11	1.756	2.65	9.56	0.0006
Placebo	44	2.48	1.318	--	--	--	--	--
Week 12								
Tofacitinib 5 mg BID	56	3.40	1.172	-0.33	1.666	-3.60	2.95	0.8441
Tofacitinib 15 mg BID	62	4.38	1.112	0.64	1.644	-2.59	3.88	0.6954
Tofacitinib 30 mg BID	55	6.68	1.179	2.95	1.683	-0.36	6.26	0.0806
Placebo	51	3.73	1.241	--	--	--	--	--
Role-Physical								
Week 6								
Tofacitinib 5 mg BID	56	8.36	1.172	6.27	1.719	2.89	9.65	0.0003
Tofacitinib 15 mg BID	55	7.50	1.156	5.41	1.727	2.02	8.81	0.0019
Tofacitinib 30 mg BID	52	9.08	1.196	6.99	1.748	3.55	10.43	<0.0001
Placebo	44	2.09	1.312	--	--	--	--	--
Week 12								
Tofacitinib 5 mg BID	56	5.33	1.168	3.13	1.657	-0.13	6.38	0.0600
Tofacitinib 15 mg BID	62	3.90	1.102	1.70	1.633	-1.51	4.92	0.2973
Tofacitinib 30 mg BID	55	6.80	1.172	4.60	1.674	1.30	7.89	0.0063
Placebo	51	2.20	1.234	--	--	--	--	--
Bodily Pain								
Week 6								
Tofacitinib 5 mg BID	56	12.14	1.213	8.49	1.795	4.96	12.02	<0.0001
Tofacitinib 15 mg BID	56	13.62	1.200	9.97	1.802	6.42	13.51	<0.0001
Tofacitinib 30 mg BID	52	15.11	1.252	11.46	1.834	7.85	15.06	<0.0001
Placebo	44	3.65	1.374	--	--	--	--	--
Week 12								
Tofacitinib 5 mg BID	56	6.34	1.211	1.99	1.723	-1.40	5.38	0.2492
Tofacitinib 15 mg BID	62	6.24	1.146	1.89	1.698	-1.44	5.23	0.2653
Tofacitinib 30 mg BID	55	9.06	1.222	4.72	1.747	1.28	8.15	0.0073
Placebo	51	4.35	1.281	--	--	--	--	--
General Health								
Week 6								
Tofacitinib 5 mg BID	56	5.55	1.012	3.22	1.488	0.29	6.14	0.0314
Tofacitinib 15 mg BID	56	5.83	0.992	3.50	1.488	0.57	6.42	0.0193
Tofacitinib 30 mg BID	52	7.99	1.035	5.66	1.510	2.68	8.63	0.0002
Placebo	44	2.33	1.136	--	--	--	--	--
Week 12								
Tofacitinib 5 mg BID	56	3.03	1.011	0.82	1.442	-2.02	3.65	0.5717
Tofacitinib 15 mg BID	62	4.13	0.957	1.92	1.422	-0.88	4.71	0.1787
Tofacitinib 30 mg BID	55	4.40	1.017	2.18	1.455	-0.68	5.05	0.1345
Placebo	51	2.21	1.076	--	--	--	--	--
Vitality								
Week 6								
Tofacitinib 5 mg BID	56	5.99	1.253	2.89	1.844	-0.73	6.52	0.1177
Tofacitinib 15 mg BID	56	8.61	1.237	5.52	1.851	1.88	9.16	0.0031
Tofacitinib 30 mg BID	52	11.84	1.286	8.75	1.880	5.05	12.44	<0.0001
Placebo	44	3.09	1.412	--	--	--	--	--

Table 17. Mean Change From Baseline in SF-36 at Week 6 and 12, FAS

	N	Mean	SE of Mean	Difference From Placebo				
				Difference	SE of Difference	95% Confidence Lower	95% Confidence Upper	p-Value
Week 12								
Tofacitinib 5 mg BID	56	3.52	1.252	1.03	1.781	-2.47	4.53	0.5633
Tofacitinib 15 mg BID	62	4.68	1.190	2.20	1.759	-1.27	5.66	0.2129
Tofacitinib 30 mg BID	55	8.33	1.262	5.85	1.802	2.30	9.39	0.0013
Placebo	51	2.48	1.330	--	--	--	--	--
Social Function								
Week 6								
Tofacitinib 5 mg BID	56	7.36	1.376	3.14	2.023	-0.84	7.12	0.1216
Tofacitinib 15 mg BID	56	7.81	1.355	3.59	2.029	-0.40	7.58	0.0776
Tofacitinib 30 mg BID	52	10.88	1.411	6.66	2.063	2.61	10.72	0.0014
Placebo	44	4.22	1.547	--	--	--	--	--
Week 12								
Tofacitinib 5 mg BID	56	5.48	1.374	0.93	1.951	-2.90	4.77	0.6330
Tofacitinib 15 mg BID	62	4.11	1.301	-0.44	1.925	-4.23	3.34	0.8175
Tofacitinib 30 mg BID	55	9.00	1.383	4.45	1.976	0.56	8.33	0.0251
Placebo	51	4.55	1.454	--	--	--	--	--
Role-Emotional								
Week 6								
Tofacitinib 5 mg BID	56	6.07	1.510	5.00	2.230	0.62	9.39	0.0255
Tofacitinib 15 mg BID	56	5.26	1.493	4.19	2.237	-0.21	8.59	0.0617
Tofacitinib 30 mg BID	52	8.89	1.554	7.83	2.275	3.35	12.30	0.0006
Placebo	44	1.06	1.707	--	--	--	--	--
Week 12								
Tofacitinib 5 mg BID	56	1.60	1.509	-2.13	2.151	-6.36	2.10	0.3237
Tofacitinib 15 mg BID	62	1.25	1.432	-2.48	2.120	-6.65	1.69	0.2423
Tofacitinib 30 mg BID	55	5.59	1.522	1.86	2.175	-2.41	6.14	0.3921
Placebo	51	3.73	1.602	--	--	--	--	--
Mental Health								
Week 6								
Tofacitinib 5 mg BID	56	5.88	1.330	2.84	1.956	-1.01	6.68	0.1480
Tofacitinib 15 mg BID	56	6.60	1.311	3.56	1.964	-0.30	7.42	0.0705
Tofacitinib 30 mg BID	52	10.15	1.371	7.11	1.996	3.18	11.03	0.0004
Placebo	44	3.04	1.497	--	--	--	--	--
Week 12								
Tofacitinib 5 mg BID	56	3.26	1.329	-0.23	1.892	-3.95	3.49	0.9025
Tofacitinib 15 mg BID	62	3.13	1.262	-0.36	1.870	-4.04	3.32	0.8464
Tofacitinib 30 mg BID	55	7.49	1.346	4.00	1.918	0.22	7.77	0.0380
Placebo	51	3.50	1.412	--	--	--	--	--

BID = twice daily; FAS = full-analysis set; N = total number of subject; SE = standard error; SF-36= SF-36 health survey.

Pharmacokinetic and Pharmacodynamics Results: Data not available.

Safety Results:

Serious Adverse Events (SAEs): Overall, 13 subjects reported 16 SAEs, including 3 subjects who had 5 SAEs prior to initiation of treatment. Of the 10 subjects who had treatment-emergent SAEs, 3 subjects had SAEs that were attributed to the study drug.

The SAEs that occurred while on treatment were as follows: in the tofacitinib 5 mg BID treatment group - subarachnoid haemorrhage, in the 15 mg BID group - infectious gastroenteritis, drug exposure in utero and spontaneous abortion, vasovagal attack, leukopenia, worsening of RA, in the 30 mg BID group - cardiac ischemia, exacerbation of morbus Whipple, acute pyelonephritis and in the placebo group - *staphylococcus aureus* pneumonia.

Adverse Events: There was a treatment-related increase in the number of subjects reporting treatment-emergent AEs in the 15 and 30 mg tofacitinib BID groups. The 15 and 30 mg tofacitinib BID groups had 16% and 18%, respectively, more subjects reporting AEs than the 5 mg tofacitinib BID group and placebo group. AEs occurring at a higher incidence in the 30 mg tofacitinib BID group than the other 3 groups included leukopenia, anemia, urinary tract infection, nausea, and influenza. Hypercholesterolemia was only observed in the 5 mg and 15 mg tofacitinib BID groups. AEs that occurred at a frequency of 5% or greater were comparable between the placebo and tofacitinib-treated groups which are represented in Table 18.

Table 18. Treatment-Emergent AEs Occurring at an Incidence of 5% or Greater

System Organ Class/ Preferred Term (MedDRA)	Tofacitinib						Placebo	
	5 mg BID N =61 n (%)		15 mg BID N =69 n (%)		30 mg BID N =69 n (%)		N =65 n (%)	
	AC	TR	AC	TR	AC	TR	AC	TR
Any adverse event, n (%)	36 (59)	23 (38)	52 (75)	29 (42)	53 (77)	33 (48)	38 (59)	21 (32)
Blood and lymphatic system disorders	6 (9.8)	4 (6.6)	6 (8.7)	3 (4.3)	12 (17.4)	10 (14.5)	3 (4.6)	1 (1.5)
Anemia	1 (1.6)	0 (0)	2 (2.9)	1 (1.4)	4 (5.8)	3 (4.3)	3 (4.6)	1 (1.5)
Leukopenia	2 (3.3)	1 (1.6)	2 (2.9)	2 (2.9)	7 (10.1)	6 (8.7)	1 (1.5)	1 (1.5)
Gastrointestinal disorders	13 (21.3)	12 (19.7)	15 (21.7)	11 (15.9)	15 (21.7)	9 (13.0)	15 (23.1)	5 (7.7)
Abdominal pain upper	4 (6.6)	4 (6.6)	2 (2.9)	2 (2.9)	2 (2.9)	1 (1.4)	0 (0)	0 (0)
Nausea	4 (6.6)	4 (6.6)	3 (4.3)	3 (4.3)	6 (8.7)	3 (4.3)	3 (4.6)	2 (3.1)
Infections and infestations	15 (24.6)	6 (9.8)	21 (30.4)	13 (18.8)	21 (30.4)	10 (14.5)	17 (26.2)	9 (13.8)
Influenza	3 (4.9)	1 (1.6)	2 (2.9)	0 (0)	4 (5.8)	2 (2.9)	2 (3.1)	0 (0)
Upper respiratory tract infection	0 (0)	0 (0)	3 (4.3)	1 (1.4)	1 (1.4)	0 (0)	4 (6.2)	3 (4.6)
Urinary tract infection	1 (1.6)	1 (1.6)	0 (0)	0 (0)	5 (7.2)	4 (5.8)	2 (3.1)	1 (1.5)
Metabolism and nutritional disorders	2 (3.3)	2 (3.3)	5 (7.2)	3 (4.3)	4 (5.8)	3 (4.3)	1 (1.5)	0 (0)
Hypercholesterolemia	2 (3.3)	2 (3.3)	4 (5.8)	3 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	7 (11.5)	2 (3.3)	17 (24.6)	0 (0)	7 (10.1)	2 (2.9)	13 (20.0)	2 (3.1)
Arthralgia	3 (4.9)	0 (0)	0 (0)	0 (0)	3 (4.3)	2 (2.9)	6 (9.2)	1 (1.5)
Rheumatoid arthritis	1 (1.6)	1 (1.6)	4 (5.8)	0 (0)	2 (2.9)	0 (0)	4 (6.2)	0 (0)
Nervous system disorders	11 (18)	8 (13.1)	13 (18.8)	11 (15.9)	21 (30.4)	11 (15.9)	6 (9.2)	5 (7.7)
Dizziness	0 (0)	0 (0)	4 (5.8)	3 (4.3)	3 (4.3)	3 (4.3)	1 (1.5)	1 (1.5)
Headache	10 (16.4)	8 (13.1)	8 (11.6)	7 (10.1)	17 (24.6)	10 (14.5)	6 (9.2)	5 (7.7)

AC = all causalities; AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with AE; N = total number of subjects; TR = treatment-related.

Discontinuations due to Adverse Events: A total of 17 subjects discontinued due to AEs and 2 additional subjects discontinued due to laboratory investigations (leukopenia and neutropenia). Drug-related events included 1, 3, and 6 subjects in the 5, 15, and 30 mg tofacitinib BID groups, respectively, compared to 1 subject in the placebo group.

Deaths: No deaths were reported during the study.

Clinical Laboratory Results: The incidence of clinical laboratory abnormalities was a dose response in mean change from Baseline in neutrophil counts (decreases) and in total high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol (increases), and consistent decreases in estimated creatinine clearance. EBV levels were comparable among all groups, though there were increases in the 30 mg tofacitinib BID group.

CONCLUSIONS:

- Tofacitinib administered at doses of 5, 15, and 30 mg BID was highly efficacious, exceeding 30% points in improvement over placebo in the ACR 20 response rate at Week 6. Statistically significant changes were consistently observed in the efficacy parameters supporting clinically meaningful reductions in the signs and symptoms of RA.

- Clinically meaningful and statistically significant changes in the efficacy parameters of all 3 dose levels of tofacitinib were observed at Week 1 (the earliest post-Baseline time point measured) and sustained for >6 weeks when compared to placebo, in the treatment of signs and symptoms of RA.

- Both the 15 and 30 mg tofacitinib BID doses appeared to be on the plateau of the dose-efficacy curve.

- All 3 doses of tofacitinib were associated with AEs within 6 weeks. Some of these side effects could be anticipated from known pharmacology (ie, anemia, neutropenia, infections); others are currently less well understood (ie, reduced estimated glomerular filtration rate, increased total, HDL and LDL cholesterol). All AEs can be monitored and appear to be reversible/treatable.

- Lower doses of tofacitinib will need to be studied in order to characterize the dose response more completely.

- Dose levels of 15 mg tofacitinib BID and below were better tolerated than 30 mg tofacitinib BID, and should be investigated in studies of longer duration.

- This study establishes proof of concept for this study drug.