PFIZER INC.

These results are supplied for informational purpose only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: A3921040

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Confirm Dose Responsiveness Following 12 Weeks of the Administration of CP-690,550 (5 Doses) or Placebo in Subjects With Active Rheumatoid Arthritis Inadequately Responding to At Least 1 DMARD

Study Centers: Forty-seven centers took part in the study and enrolled subjects. All the study centers were in Japan.

Study Initiation and Final Completion Dates: 26 March 2009 to 08 July 2010

Phase of Development: Phase 2

Study Objectives:

Primary Objective

To evaluate the dose-response relationship of 5 tofacitinib (1, 3, 5, 10, and 15 mg twice daily [BID]) doses compared to placebo for the treatment of signs and symptoms in subjects with active rheumatoid arthritis (RA) who failed an adequate trial of therapy with at least 1 disease-modifying antirheumatic drug (DMARD) (including methotrexate) in a 12-week therapy.

Secondary Objectives

- When tofacitinib (1, 3, 5, 10 and 15 mg BID) is used in a 12-week study in active RA subjects, to evaluate the safety and tolerability of all dose levels of tofacitinib versus placebo.
- When tofacitinib (1, 3, 5, 10, and 15 mg BID) is used in a 12-week study in active RA subjects, to evaluate subjects' quality of life (QOL) and functional status.
- When tofacitinib (1, 3, 5, 10, and 15 mg BID) is used in a 12-week study in active RA subjects, to characterize the relationship between plasma concentrations of tofacitinib and efficacy and safety outcomes.
- When tofacitinib (1, 3, 5, 10, and 15 mg BID) is used in a 12-week study in active RA subjects, to conduct Population pharmacokinetics (PK) analyses in active RA subjects.

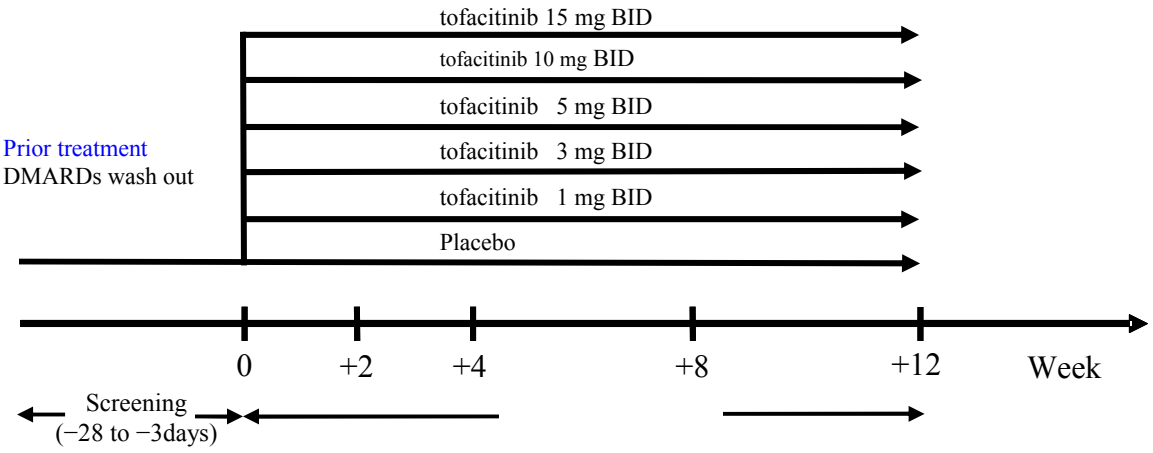
METHODS

Study Design:

This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Subjects were randomized in a 1:1:1:1:1:1 ratio to receive 1 of 5 doses of tofacitinib (1, 3, 5, 10 and 15 mg, BID) or placebo. A total of 300 subjects were required; 50 subjects for each study group.

For each subject, the study comprised screening period (at least 3 days but not longer than 28 days prior to first study drug administration) and treatment period (12 weeks). Three tablets of tofacitinib 1 mg or 5 mg, or placebo were administered orally BID (separated by 12±2 hours), for a total of 6 tablets/day per treatment period. The study design is presented in Figure 1.

Figure 1. Study Design



BID = twice daily; DMARDs = disease-modifying antirheumatic drugs.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Items		Screening[a]	Baseline	Visits During Treatment Phase[b]			EOT[b]
		Day -28 (-28 to-3 Day)	Week 0 (0)	Week 2 (±3 Days)	Week 4 (±3 Days)	Week 8 (±3 Days)	Week 12/Discontinuation (±3 Days)
Informed consent		X					
Randomization			X				
Subjects characteristics	Background investigation (eg complications, medical history, treatment conditions)[c]	X					
	Questions/examinations by physician (physical examination etc)[d]	X[d]	X	X	X	X	X[d]
	Measurement of height, abdominal circumference	X					
	Measurement of body weight	X	X	X	X	X	X
	RA diagnosis (ACR classification criteria 1987)	X					
	Eligibility confirmation (eg inclusion/exclusion criteria)	X	X				
Assessments	ACR assessments[e]	X	X	X	X	X	X
	DAS 28-3 (CRP),DAS 28-4 (ESR) assessments	X	X	X	X	X	X
	QOL1 (SF-36v2, EQ-5D)		X				X
	QOL2 (MOS-sleep, FACIT fatigue)		X	X			X
	Vital signs (sitting blood pressure/pulse rate, axillary body temperature)	X	X	X	X	X	X
	Adverse event assessment		X	X	X	X	X
Lab tests/exploratory tests/physiological test	ESR (Westergren method)	X	X	X	X	X	X
	Serum rheumatoid factor	X					
	QuantiFERON®-TB or Tuberculosis test[f]	X					
	HIV test, Hepatitis test (hepatitis B virus antigen, hepatitis C virus antibody)	X					
	Hematology[g]	X	X	X	X	X	X
	Biochemistry: standard (fasting)[h]	X	X		X	X	X
	Biochemistry: hepatic/renal function (fasting)[i]			X			
	Biochemistry: lipid special (fasting)[j]		X	X	X	X	X
	CRP	X	X	X	X	X	X
	Lymphocyte subset markers (FACS analysis)		X				X
	Serum IgG, IgM, and IgA levels		X				X
	Urinalysis (general/pregnancy)[k]	X	X	X	X	X	X
	PK sampling[l]				X	X	

Table 1. Schedule of Activities

	Pharmacogenomic sampling (DNA)[m]		X				
	Exploratory RNA sampling[m]		X	X	X		X
	Retained Serum/Plasma sampling[m]		X	X	X		X
	Standard 12-lead ECG	X	X				X
	SpO_2	X	X	X	X	X	X
	Chest X-rays	X[n]					X
	Serum KL-6, β-D glucan	X					
Drug supplies	Study drug dispensing[o]		X		X	X	
	Study drug recovery, remaining drug check			X	X	X	X
	Confirmation of concomitant medications	X	X	X	X	X	X
	Instructions on the use of drugs[o]	X	X	X	X	X	
Eligibility confirmation (for subjects who would enter into the continuous study)						X	X

Table 1. Schedule of Activities

ACR = American College of Rheumatology, ALT = alanine aminotransferase, AST = aspartate aminotransferase, Ca = calcium, Cl - chlorine, CRP = C-reactive protein, DAS = disease activity score, , DNA = deoxyribonucleic acid, ESR = erythrocyte sedimentation rate, EOT = end of treatment, EQ-5D = EuroQol-5dimensions, FSH = follicle-stimulating hormone, FACIT = functional assessment of chronic illness therapy, FACS = fluorescence activated cell sorting, HCO3 = bicarbonate, HAQ-DI = health assessment questionnaire - disability index, HDL = high-density lipoprotein, HIV = human immunodeficiency virus, IgG = immunoglobulin G, IgM = immunoglobulin M, IgA = immunoglobulin A, K = pottasium, MOS = medical outcomes study, Na = sodium, QOL = quality of life, SF-36 = SF-36 health survey, RA = rheumatoid arthritis, SpO2 = percutaneous arterial oxygen saturation., RBC = red blood cell RNA = ribo-nucleic acid, , TB = Mycobacterium tuberculosis, WBC = white blood cell, LDL = low-density lipoprotein, VAS = visual analogue scale.

a. The screening visit took place within 28 days prior to the Baseline Visit. Subject's informed consent was obtained before initiating assessments or tests in the screening period.
b. The data observed for the observation/test parameters specified for all visits were accepted within a time window of ±3 days relative to the Day of Treatment Initiation.
c. Subject characteristics (eg complications, past medical history, treatment status) were investigated at the time of the interview. Subjects were questioned about their family history of cardiovascular disease which was developed under 55 and 65 years old in male and female each. Subjects were also questioned about their preferences regarding smoking and the average amount of alcohol consumption in 1 week (eg, presence or absence of alcohol dependency or drug abuse).
d. Questioning/examination by physician consisted of weight measurement and the examination of heart, lungs, abdomen, and lymph nodes, which were to be monitored carefully at Screening and the EOT.
e. The following assessments based on the ACR core set were to be performed at all visits: painful joint count (68); swollen joint count (66); patients assessment of arthritis pain (VAS); patients Global Assessment of Active Arthritis (VAS); Physician's Global Assessment of Active Arthritis (VAS); HAQ-DI.
f. QuantiFERON®-TB or tuberculin test was performed only if a tuberculin test had not been performed in the 3 months prior to the start of the study (the assessment of tuberculin test was made within 48-72 hours).
g. WBC, differential WBC, RBC; hemoglobin, hematocrit, reticulocytes, platelet count.
h. Biochemistry tests (standard): protein, total bilirubin, albumin, ALP, BUN, creatinine, blood glucose, AST, ALT, Na^+, K^+, Cl^-, Ca^{++}, HCO_3^-, uric acid, LDH, (all measured after fasting for at least 9 hours; this may not apply if the informed consent was obtained on the day of screening).
i. Biochemistry tests (hepatic/renal function): AST, ALT, total bilirubin, albumin, creatinine (all measured after fasting for at least 9 hours).
j. Biochemistry tests (lipid): T-Chol, LDL, HDL, TG (all measured after fasting for at least 9 hours) at Baseline, Weeks 2, 4, 8 and 12/Early Termination. Apolipoprotein A-I and A-II, apolipoprotein B (all measured after fasting for at least 9 hours) at Baseline and Week 12/Early Termination.
k. Pregnancy test was performed for women of child-bearing potential (serum FSH [test] was optional). The pregnancy test was qualitative tests using urine test paper. Urinalysis was performed using dipsticks and, if a clinically significant abnormality was observed or at the discretion of the Investigator, additional examination by means of, for example, microscopy was performed.
l. Blood samples were obtained for pharmacokinetic measurements at Weeks 4 and 8. The Investigator had the subjects come in for the visit without taking study medication at Weeks 4 and 8, so that blood samples could be collected at 1 hour predose and at 0.5, 1, and 2 hours postdose.
m. In principle, the blood samples for pharmacogenomic analysis were collected at Baseline concurrently with other blood samples (for the pharmacogenomic sampling, a separate informed consent had to be obtained). If the informed consent was not obtained at Baseline, the samples could be collected at other blood sampling times after obtaining the consent.
n. Chest X-rays (frontal, lateral) to check for respiratory disorders in the 3 months prior to Screening.
o. Subjects were instructed to start taking study medication after the evening meal on the treatment initiation Day (Baseline). Similarly, at Week 4 and 8 visits, when study medications were dispensed, subjects were instructed to take the study medication after their evening meal. Subjects were instructed to return all remaining study medication to the Investigator at Week 4, 8 and EOT (including the visit following discontinuation).

Number of Subjects (Planned and Analyzed): The study planned to enroll approximately 300 subjects (50 subjects per group × 6 groups). A total of 383 subjects were screened and 318 subjects were randomized to 6 treatment groups. One subject withdrew after randomization but prior to treatment because of protocol violation (Indeterminate QuantiFERON-TB). In each group, 53, 53, 52, 53, 54, and 52 subjects took study medication for the 1, 3, 5, 10, and 15 mg tofacitinib BID and placebo groups, respectively.

All subjects were enrolled in Japan.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged between 20 years to 70 years and must have failed an adequate trial of therapy with at least 1 DMARD due to lack of efficacy or toxicity.

Excluded were the subjects who undergone current therapy with any DMARD.

Study Treatment: At each visit, the Investigator instructed the subject to take 1 tablet from each 3 bottles, BID (a total of 6 tablets/day) separated by 12±2 hours with a cup of water (about 200 mL), without chewing. At Baseline (Week 0), the subject took the study medication just after examination, and the Investigator instructed the subject to take the study medication in next morning and evening.

Based on this randomization table, subjects were randomly allocated at treatment initiation (Baseline) to placebo or tofacitinib 1, 3, 5, 10, or 15 mg BID, in a 1:1:1:1:1:1 ratio and received 1, 3, 5, 10 or 15 mg of tofacitinib or placebo administered orally.

Efficacy, Pharmacokinetics, and Safety Endpoints:

Efficacy Endpoints

Primary Endpoints

American college of rheumatology (ACR) 20 responder rate at Week 12.

Secondary Endpoints

- ACR20 responder rate at all other than Week 12.
- ACR50, 70, and 90 responder rates at all timepoints.
- Observed values and changes from Baseline of the 7 components of the ACR Core set.

  Tender/painful joint count (68), swollen joint count (66), patient's Assessment of Arthritis Pain visual analogue scale (VAS), patient's Global Assessment of Active Arthritis (VAS), Physician's Global Assessment of Active Arthritis (VAS), health assessment questionnaire - disability index (HAQ–DI), C-reactive protein (CRP).
- Area under the American college of rheumatology N (ACR-N) curve.
- Disease activity score 28 (DAS28-3) (CRP), DAS28-4 (erythrocyte sedimentation rate [ESR]).
- QOL assessments (SF-36, HAQ-DI, EQ-5D).

Safety Endpoints

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

Safety Evaluations: Safety was assessed by reporting AEs , reporting results of clinical laboratory tests, measuring vital signs (sitting blood pressure, pulse rate, axillary body temperature, performed at Screening, Baseline, and at Weeks 2, 4, 8, and 12 or early termination); all of these assessments were made at Baseline and Weeks 2, 4, 8, and 12 or at early termination. In addition, standard 12-lead ECGs was assessed at Screening, Baseline, and at Week 12 or early termination.

Statistical Methods:

The primary analysis population for this study was the full analysis set (FAS) of enrolled and randomized subjects. The FAS study population included all subjects who were randomized to the study and received at least 1 dose of study medication. Subjects who had a protocol deviation thought to affect the efficacy analysis were excluded from the 'Per Protocol' (PP) efficacy analysis. The analyses were conducted to evaluate the robustness of the primary

analysis. The safety analysis set was defined as the subjects who received at least 1 dose of study medication.

Analysis of Primary Endpoint:

For ACR20 response rate at Week 12, the pair-wise comparisons of the tofacitinib 1, 3, 5, 10, and 15 mg BID to placebo were conducted using chi-square (χ^2) test with 2-sided significance level of 0.05. The type I error rate for the pair-wise comparisons was protected from being inflated by using a step-down procedure. If the result was not significant, no further tests were carried out for the primary endpoint. If there was a significant difference between 15 mg BID and placebo, the test between 10 mg BID and placebo was applied in the same way. The test between 5, 3, and 1 mg BID versus placebo was also applied in that order in the same way. Missing values were handled using the Last Observation Carried Forward (LOCF) method. This analysis was based on the FAS.

Analysis of Secondary Endpoints:

ACR20 response rates were assessed at Weeks 2, 4, and 8, and at Weeks 2, 4, 8, and 12 for assessment of the response rates after treatment with ACR50, ACR70, and ACR90. Differences in these ACR response rates between each tofacitinib group and versus the placebo group were calculated using normal approximation method (ie, a 95% confidence interval). The LOCF approach also used to address any missing values for these endpoint assessment. In the case of "no evaluable" ACR data after Baseline, the ACR response was referred to as a "Non-response."

For the component variables of the ACR criteria (obtained at Weeks 2, 4, 8, 12 or early termination), a longitudinal linear model was employed for change from Baseline values. The actual baseline value was included as a covariate. The fixed effects of treatment, visit, and treatment-by-week interaction were included, along with subject as a random effect. Compound symmetry covariate structure was used. Estimates of mean values and the mean differences from placebo at each week were derived from the model. Contrasts versus placebo were formed at a significance level of 5%, along with 95% confidence intervals. Observed data were used without imputation. Descriptive statistics of the actual and change from baseline values were calculated. For ACR-N, descriptive statistics were used to assess data (ie, area under the ACR-N curve); this analyses plan was also used to assess the DAS of each subject, DAS28-3(CRP) and DAS28-4(ESR), which were measured and categorized at each visit. Numbers and percentages of subjects in each category were displayed for each treatment group at each visit.

Safety Parameters:

All the safety data was summarized through appropriate data tabulations, descriptive statistics, and graphical presentations.

RESULTS

Subject Disposition and Demography:

Table 2 summarizes the number of subjects that were included in the efficacy and safety analyses.

Table 2. Subject Evaluation Groups

	Tofacitinib BID					Placebo
	1 mg	3 mg	5 mg	10 mg	15 mg	
Number of Subjects (%)						
Screened: 383						
Assigned to study treatment	53	53	52	53	54	53
Treated	53	53	52	53	54	52
Completed	51 (96.2)	49 (92.5)	50 (96.2)	49 (92.5)	52 (96.3)	48 (90.6)
Discontinued	2 (3.8)	4 (7.5)	2 (3.8)	4 (7.5)	2 (3.7)	4 (7.5)
Analyzed for efficacy						
Full analysis set	53 (100)	53 (100)	52 (100)	53 (100)	54 (100)	52 (98.1)
Per protocol set	53 (100)	50 (94.3)	51 (98.1)	51 (96.2)	53 (98.1)	50 (94.3)
Analyzed for safety						
Adverse events	53 (100)	53 (100)	52 (100)	53 (100)	54 (100)	52 (98.1)
Laboratory data	53 (100)	53 (100)	52 (100)	53 (100)	54 (100)	52 (98.1)

BID = twice daily.

Subject disposition is shown in Table 3.

Table 3. Subject Disposition

	Tofacitinib										Placebo	
	1 mg	BID	3 mg	BID	5 mg	BID	10 mg	BID	15 mg	BID		
Number (%) of Subjects	53		53		52		53		54		52	
Screened N =383												
Assigned to study treatment	53		53		52		53		54		53	
Treated	53		53		52		53		54		52	
Completed	51	(96.2)	49	(92.5)	50	(96.2)	49	(92.5)	52	(96.3)	48	(90.6)
Discontinued	2	(3.8)	4	(7.5)	2	(3.8)	4	(7.5)	2	(3.7)	4	(7.5)
Related to Study Drug	1	(1.9)	2	(3.8)	1	(1.9)	2	(3.8)	0		4	(7.7)
Adverse event	0		1	(1.9)	1	(1.9)	2	(3.8)	0		2	(3.8)
Lack of efficacy	1	(1.9)	1	(1.9)	0		0		0		2	(3.8)
Not Related to Study Drug	1	(1.9)	2	(3.8)	1	(1.9)	2	(3.8)	2	(3.7)	0	
Adverse event	0		0		1	(1.9)	1	(1.9)	0		0	
Other	1	(1.9)	2	(3.8)	0		1	(1.9)	2	(3.7)	0	
Total	2	(3.8)	4	(7.5)	2	(3.8)	4	(7.5)	2	(3.7)	4	(7.7)

BID = twice daily

Table 4 summarizes the demographic distribution by age, race, sex, weight, body mass index, and height by treatment groups.

Table 4. Demography Characteristics

Number of Subjects	Tofacitinib						
	1 mg BID 53	3 mg BID 53	5 mg BID 52	10 mg BID 53	15 mg BID 54	Placebo 52	Total 317
Age (years)							
<18	0	0	0	0	0	0	0
18-44	8 (15.1)	11 (20.8)	13 (25.0)	9 (17.0)	12 (22.2)	14 (26.9)	67 (21.1)
45-64	39 (73.6)	33 (62.3)	31 (59.6)	32 (60.4)	30 (55.6)	29 (55.8)	194 (61.2)
≥65	6 (11.3)	9 (17.0)	8 (15.4)	12 (22.6)	12 (22.2)	9 (17.3)	56 (17.7)
Mean	53.3	52.8	52.6	54.7	53.6	53.3	53.4
SD	9.9	11.6	10.9	10.8	12.5	11.4	11.2
Range	25-69	20-69	26-70	26-70	22-70	20-70	20-70
Race							
Asian	53 (100)	53 (100)	52 (100)	53 (100)	54 (100)	52 (100)	317 (100)
Sex							
Male	11	6	8	9	10	9	53
Female	42	47	44	44	44	43	264
Weight (kg)							
Mean	52.9	54.1	54.2	54.1	53.8	57.4	54.4
SD	9.4	10.2	6.6	10.0	9.9	11.7	9.8
Range	34.3-83.6	38.7-84.7	42.7-71.8	31.4-79.0	38.0-78.8	32.0-85.6	31.4-85.6
Body Mass Index(kg/m^2)							
Mean	21.5	21.9	22.2	21.9	22.1	22.8	22.1
SD	3.2	3.8	2.9	3.9	3.2	3.8	3.5
Range	16.2-28.2	16.4-35.3	17.1-29.2	16.1-33.7	16.8-29.4	14.9-32.9	14.9-35.3
Height (cm)							
Mean	156.8	157.2	156.4	157.1	155.9	158.3	157.0
SD	6.8	6.9	7.2	8.0	7.3	6.9	7.2
Range	145.7-177.0	142.0-174.1	142.8-173.3	139.8-176.7	140.6-174.5	142.7-171.0	139.8-177.0

Body Mass Index was calculated as weight/(height/100)2.
BID = twice daily, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Efficacy Results:

The ACR20 response rates using LOCF method for handling missing components at Week 12 on the FAS were 37.74%, 67.92%, 73.08%, 84.91% and 90.74% for 1-, 3-, 5-, 10-, and 15-mg BID, respectively compared with 15.38% for placebo as shown in Table 5.

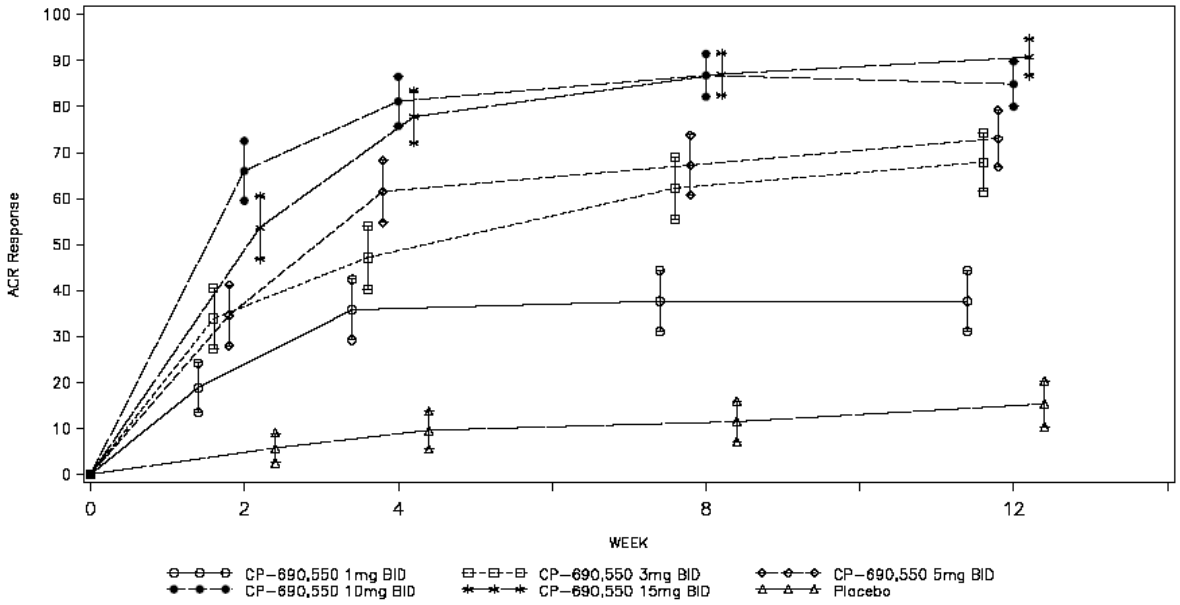
Table 5. Chi-Square Test on ACR 20 Response Rates at Week 12 (FAS, LOCF)

Treatment	N	n	Percent	Difference From Placebo		
				Difference	Chi-Square	p-Value
1 mg BID	53	20	37.74	22.35	6.71	0.0096
3 mg BID	53	36	67.92	52.54	29.76	<0.0001
5 mg BID	52	38	73.08	57.69	35.08	<0.0001
10 mg BID	53	45	84.91	69.52	50.75	<0.0001
15 mg BID	54	49	90.74	75.36	60.52	<0.0001
Placebo	52	8	15.38	–	–	–

BID = twice daily, ACR = American college of rheumatology, FAS = full analysis set, LOCF = last observation carried forward, N = total number of subjects, n = number of subjects in sub group.

The ACR20 response rates are shown in Figure 2.

Figure 2. ACR20 Response Rates (Percent ± SE) at Baseline and Weeks 2, 4, 8 and 12 (FAS, LOCF)



ACR = American college of rheumatology, FAS = full analysis set, LOCF = last observation carried forward CP-690,550 = tofacitinib.

The ACR20 response rates at Weeks 2, 4, 8 and 12. are shown in Table 6.

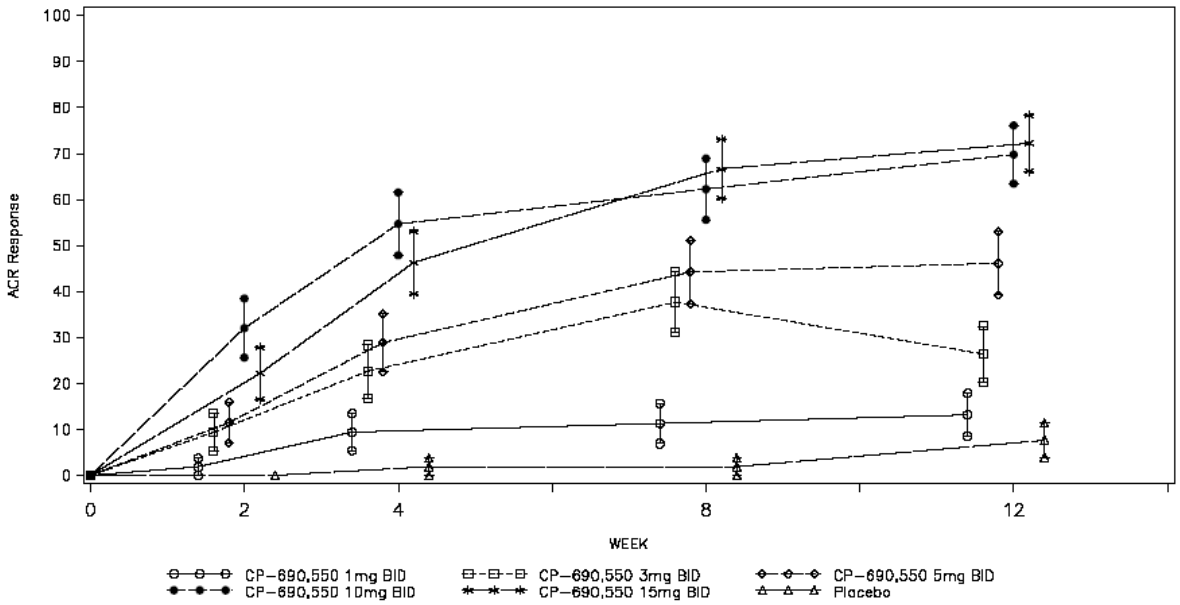
Table 6. ACR20 Response Rates at Weeks 2, 4, 8 and 12 (FAS, LOCF)

					Difference From Placebo				
							95% CI		
	N	n	Percent	SE	Difference (%)	SE	Lower	Upper	p-Value
Week 2									
1 mg BID	53	10	18.87	5.37	13.10	6.27	0.81	25.39	0.0368
3 mg BID	53	18	33.96	6.51	28.19	7.26	13.95	42.43	0.0001
5 mg BID	52	18	34.62	6.60	28.85	7.35	14.45	43.25	<0.0001
10 mg BID	53	35	66.04	6.51	60.27	7.26	46.03	74.51	<0.0001
15 mg BID	54	29	53.70	6.79	47.93	7.52	33.20	62.67	<0.0001
Placebo	52	3	5.77	3.23	–	–	–	–	–
Week 4									
1 mg BID	53	19	35.85	6.59	26.23	7.75	11.04	41.43	0.0007
3 mg BID	53	25	47.17	6.86	37.55	7.98	21.91	53.20	<0.0001
5 mg BID	52	32	61.54	6.75	51.92	7.89	36.46	67.38	<0.0001
10 mg BID	53	43	81.13	5.37	71.52	6.75	58.28	84.75	<0.0001
15 mg BID	54	42	77.78	5.66	68.16	6.98	54.48	81.84	<0.0001
Placebo	52	5	9.62	4.09	–	–	–	–	–
Week 8									
1 mg BID	53	20	37.74	6.66	26.20	8.00	10.52	41.87	0.0011
3 mg BID	53	33	62.26	6.66	50.73	8.00	35.05	66.40	<0.0001
5 mg BID	52	35	67.31	6.51	55.77	7.87	40.34	71.20	<0.0001
10 mg BID	53	46	86.79	4.65	75.25	6.42	62.66	87.84	<0.0001
15 mg BID	54	47	87.04	4.57	75.50	6.37	63.02	87.98	<0.0001
Placebo	52	6	11.54	4.43	–	–	–	–	–
Week 12									
1 mg BID	53	20	37.74	6.66	22.35	8.33	6.03	38.68	0.0073
3 mg BID	53	36	67.92	6.41	52.54	8.13	36.60	68.48	<0.0001
5 mg BID	52	38	73.08	6.15	57.69	7.93	42.15	73.23	<0.0001
10 mg BID	53	45	84.91	4.92	69.52	7.02	55.77	83.27	<0.0001
15 mg BID	54	49	90.74	3.94	75.36	6.37	62.87	87.84	<0.0001
Placebo	52	8	15.38	5.00	–	–	–	–	–

ACR = American college of rheumatology, BID = twice daily, CP-690,550 = tofacitinib, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, SE = standard error.

ACR50 response rates are shown in Figure 3 .

Figure 3. ACR50 Response Rates (Percent±SE) at Baseline and Weeks 2, 4, 8 and 12 (FAS, LOCF)



ACR = American college of rheumatology, BID = twice daily, FAS = full analysis set, LOCF = last observation carried forward CP-690,550 = tofacitinib, SE = standard error.

ACR50 response rates are shown in Table 7.

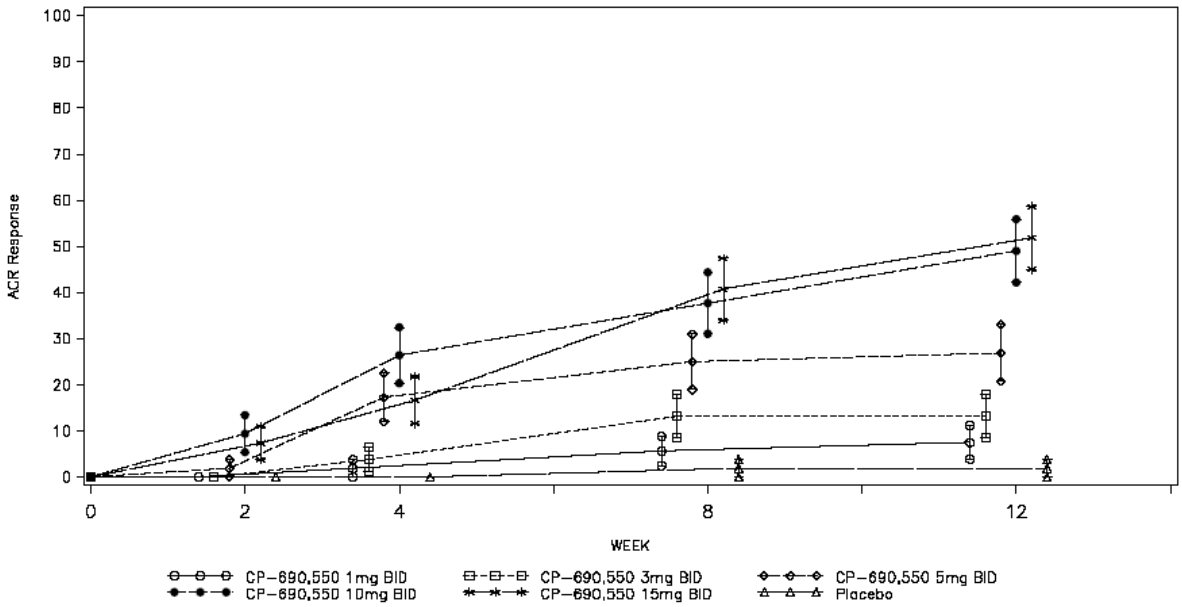
Table 7. ACR50 Response Rates at Weeks 2, 4, 8 and 12 (FAS, LOCF)

					Difference From Placebo				
							95% CI		
	N	n	Percent	SE	Difference (%)	SE	Lower	Upper	p-Value
Week 2									
1 mg BID	53	1	1.89	1.87	1.89	1.87	-1.78	5.55	0.3127
3 mg BID	53	5	9.43	4.02	9.43	4.02	1.56	17.30	0.0188
5 mg BID	52	6	11.54	4.43	11.54	4.43	2.85	20.22	0.0092
10 mg BID	53	17	32.08	6.41	32.08	6.41	19.51	44.64	<0.0001
15 mg BID	54	12	22.22	5.66	22.22	5.66	11.13	33.31	<0.0001
Placebo	52	0	0.00	–	–	–	–	–	–
Week 4									
1 mg BID	53	5	9.43	4.02	7.51	4.44	-1.20	16.22	0.0910
3 mg BID	53	12	22.64	5.75	20.72	6.06	8.85	32.59	0.0006
5 mg BID	52	15	28.85	6.28	26.92	6.56	14.06	39.79	<0.0001
10 mg BID	53	29	54.72	6.84	52.79	7.10	38.88	66.71	<0.0001
15 mg BID	54	25	46.30	6.79	44.37	7.05	30.56	58.19	<0.0001
Placebo	52	1	1.92	1.90	–	–	–	–	–
Week 8									
1 mg BID	53	6	11.32	4.35	9.40	4.75	0.09	18.71	0.0479
3 mg BID	53	20	37.74	6.66	35.81	6.93	22.24	49.39	<0.0001
5 mg BID	52	23	44.23	6.89	42.31	7.15	28.30	56.31	<0.0001
10 mg BID	53	33	62.26	6.66	60.34	6.93	46.77	73.91	<0.0001
15 mg BID	54	36	66.67	6.42	64.74	6.69	51.63	77.86	<0.0001
Placebo	52	1	1.92	1.90	–	–	–	–	–
Week 12									
1 mg BID	53	7	13.21	4.65	5.52	5.94	-6.13	17.16	0.3532
3 mg BID	53	14	26.42	6.06	18.72	7.09	4.82	32.63	0.0083
5 mg BID	52	24	46.15	6.91	38.46	7.84	23.10	53.83	<0.0001
10 mg BID	53	37	69.81	6.31	62.12	7.31	47.79	76.44	<0.0001
15 mg BID	54	39	72.22	6.10	64.53	7.13	50.56	78.50	<0.0001
Placebo	52	4	7.69	3.70	–	–	–	–	–

ACR = American college of rheumatology, BID = twice daily, SE = standard error, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = total number of subjects, n = number of subjects in sub group.

ACR70 response rates are shown in Figure 4.

Figure 4. ACR70 Response Rates (Percent ± SE) at Baseline and Weeks 2, 4, 8 and 12 (FAS, LOCF)



ACR = American college of rheumatology, BID = twice daily, SE = standard error, FAS = full analysis set, LOCF = last observation carried forward, CP-690,550 = tofacitinib, SE = standard error.

ACR70 response rates are shown in Table 8.

Table 8. ACR70 Response Rates at Weeks 2, 4, 8 and 12 (FAS, LOCF)

					Difference From Placebo				
							95% CI		
	N	n	Percent	SE	Difference (%)	SE	Lower	Upper	p-Value
Week 2									
1 mg BID	53	0	0.00	–	0.00	–	–	–	1.000
3 mg BID	53	0	0.00	–	0.00	–	–	–	1.000
5 mg BID	52	1	1.92	1.90	1.92	1.90	-1.81	5.66	0.3126
10 mg BID	53	5	9.43	4.02	9.43	4.02	1.56	17.30	0.0188
15 mg BID	54	4	7.41	3.56	7.41	3.56	0.42	14.39	0.0377
Placebo	52	0	0.00	–	–	–	–	–	–
Week 4									
1 mg BID	53	1	1.89	1.87	1.89	1.87	-1.78	5.55	0.3127
3 mg BID	53	2	3.77	2.62	3.77	2.62	-1.36	8.90	0.1494
5 mg BID	52	9	17.31	5.25	17.31	5.25	7.03	27.59	0.0010
10 mg BID	53	14	26.42	6.06	26.42	6.06	14.55	38.28	<0.0001
15 mg BID	54	9	16.67	5.07	16.67	5.07	6.73	26.61	0.0010
Placebo	52	0	0.00	–	–	–	–	–	–
Week 8									
1 mg BID	53	3	5.66	3.17	3.74	3.70	-3.52	10.99	0.3127
3 mg BID	53	7	13.21	4.65	11.28	5.03	1.43	21.13	0.0247
5 mg BID	52	13	25.00	6.00	23.08	6.30	10.73	35.42	0.0002
10 mg BID	53	20	37.74	6.66	35.81	6.93	22.24	49.39	<0.0001
15 mg BID	54	22	40.74	6.69	38.82	6.95	25.19	52.44	<0.0001
Placebo	52	1	1.92	1.90	–	–	–	–	–
Week 12									
1 mg BID	53	4	7.55	3.63	5.62	4.10	-2.41	13.66	0.1699
3 mg BID	53	7	13.21	4.65	11.28	5.03	1.43	21.13	0.0247
5 mg BID	52	14	26.92	6.15	25.00	6.44	12.38	37.62	0.0001
10 mg BID	53	26	49.06	6.87	47.13	7.13	33.17	61.10	<0.0001
15 mg BID	54	28	51.85	6.80	49.93	7.06	36.09	63.77	<0.0001
Placebo	52	1	1.92	1.90	–	–	–	–	–

ACR = American college of rheumatology, BID = twice daily, SE = standard error, CI = confidence interval, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = total number of subjects, n = number of subjects in sub group

ACR90 response rates are shown in Table 9.

Table 9. ACR90 Response Rates at Weeks 2, 4, 8 and 12 (FAS, LOCF)

					Difference From Placebo				
							95% CI		
	N	n	Percent	SE	Difference (%)	SE	Lower	Upper	p-Value
Week 2									
1 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
5 mg BID	52	0	0.00	–	0.00	–	–	–	1.0000
10 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
15 mg BID	54	0	0.00	–	0.00	–	–	–	1.0000
Placebo	52	0	0.00	–	–	–	–	–	–
Week 4									
1 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
5 mg BID	52	0	0.00	–	0.00	–	–	–	1.0000
10 mg BID	53	2	3.77	2.62	3.77	2.62	-1.36	8.90	0.1494
15 mg BID	54	3	5.56	3.12	5.56	3.12	-0.55	11.67	0.0747
Placebo	52	0	0.00	–	–	–	–	–	–
Week 8									
1 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
5 mg BID	52	3	5.77	3.23	5.77	3.23	-0.57	12.11	0.0744
10 mg BID	53	7	13.21	4.65	13.21	4.65	4.09	22.32	0.0045
15 mg BID	54	5	9.26	3.94	9.26	3.94	1.53	16.99	0.0189
Placebo	52	0	0.00	–	–	–	–	–	–
Week 12									
1 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
3 mg BID	53	0	0.00	–	0.00	–	–	–	1.0000
5 mg BID	52	2	3.85	2.67	3.85	2.67	-1.38	9.07	0.1492
10 mg BID	53	8	15.09	4.92	15.09	4.92	5.46	24.73	0.0021
15 mg BID	54	6	11.11	4.28	11.11	4.28	2.73	19.49	0.0094
Placebo	52	0	0.00	–	–	–	–	–	–

ACR = American college of rheumatology, BID = twice daily, SE = standard error, CI = confidence interval, CI = confidence interval, FAS = full analysis set, LOCF = last observation carried forward, N = total number of subjects, n = number of subjects in sub group.

The mean changes from Baseline in painful and tender joint counts are presented in Table 10.

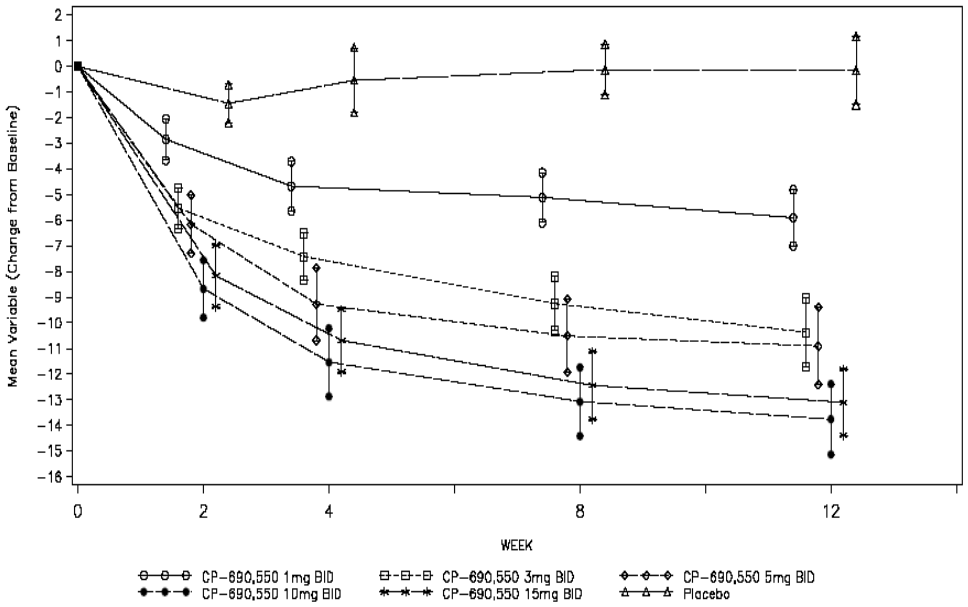
Table 10. Mean Change From Baseline in Tender-Joint Counts at Weeks 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	53	-4.14	0.98	-2.11	1.38	-4.82	0.60	0.1271
3 mg BID	53	-5.13	0.97	-3.10	1.38	-5.82	-0.39	0.0250
5 mg BID	51	-5.29	0.99	-3.27	1.40	-6.01	-0.52	0.0198
10 mg BID	52	-8.48	0.98	-6.46	1.39	-9.18	-3.73	<0.0001
15 mg BID	54	-7.73	0.96	-5.70	1.37	-8.40	-3.00	<0.0001
Placebo	52	-2.03	0.98	–	–	–	–	–
Week 4								
1 mg BID	52	-5.92	0.98	-4.79	1.38	-7.51	-2.08	0.0006
3 mg BID	51	-6.95	0.98	-5.83	1.39	-8.56	-3.10	<0.0001
5 mg BID	51	-8.41	0.99	-7.29	1.40	-10.03	-4.54	<0.0001
10 mg BID	52	-11.35	0.98	-10.22	1.39	-12.95	-7.50	<0.0001
15 mg BID	52	-10.41	0.97	-9.28	1.38	-12.00	-6.57	<0.0001
Placebo	52	-1.12	0.98	–	–	–	–	–
Week 8								
1 mg BID	51	-6.27	0.98	-5.78	1.39	-8.52	-3.05	<0.0001
3 mg BID	51	-8.80	0.98	-8.31	1.39	-11.05	-5.57	<0.0001
5 mg BID	51	-9.65	0.99	-9.16	1.40	-11.92	-6.40	<0.0001
10 mg BID	52	-12.89	0.98	-12.40	1.39	-15.14	-9.66	<0.0001
15 mg BID	52	-12.16	0.97	-11.67	1.39	-14.40	-8.95	<0.0001
Placebo	50	-0.49	0.99	–	–	–	–	–
Week 12								
1 mg BID	51	-7.05	0.98	-6.38	1.40	-9.13	-3.63	<0.0001
3 mg BID	49	-10.01	0.99	-9.34	1.41	-12.10	-6.58	<0.0001
5 mg BID	50	-10.08	1.00	-9.41	1.41	-12.18	-6.64	<0.0001
10 mg BID	49	-13.67	0.99	-13.00	1.41	-15.76	-10.23	<0.0001
15 mg BID	52	-12.81	0.97	-12.14	1.39	-14.88	-9.40	<0.0001
Placebo	48	-0.67	1.00	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect.
ACR = American college of rheumatology, BID = twice daily, SE = standard error, CI = confidence interval, FAS = full analysis set, N= total number of subjects, n = number of subjects in sub group.

The mean changes from Baseline in painful and tender joint counts are presented in Figure 5.

Figure 5. Mean Change (Mean ± SE) From Baseline in Tender-Joint Counts at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The mean changes from Baseline in swollen joint counts are presented in Table 11.

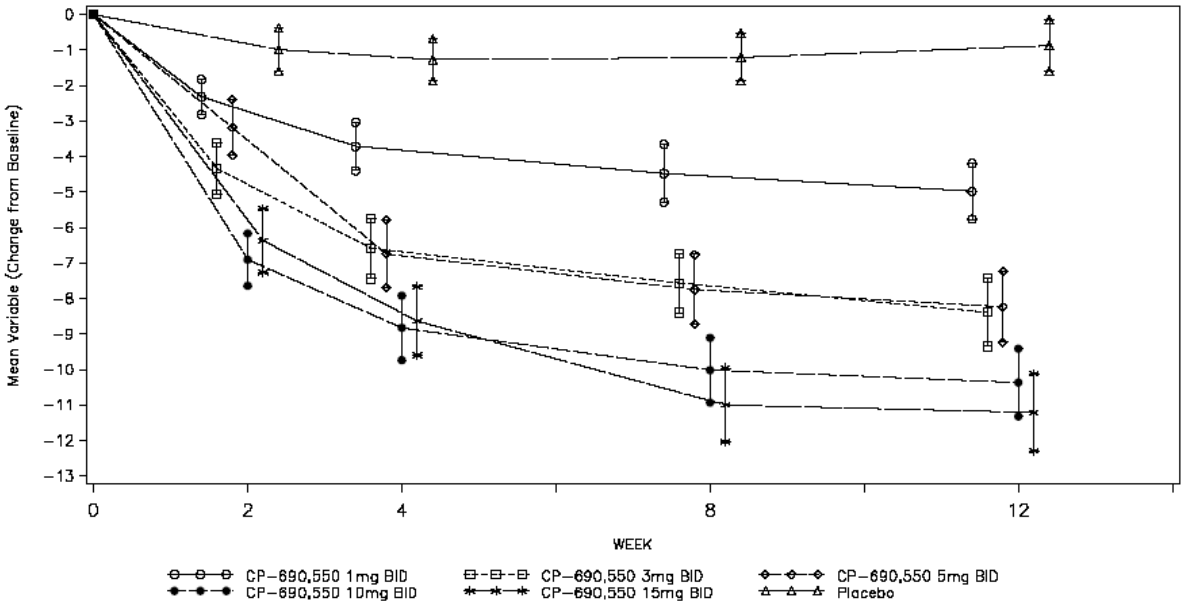
Table 11. Mean Change From Baseline in Swollen Joint Counts at Weeks 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	53	-3.19	0.69	-1.61	0.97	-3.52	0.30	0.0983
3 mg BID	53	-3.85	0.68	-2.27	0.97	-4.18	-0.36	0.0202
5 mg BID	51	-2.58	0.70	-1.00	0.98	-2.93	0.93	0.3102
10 mg BID	52	-6.93	0.69	-5.34	0.98	-7.26	-3.43	<0.0001
15 mg BID	54	-5.95	0.68	-4.36	0.97	-6.27	-2.46	<0.0001
Placebo	52	-1.58	0.69	–	–	–	–	–
Week 4								
1 mg BID	52	-4.57	0.69	-2.70	0.97	-4.61	-0.78	0.0058
3 mg BID	51	-6.10	0.69	-4.23	0.98	-6.16	-2.31	<0.0001
5 mg BID	51	-6.15	0.70	-4.28	0.98	-6.21	-2.35	<0.0001
10 mg BID	52	-8.85	0.69	-6.98	0.98	-8.90	-5.06	<0.0001
15 mg BID	52	-8.15	0.68	-6.28	0.97	-8.20	-4.37	<0.0001
Placebo	52	-1.87	0.69	–	–	–	–	–
Week 8								
1 mg BID	51	-5.25	0.69	-3.55	0.98	-5.48	-1.62	0.0003
3 mg BID	51	-7.08	0.69	-5.38	0.98	-7.32	-3.45	<0.0001
5 mg BID	51	-7.15	0.70	-5.45	0.99	-7.39	-3.51	<0.0001
10 mg BID	52	-10.04	0.69	-8.34	0.98	-10.27	-6.42	<0.0001
15 mg BID	52	-10.52	0.68	-8.82	0.98	-10.74	-6.90	<0.0001
Placebo	50	-1.70	0.70	–	–	–	–	–
Week 12								
1 mg BID	51	-5.76	0.69	-4.47	0.98	-6.40	-2.53	<0.0001
3 mg BID	49	-7.94	0.70	-6.65	0.99	-8.60	-4.70	<0.0001
5 mg BID	50	-7.75	0.70	-6.46	1.00	-8.42	-4.51	<0.0001
10 mg BID	49	-10.44	0.70	-9.15	0.99	-11.10	-7.20	<0.0001
15 mg BID	52	-10.73	0.68	-9.44	0.98	-11.37	-7.51	<0.0001
Placebo	48	-1.29	0.70	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect.
BID = twice daily, SE = standard error, CI = confidence interval, FAS = full analysis set, N= total number of subjects, n = number of subjects in sub.

The mean changes from Baseline in swollen joint counts are presented in Figure 6.

Figure 6. Mean Change (Mean ± SE) from Baseline in Swollen-Joint Counts at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The mean changes from Baseline in Patient's assessment of pain VAS scores are presented in Table 12.

Table 12. Mean Change from Baseline in Pain Visual Analog Score at Weeks 2, 4, 8 and 12 (FAS)

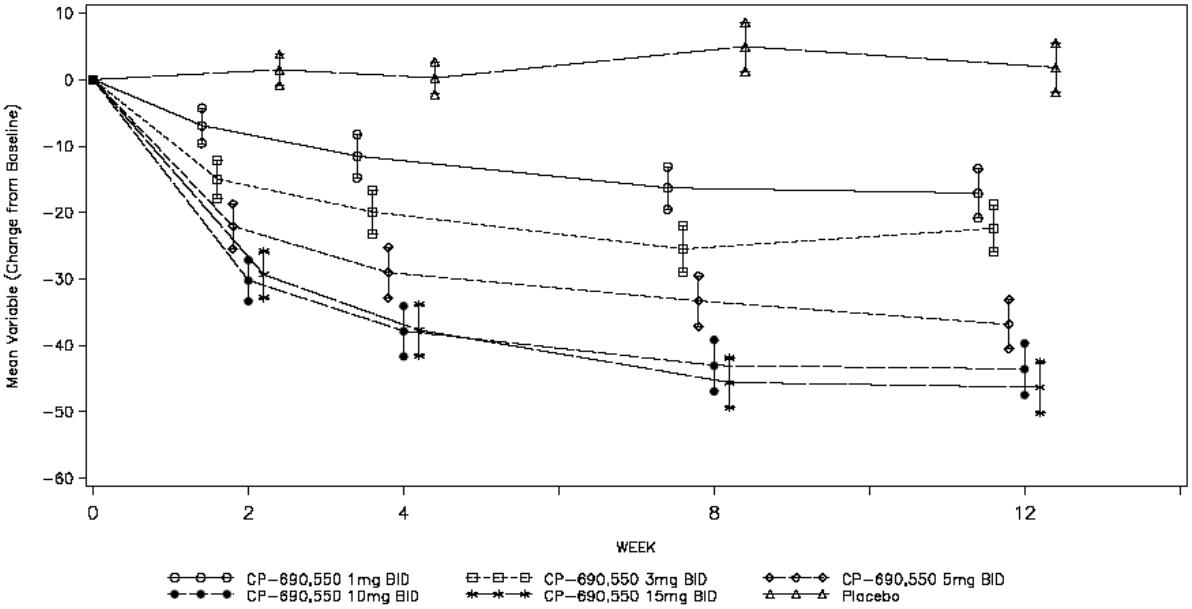
				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	53	-8.63	2.94	-7.18	4.18	-15.38	1.03	0.0864
3 mg BID	53	-16.70	2.94	-15.24	4.18	-23.45	-7.04	0.0003
5 mg BID	51	-19.13	3.01	-17.68	4.24	-26.02	-9.34	<0.0001
10 mg BID	52	-29.03	2.97	-27.58	4.21	-35.85	-19.31	<0.0001
15 mg BID	54	-26.45	2.92	-24.99	4.18	-33.21	-16.77	<0.0001
Placebo	52	-1.46	2.98	–	–	–	–	–
Week 4								
1 mg BID	52	-12.97	2.96	-10.24	4.19	-18.47	-2.02	0.0148
3 mg BID	51	-21.19	2.98	-18.47	4.20	-26.72	-10.22	<0.0001
5 mg BID	51	-26.06	3.01	-23.33	4.24	-31.67	-14.99	<0.0001
10 mg BID	52	-36.65	2.97	-33.92	4.21	-42.19	-25.65	<0.0001
15 mg BID	52	-35.16	2.95	-32.43	4.21	-40.70	-24.17	<0.0001
Placebo	52	-2.73	2.98	–	–	–	–	–
Week 8								
1 mg BID	51	-17.57	2.97	-19.22	4.22	-27.50	-10.93	<0.0001
3 mg BID	50	-26.15	2.99	-27.80	4.23	-36.11	-19.49	<0.0001
5 mg BID	51	-30.37	3.01	-32.01	4.27	-40.39	-23.64	<0.0001
10 mg BID	52	-41.84	2.97	-43.49	4.23	-51.80	-35.18	<0.0001
15 mg BID	52	-43.08	2.95	-44.73	4.23	-53.03	-36.42	<0.0001
Placebo	50	1.65	3.01	–	–	–	–	–
Week 12								
1 mg BID	51	-18.38	2.97	-17.31	4.24	-25.64	-8.99	<0.0001
3 mg BID	49	-22.33	3.00	-21.26	4.26	-29.63	-12.90	<0.0001
5 mg BID	50	-34.37	3.02	-33.31	4.29	-41.75	-24.88	<0.0001
10 mg BID	49	-42.91	3.01	-41.85	4.28	-50.25	-33.44	<0.0001
15 mg BID	52	-43.79	2.95	-42.73	4.25	-51.07	-34.39	<0.0001
Placebo	48	-1.06	3.03	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect. BID = twice daily, SE = standard error, CI = confidence interval, FAS = full analysis set, N= total number of subjects, n = number of subjects in sub.

The mean changes from Baseline in pain VAS scores are presented in

Figure 7.

Figure 7. Mean Change (Mean ± SE) From Baseline in Pain Visual Analog (VAS) Score at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The mean changes from Baseline in the subject's global assessment of arthritis are presented in Table 13.

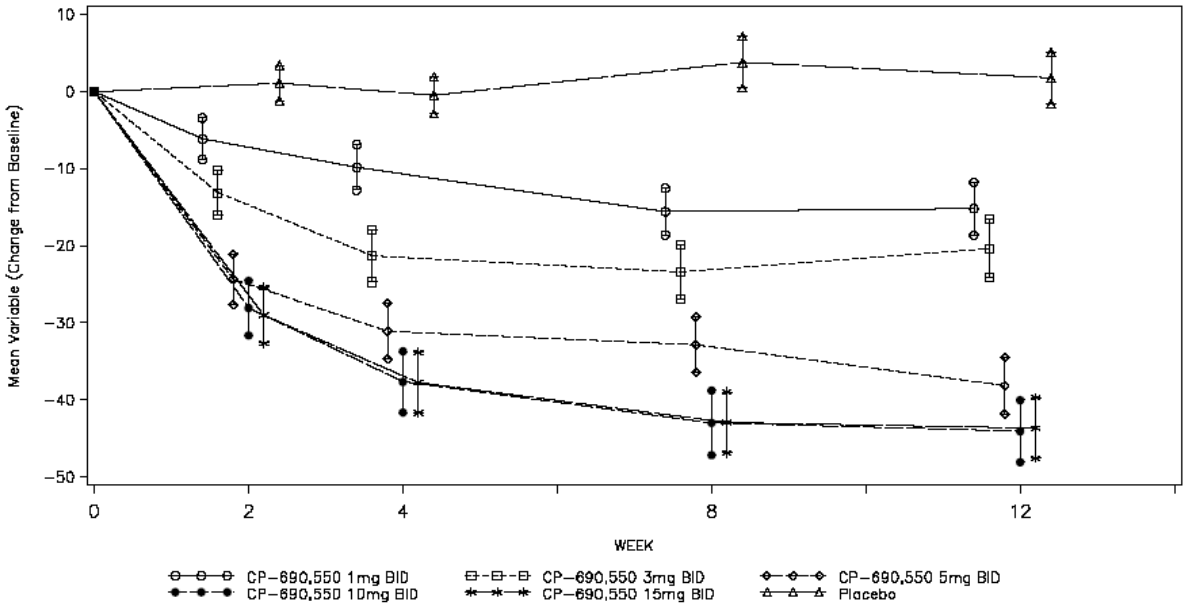
Table 13. Mean Change from Baseline in Subjects Global Assessment at Weeks 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	53	-7.66	2.96	-5.93	4.21	-14.20	2.34	0.1594
3 mg BID	53	-15.25	2.97	-13.51	4.21	-21.78	-5.25	0.0014
5 mg BID	51	-20.32	3.04	-18.59	4.29	-27.02	-10.16	<0.0001
10 mg BID	52	-27.06	2.99	-25.33	4.24	-33.66	-17.00	<0.0001
15 mg BID	54	-26.80	2.94	-25.06	4.21	-33.34	-16.79	<0.0001
Placebo	52	-1.73	3.00	–	–	–	–	–
Week 4								
1 mg BID	52	-11.22	2.98	-7.91	4.22	-16.20	0.38	0.0614
3 mg BID	51	-23.17	3.00	-19.86	4.23	-28.17	-11.56	<0.0001
5 mg BID	51	-27.03	3.04	-23.72	4.29	-32.15	-15.29	<0.0001
10 mg BID	52	-36.64	2.99	-33.33	4.24	-41.66	-25.00	<0.0001
15 mg BID	52	-35.96	2.97	-32.65	4.23	-40.96	-24.33	<0.0001
Placebo	52	-3.31	3.00	–	–	–	–	–
Week 8								
1 mg BID	51	-16.66	2.99	-17.45	4.25	-25.79	-9.10	<0.0001
3 mg BID	50	-24.60	3.01	-25.39	4.26	-33.76	-17.02	<0.0001
5 mg BID	51	-28.78	3.04	-29.56	4.31	-38.03	-21.10	<0.0001
10 mg BID	52	-41.97	2.99	-42.75	4.26	-51.12	-34.39	<0.0001
15 mg BID	52	-41.13	2.97	-41.92	4.25	-50.27	-33.56	<0.0001
Placebo	50	0.79	3.03	–	–	–	–	–
Week 12								
1 mg BID	51	-16.29	2.99	-15.27	4.27	-23.65	-6.88	0.0004
3 mg BID	49	-20.91	3.03	-19.89	4.29	-28.32	-11.47	<0.0001
5 mg BID	50	-34.59	3.05	-33.56	4.34	-42.08	-25.05	<0.0001
10 mg BID	49	-43.55	3.03	-42.53	4.31	-50.99	-34.07	<0.0001
15 mg BID	52	-41.86	2.97	-40.84	4.27	-49.23	-32.45	<0.0001
Placebo	48	-1.02	3.05	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect.
BID = twice daily, SE = standard error, CI = confidence interval, FAS = full analysis set, N= total number of subjects, n = number of subjects in sub.

The mean changes from Baseline in the subject's global assessment of arthritis are presented in Figure 8.

Figure 8. Mean Change (Mean ± SE) From Baseline in Subjects Global Assessment at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The mean changes from baseline in the physician's global assessment of arthritis are presented in Table 14.

Table 14. Mean Change from Baseline in Physician Global Assessment at Weeks 2, 4, 8 and 12 (FAS)

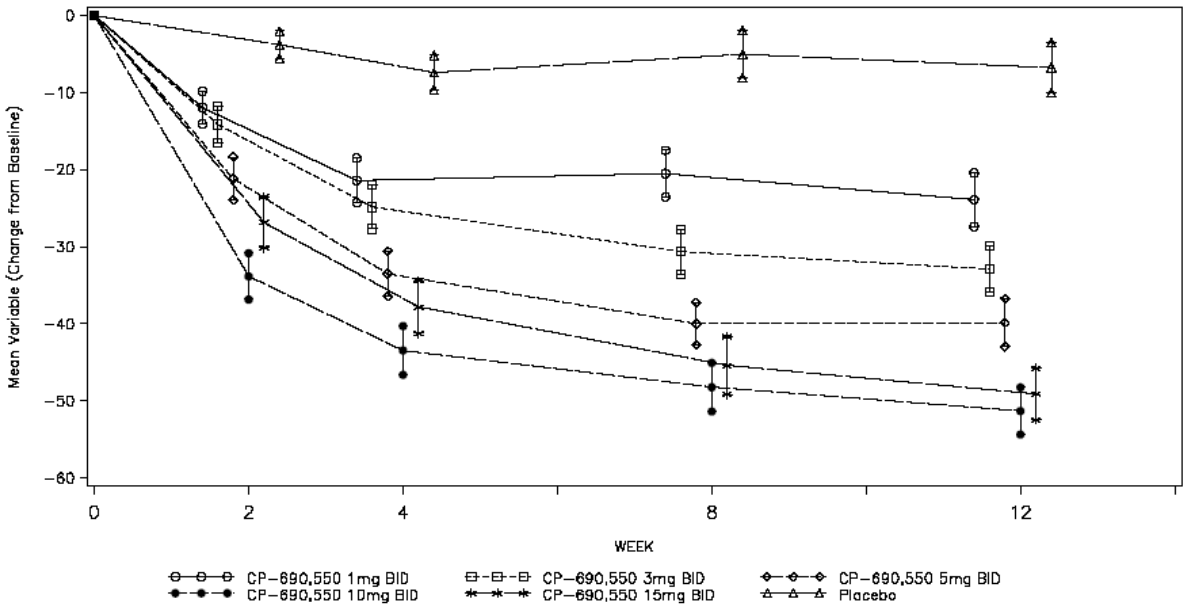
				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	53	-13.97	2.64	-7.88	3.74	-15.22	-0.55	0.0352
3 mg BID	53	-15.86	2.63	-9.78	3.74	-17.12	-2.44	0.0091
5 mg BID	51	-18.10	2.70	-12.01	3.81	-19.49	-4.53	0.0017
10 mg BID	52	-31.59	2.66	-25.51	3.78	-32.93	-18.08	<0.0001
15 mg BID	54	-25.93	2.61	-19.84	3.73	-27.17	-12.51	<0.0001
Placebo	52	-6.09	2.66	–	–	–	–	–
Week 4								
1 mg BID	52	-23.31	2.65	-13.61	3.75	-20.97	-6.25	0.0003
3 mg BID	51	-26.22	2.67	-16.52	3.76	-23.90	-9.14	<0.0001
5 mg BID	51	-30.45	2.70	-20.75	3.81	-28.23	-13.27	<0.0001
10 mg BID	52	-41.21	2.66	-31.51	3.78	-38.93	-24.08	<0.0001
15 mg BID	52	-37.07	2.64	-27.37	3.75	-34.74	-20.00	<0.0001
Placebo	52	-9.070	2.66	–	–	–	–	–
Week 8								
1 mg BID	51	-21.99	2.66	-15.15	3.77	-22.56	-7.74	<0.0001
3 mg BID	51	-32.04	2.67	-25.21	3.78	-32.62	-17.79	<0.0001
5 mg BID	51	-36.92	2.70	-30.08	3.83	-37.60	-22.57	<0.0001
10 mg BID	52	-45.98	2.66	-39.14	3.80	-46.60	-31.68	<0.0001
15 mg BID	52	-44.66	2.64	-37.83	3.77	-45.24	-30.42	<0.0001
Placebo	50	-6.84	2.69	–	–	–	–	–
Week 12								
1 mg BID	51	-25.38	2.66	-17.03	3.79	-24.48	-9.58	<0.0001
3 mg BID	49	-33.47	2.69	-25.13	3.81	-32.61	-17.64	<0.0001
5 mg BID	50	-36.89	2.71	-28.54	3.85	-36.11	-20.98	<0.0001
10 mg BID	49	-49.38	2.70	-41.03	3.84	-48.57	-33.48	<0.0001
15 mg BID	52	-48.36	2.64	-40.01	3.79	-47.45	-32.56	<0.0001
Placebo	48	-8.35	2.72	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect.
BID = twice daily, SE = standard error, CI = confidence interval, FAS = full analysis set, N= total number of subjects, n = number of subjects in sub.

The mean changes from baseline in the physician's global assessment of arthritis are presented in

Figure 9.

Figure 9. Mean Change (Mean ± SE) From Baseline in Physician Global Assessment at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The HAQ-DI values decreased over time and with increased dose of tofacitinib, which was indicative of improved functional status. The changes from Baseline in HAQ-DI values are presented in Table 15.

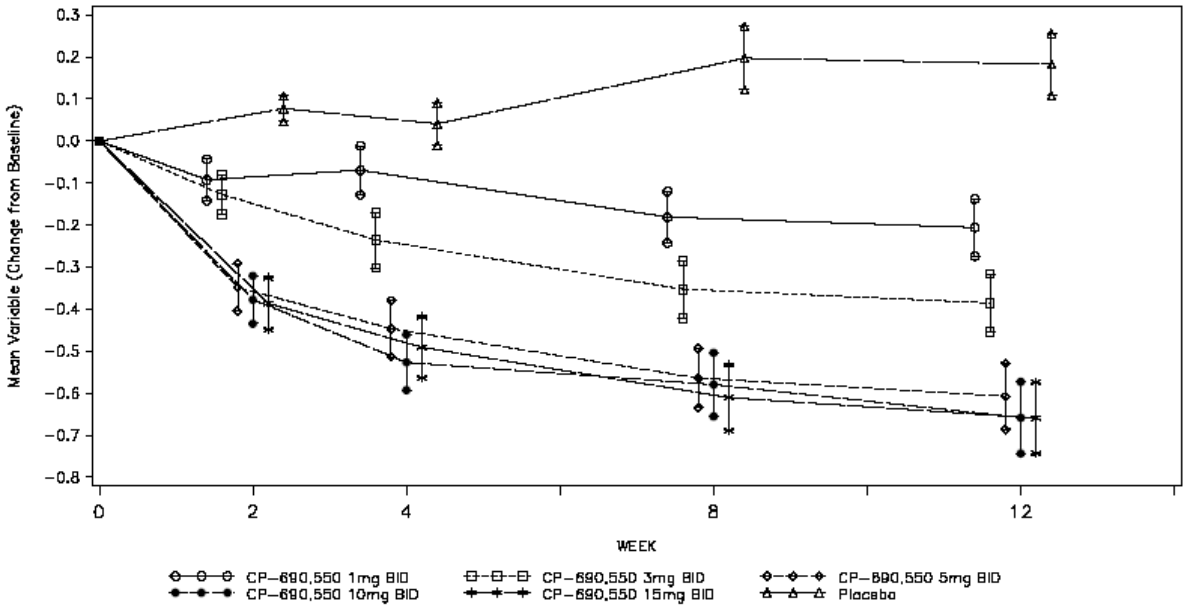
Table 15. Mean Change from Baseline in HAQ-DI at Weeks 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	53	-0.10	0.06	-0.16	0.09	-0.33	0.01	0.0640
3 mg BID	53	-0.15	0.06	-0.21	0.09	-0.38	-0.04	0.0140
5 mg BID	51	-0.28	0.06	-0.34	0.09	-0.51	-0.17	0.0001
10 mg BID	52	-0.39	0.06	-0.45	0.09	-0.62	-0.28	<0.0001
15 mg BID	54	-0.40	0.06	-0.47	0.09	-0.63	-0.30	<0.0001
Placebo	52	0.06	0.06	–	–	–	–	–
Week 4								
1 mg BID	52	-0.07	0.06	-0.10	0.09	-0.26	0.07	0.2620
3 mg BID	51	-0.25	0.06	-0.28	0.09	-0.45	-0.11	0.0011
5 mg BID	51	-0.38	0.06	-0.40	0.09	-0.57	-0.23	<0.0001
10 mg BID	52	-0.54	0.06	-0.56	0.09	-0.73	-0.40	<0.0001
15 mg BID	52	-0.51	0.06	-0.54	0.09	-0.71	-0.37	<0.0001
Placebo	52	0.03	0.06	–	–	–	–	–
Week 8								
1 mg BID	51	-0.17	0.06	-0.35	0.09	-0.52	-0.18	<0.0001
3 mg BID	50	-0.36	0.06	-0.54	0.09	-0.71	-0.37	<0.0001
5 mg BID	51	-0.49	0.06	-0.67	0.09	-0.84	-0.50	<0.0001
10 mg BID	52	-0.59	0.06	-0.77	0.09	-0.94	-0.60	<0.0001
15 mg BID	52	-0.63	0.06	-0.81	0.09	-0.98	-0.64	<0.0001
Placebo	50	0.18	0.06	–	–	–	–	–
Week 12								
1 mg BID	51	-0.19	0.06	-0.37	0.09	-0.54	-0.20	<0.0001
3 mg BID	49	-0.38	0.06	-0.56	0.09	-0.73	-0.39	<0.0001
5 mg BID	50	-0.55	0.06	-0.73	0.09	-0.90	-0.56	<0.0001
10 mg BID	49	-0.67	0.06	-0.84	0.09	-1.01	-0.67	<0.0001
15 mg BID	52	-0.68	0.06	-0.86	0.09	-1.02	-0.69	<0.0001
Placebo	48	0.18	0.06	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect.
BID = twice daily, SE = standard error, CI = confidence interval, FAS = full analysis set, HAQ-DI = health assessment questionnaire - disability index, N= total number of subjects, n = number of subjects in sub.

The changes from Baseline in HAQ-DI values are presented in Figure 10.

Figure 10. Mean Change (Mean ± SE) From Baseline in HAQ-DI at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, HAQ-DI = health assessment questionnaire - disability index, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The mean changes from Baseline in serum CRP level are presented in Table 16.

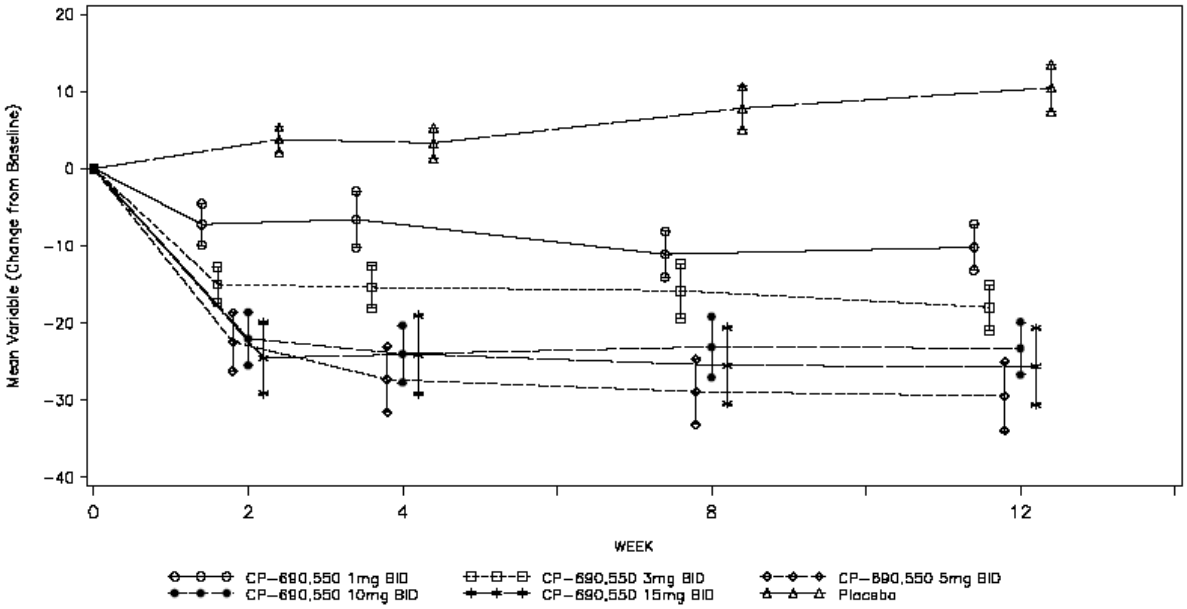
Table 16. Mean Change from Baseline in C-Reactive Protein (mg/L) at Weeks 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	53	-5.69	2.24	-6.70	3.19	-12.96	-0.44	0.0358
3 mg BID	53	-16.61	2.24	-17.63	3.18	-23.88	-11.38	<0.0001
5 mg BID	51	-17.32	2.29	-18.33	3.23	-24.67	-12.00	<0.0001
10 mg BID	52	-22.50	2.26	-23.51	3.20	-29.79	-17.23	<0.0001
15 mg BID	54	-24.95	2.22	-25.96	3.17	-32.19	-19.74	<0.0001
Placebo	52	1.02	2.26	–	–	–	–	–
Week 4								
1 mg BID	52	-5.56	2.25	-6.15	3.20	-12.42	0.13	0.0549
3 mg BID	51	-16.26	2.27	-16.85	3.20	-23.14	-10.56	<0.0001
5 mg BID	51	-22.20	2.29	-22.79	3.23	-29.13	-16.45	<0.0001
10 mg BID	52	-24.47	2.26	-25.06	3.20	-31.34	-18.78	<0.0001
15 mg BID	52	-24.59	2.25	-25.18	3.19	-31.44	-18.92	<0.0001
Placebo	52	0.59	2.26	–	–	–	–	–
Week 8								
1 mg BID	51	-9.79	2.27	-15.07	3.22	-21.40	-8.74	<0.0001
3 mg BID	51	-16.71	2.27	-21.98	3.22	-28.31	-15.66	<0.0001
5 mg BID	51	-23.80	2.29	-29.08	3.22	-35.45	-22.70	<0.0001
10 mg BID	52	-23.56	2.26	-28.84	3.25	-35.15	-22.52	<0.0001
15 mg BID	52	-26.03	2.25	-31.30	3.22	-37.60	-25.00	<0.0001
Placebo	50	5.27	2.29	–	3.21	–	–	–
Week 12								
1 mg BID	51	-8.88	2.27	-17.10	3.24	-23.46	-10.73	<0.0001
3 mg BID	49	-18.34	2.30	-26.56	3.26	-32.95	-20.16	<0.0001
5 mg BID	50	-23.97	2.30	-32.18	3.27	-38.61	-25.76	<0.0001
10 mg BID	49	-25.11	2.30	-33.33	3.26	-39.74	-26.93	<0.0001
15 mg BID	52	-26.14	2.25	-34.36	3.23	-40.69	-28.02	<0.0001
Placebo	48	8.22	2.32	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect.
BID = twice daily, SE = standard error, CI = confidence interval, FAS = full analysis set, N= total number of subjects, n = number of subjects in sub.

The mean changes from Baseline in serum CRP level are presented in Figure 11.

Figure 11. Mean Change (Mean ± SE) From Baseline in C-Reactive Protein (mg/L) at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The mean changes from Baseline in ACR-N are presented in Table 17.

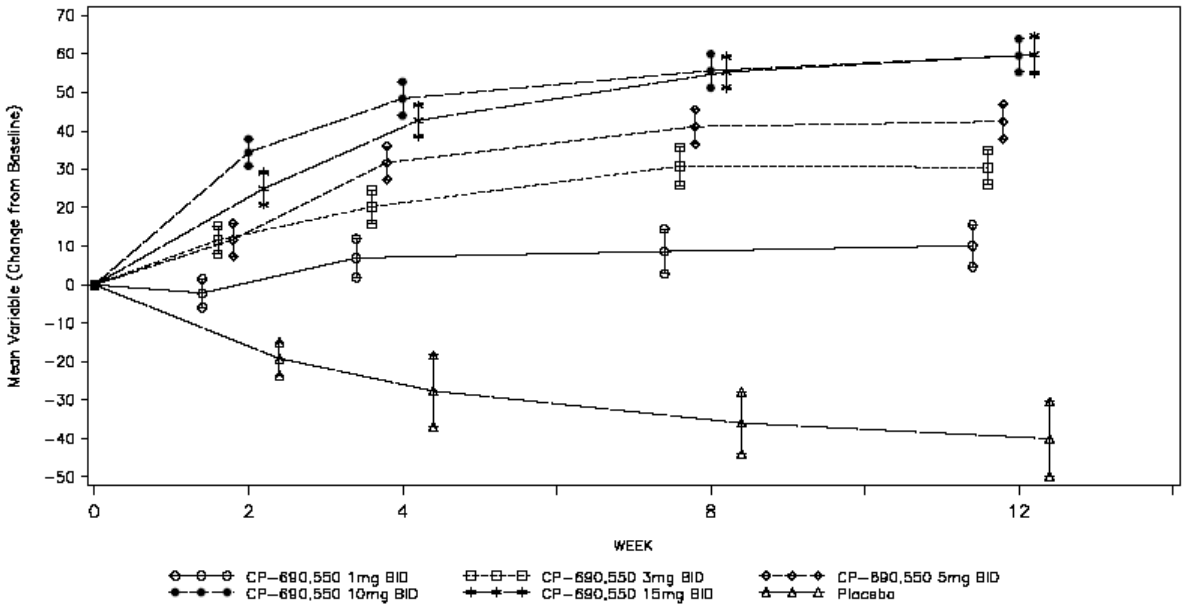
Table 17. Mean Change From Baseline in ACR-N at Weeks 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2 (LOCF)								
1 mg BID	53	-2.22	5.22	16.98	7.42	2.41	31.55	0.0025
3 mg BID	53	11.58	5.22	30.78	7.42	16.21	45.35	<0.0001
5 mg BID	52	11.67	5.27	30.87	7.46	16.23	45.51	<0.0001
10 mg BID	53	34.38	5.22	53.58	7.42	39.01	68.16	<0.0001
15 mg BID	54	24.99	5.17	44.20	7.39	29.69	58.70	<0.0001
Placebo	52	-19.20	5.27	–	–	–	–	–
Week 4 (LOCF)								
1 mg BID	53	6.92	5.22	34.53	7.42	19.96	49.10	<0.0001
3 mg BID	53	20.20	5.22	47.81	7.42	33.24	62.38	<0.0001
5 mg BID	52	31.70	5.27	59.31	7.46	44.67	73.95	<0.0001
10 mg BID	53	48.36	5.22	75.97	7.42	61.40	90.55	<0.0001
15 mg BID	54	42.64	5.17	70.25	7.39	55.74	84.75	<0.0001
Placebo	52	-27.61	5.27	–	–	–	–	–
Week 8 (LOCF)								
1 mg BID	53	8.67	5.22	44.59	7.42	30.02	59.16	<0.0001
3 mg BID	53	30.82	5.22	66.75	7.42	52.18	81.32	<0.0001
5 mg BID	52	41.05	5.27	76.98	7.46	62.34	91.62	<0.0001
10 mg BID	53	55.59	5.22	91.52	7.42	76.95	106.09	<0.0001
15 mg BID	54	55.24	5.17	91.17	7.39	76.66	105.67	<0.0001
Placebo	52	-35.93	5.27	–	–	–	–	–
Week 12 (LOCF)								
1 mg BID	53	10.11	5.22	50.15	7.42	35.58	64.72	<0.0001
3 mg BID	53	30.51	5.22	70.54	7.42	55.97	85.11	<0.0001
5 mg BID	52	42.46	5.27	82.49	7.46	67.85	97.13	<0.0001
10 mg BID	53	59.55	5.22	99.59	7.42	85.02	114.16	<0.0001
15 mg BID	54	59.77	5.17	99.80	7.39	85.30	114.31	<0.0001
Placebo	52	-40.03	5.27	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect.
ACR = American college of rheumatology, BID = twice daily, SE = standard error, CI = confidence interval
FAS = full analysis set, N= total number of subjects, n = number of subjects in sub.

The mean changes from Baseline in ACR-N are presented in Figure 12.

Figure 12. Mean Change (Mean±SE) From Baseline in ACR-N at Weeks 2, 4, 8 and 12 (FAS, LOCF)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The mean changes from Baseline in DAS28-3(CRP) are presented in Table 18.

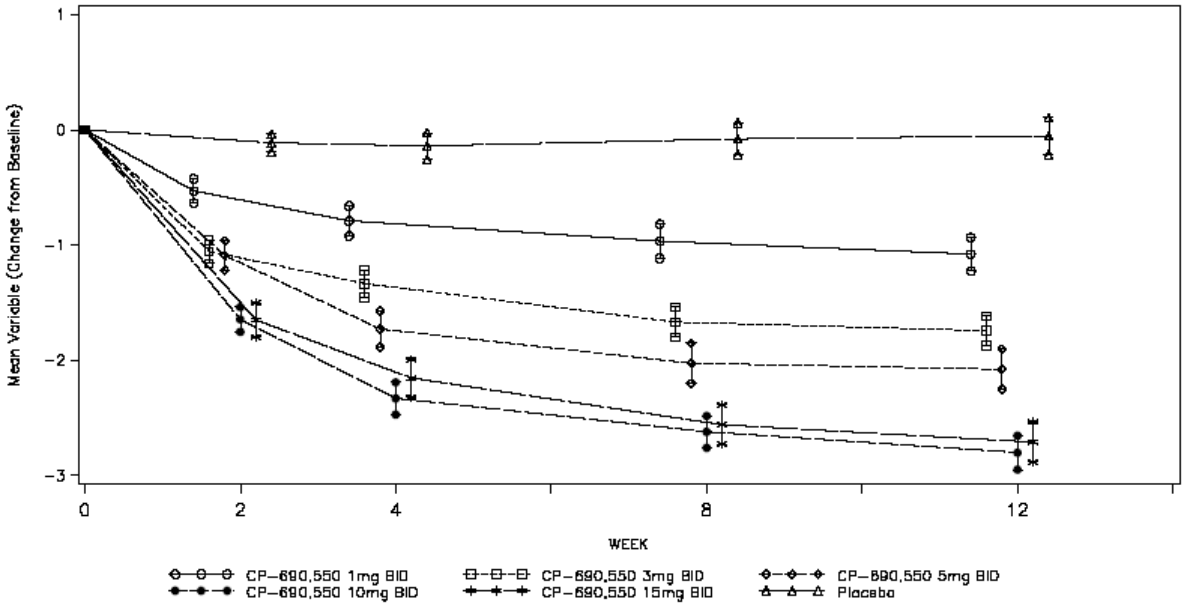
Table 18. Mean Change From Baseline in DAS28-3 (CRP) at Weeks 2, 4, 8 and 12 (FAS)

				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	53	-0.56	0.13	-0.36	0.18	-0.71	-0.00	0.0487
3 mg BID	53	-1.03	0.13	-0.83	0.18	-1.19	-0.48	<0.0001
5 mg BID	51	-1.01	0.13	-0.81	0.18	-1.17	-0.45	<0.0001
10 mg BID	52	-1.65	0.13	-1.44	0.18	-1.80	-1.09	<0.0001
15 mg BID	54	-1.63	0.13	-1.43	0.18	-1.78	-1.07	<0.0001
Placebo	52	-0.20	0.13	–	–	–	–	–
Week 4								
1 mg BID	52	-0.82	0.13	-0.59	0.18	-0.95	-0.23	0.0013
3 mg BID	51	-1.29	0.13	-1.06	0.18	-1.42	-0.70	<0.0001
5 mg BID	51	-1.65	0.13	-1.42	0.18	-1.78	-1.06	<0.0001
10 mg BID	52	-2.33	0.13	-2.10	0.18	-2.46	-1.74	<0.0001
15 mg BID	52	-2.14	0.13	-1.91	0.18	-2.27	-1.56	<0.0001
Placebo	52	-0.23	0.13	–	–	–	–	–
Week 8								
1 mg BID	51	-0.98	0.13	-0.83	0.18	-1.19	-0.47	<0.0001
3 mg BID	51	-1.63	0.13	-1.48	0.18	-1.84	-1.12	<0.0001
5 mg BID	51	-1.95	0.13	-1.80	0.19	-2.16	-1.43	<0.0001
10 mg BID	52	-2.62	0.13	-2.47	0.18	-2.83	-2.11	<0.0001
15 mg BID	52	-2.55	0.13	-2.39	0.18	-2.75	-2.04	<0.0001
Placebo	50	-0.15	0.13	–	–	–	–	–
Week 12								
1 mg BID	51	-1.09	0.13	-0.98	0.18	-1.34	-0.61	<0.0001
3 mg BID	49	-1.71	0.13	-1.59	0.19	-1.95	-1.23	<0.0001
5 mg BID	50	-2.02	0.13	-1.90	0.19	-2.27	-1.54	<0.0001
10 mg BID	49	-2.81	0.13	-2.69	0.19	-3.05	-2.32	<0.0001
15 mg BID	52	-2.70	0.13	-2.58	0.18	-2.94	-2.22	<0.0001
Placebo	48	-0.12	0.13	–	–	–	–	–

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and Baseline as fixed effects and subject as a random effect.
BID = twice daily, SE = standard error, CI = confidence interval, DAS = disease activity score, FAS = full analysis set.

The mean changes from Baseline in DAS28-3(CRP) are presented in Figure 13.

Figure 13. Mean Change (Mean ± SE) From Baseline in DAS28-3(CRP) at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The mean changes from Baseline in DAS28-4(ESR) are presented in Table 19.

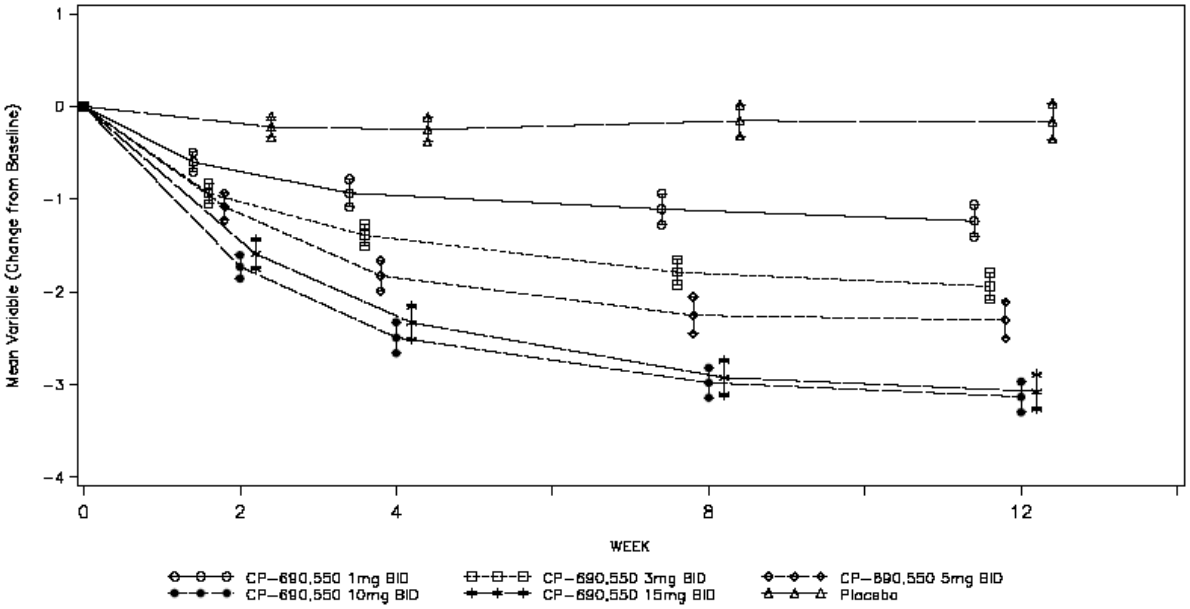
Table 19. Mean Change From Baseline in DAS28-4 (ESR) at Weeks 2, 4, 8 and 12 (FAS)

				Difference From Placebo			
					95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
Week 2								
1 mg BID	52	-0.52	0.15	-0.27	0.21	-0.68	0.13	0.1842
3 mg BID	53	-0.93	0.14	-0.68	0.21	-1.08	-0.28	0.001
5 mg BID	50	-1.0	0.15	-0.76	0.21	-1.17	-0.34	0.0003
10 mg BID	52	-1.66	0.15	-1.41	0.21	-1.82	-1.01	<0.0001
15 mg BID	54	-1.58	0.14	-1.33	0.21	-1.74	-0.93	<0.0001
Placebo	52	-0.25	0.15	-	-	-	-	-
Week 4								
1 mg BID	52	-0.79	0.15	-0.56	0.21	-0.96	-0.15	0.0075
3 mg BID	51	-1.32	0.15	-1.09	0.21	-1.5	-0.68	<0.0001
5 mg BID	51	-1.69	0.15	-1.46	0.21	-1.87	-1.04	<0.0001
10 mg BID	52	-2.42	0.15	-2.2	0.21	-2.60	-1.79	<0.0001
15 mg BID	52	-2.31	0.14	-2.08	0.21	-2.49	-1.68	<0.0001
Placebo	51	-0.23	0.15	-	-	-	-	-
Week 8								
1 mg BID	51	-1.03	0.15	-0.92	0.21	-1.32	-0.51	<0.0001
3 mg BID	50	-1.68	0.15	-1.57	0.21	-1.98	-1.16	<0.0001
5 mg BID	51	-2.05	0.15	-1.93	0.21	-2.34	-1.52	<0.0001
10 mg BID	52	-2.92	0.15	-2.8	0.21	-3.21	-2.4	<0.0001
15 mg BID	52	-2.87	0.14	-2.76	0.21	-3.16	-2.35	<0.0001
Placebo	50	-0.12	0.15	-	-	-	-	-
Week 12								
1 mg BID	51	-1.1	0.15	-1	0.21	-1.41	-0.59	<0.0001
3 mg BID	49	-1.74	0.15	-1.64	0.21	-2.05	-1.23	<0.0001
5 mg BID	50	-2.2	0.15	-2.1	0.21	-2.52	-1.68	<0.0001
10 mg BID	49	-3.05	0.15	-2.95	0.21	-3.36	-2.53	<0.0001
15 mg BID	52	-2.98	0.14	-2.88	0.21	-3.29	-2.47	<0.0001
Placebo	48	-0.10	0.15	-	-	-	-	-

Results were obtained from a longitudinal linear model with the change from Baseline as a dependent variable and treatment, week, treatment-by-week interaction and baseline as fixed effects and subject as a random effect.
BID = twice daily, CI = confidence interval, DAS = disease activity score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, SE = standard error.

The mean changes from Baseline in DAS28-4(ESR) are presented in Figure 14.

Figure 14. Mean Change (Mean ± SE) From Baseline in DAS28-4(ESR) at Weeks 2, 4, 8 and 12 (FAS)



BID = twice daily, SE = standard error, FAS = full analysis set, CP-690,550 = tofacitinib, SE = standard error.

The SF-36 health survey domain scores (physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health).

For all domains the active dose groups had higher scores than the placebo group. Statistically significant differences ($p<0.05$) from placebo in change from Baseline at Week 12 were seen in 3, 5, 10 and 15 mg BID doses for all domain scores, and 1 mg BID dose for physical function, role physical, bodily pain and role emotional.

The mean changes from Baseline of EQ-5D utility score at Week 12 are presented in Table 20.

Table 20. Mean Change From Baseline EQ-5D Utility Score at Week 12 and Statistical Test From the Mixed-Effects Model (FAS)

				Difference From Placebo				
						95% CI		
	N	Mean	SE	Difference	SE	Lower	Upper	p-Value
1 mg BID	51	0.10	0.03	0.14	0.04	0.06	0.23	0.0015
3 mg BID	49	0.21	0.03	0.25	0.04	0.16	0.34	<0.0001
5 mg BID	50	0.28	0.03	0.32	0.05	0.23	0.41	<0.0001
10 mg BID	49	0.33	0.03	0.37	0.04	0.28	0.46	<0.0001
15 mg BID	52	0.33	0.03	0.37	0.04	0.28	0.45	<0.0001
Placebo	48	-0.04	0.03	–	–	–	–	–

Results are obtained from a Mixed-Effect model with change from Baseline as a dependent variable and Treatment and Baseline as fixed effects and subject as a random effect.
BID = twice daily, CI = confidence interval, EQ-5D = EuroQol- 5 demimension FAS = full analysis set, N= total number of subjects, SE = standard error.

The HAQ-DI values decreased over time and with increased dose of tofacitinib, which was indicative of improved functional status.

Safety Results:

Treatment-emergent non-serious adverse events by system organ class and preferred term (all causalities) in >5 % of subjects is presented in Table 21.

Table 21. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5 % of Subjects

	Tofacitinib 1mg BID			Tofacitinib 3mg BID			Tofacitinib 5 mg BID		
	n (%)	n1*	n2**	n (%)	n1*	n2**	n (%)	n1*	n2**
Number (%) of Subjects:	**53**			**53**			**52**		
Evaluable for adverse events	**10 (18.9)**			**11 (20.8)**			**15 (28.8)**		
With adverse events									
Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v13.0) Preferred Term									
Gastrointestinal disorders	1 (1.9)	1	1	0	0	0	1 (1.9)	1	1
Constipation	1 (1.9)	1	1	0	0	0	1 (1.9)	1	1
Infections and infestations	6 (11.3)	8	6	4 (7.5)	4	4	7 (13.5)	8	7
Nasopharyngitis	6 (11.3)	8	6	4 (7.5)	4	4	6 (11.5)	7	6
Pharyngitis	0	0	0	0	0	0	0	0	0
Upper respiratory tract infection	0	0	0	0	0	0	1 (1.9)	1	1
Injury, poisoning and procedural complications	3 (5.7)	3	0	0	0	0	1 (1.9)	1	0
Fall	3 (5.7)	3	0	0	0	0	1 (1.9)	1	0
Investigations	0	0	0	2 (3.8)	2	2	0	0	0
Alanine aminotransferase increased	0	0	0	1 (1.9)	1	1	0	0	0
Aspartate aminotransferase increased	0	0	0	0	0	0	0	0	0
Low density lipoprotein increased	0	0	0	1 (1.9)	1	1	0	0	0
Metabolism and nutrition disorders	1 (1.9)	1	1	2 (3.8)	2	2	2 (3.8)	2	2
Hypercholesterolaemia	0	0	0	2 (3.8)	2	2	0	0	0
Hyperlipidaemia	1 (1.9)	1	1	0	0	0	2 (3.8)	2	2
Nervous system disorders	1 (1.9)	1	1	3 (5.7)	4	2	2 (3.8)	2	2
Headache	1 (1.9)	1	1	3 (5.7)	4	2	2 (3.8)	2	2
Vascular disorders	0	0	0	0	0	0	3 (5.8)	3	2
Hypertension	0	0	0	0	0	0	3 (5.8)	3	2
	Tofacitinib 10mg BID			**Tofacitinib 15mg BID**			**Placebo**		
	n (%)	**n1***	**n2****	**n (%)**	**n1***	**n2****	**n (%)**	**n1***	**n2****
Number (%) of Subjects:	**53**			**54**			**52**		
Evaluable for adverse events									
With adverse events	**17 (32.1)**			**17 (31.5)**			**11 (21.2)**		
Gastrointestinal disorders	0	0	0	3 (5.6)	3	3	2 (3.8)	2	1
Constipation	0	0	0	3 (5.6)	3	3	2 (3.8)	2	1

Infections and infestations	8 (15.1)	10	9	9 (16.7)	12	12	7 (13.5)	7	7
Nasopharyngitis	3 (5.7)	4	4	8 (14.8)	10	10	6 (11.5)	6	6
Pharyngitis	3 (5.7)	3	2	2 (3.7)	2	2	1 (1.9)	1	1
Upper respiratory tract infection	3 (5.7)	3	3	0	0	0	0	0	0
Injury, poisoning and procedural complications	1 (1.9)	1	0	0	0	0	0	0	0
Fall	1 (1.9)	1	0	0	0	0	0	0	0
Investigations	2 (3.8)	3	3	6 (11.1)	7	6	3 (5.8)	6	6
Alanine aminotransferase increased	1 (1.9)	1	1	1 (1.9)	1	1	3 (5.8)	3	3
Aspartate aminotransferase increased	1 (1.9)	1	1	0	0	0	3 (5.8)	3	3
Low density lipoprotein increased	1 (1.9)	1	1	6 (11.1)	6	5	0	0	0
Metabolism and nutrition disorders	9 (17.0)	9	9	3 (5.6)	3	3	0	0	0
Hypercholesterolaemia	3 (5.7)	3	3	0	0	0	0	0	0
Hyperlipidaemia	6 (11.3)	6	6	3 (5.6)	3	3	0	0	0
Nervous system disorders	1 (1.9)	2	0	0	0	0	1 (1.9)	1	1
Headache	1 (1.9)	2	0	0	0	0	1 (1.9)	1	1
Vascular disorders	1 (1.9)	1	1	0	0	0	0	0	0
Hypertension	1 (1.9)	1	1	0	0	0	0	0	0

Except for 'n1' and 'n2' subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events werecalculated using the corresponding gender count as denominator.
MedDRA (Version 13.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities (Version 13.0).n = the number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities; n1 = the number of occurrences of treatment-emergent all causalities adverse events; n2 (optional) = the number of occurrences of treatment-emergent causally related to treatment adverse events.

Treatment-emergent serious adverse events by system organ class and preferred term is presented in Table 22.

Table 22. Treatment-Emergent Serious Adverse Events by System Organ Class and PreferredTerm

	Tofacitinib 1 mg BID			Tofacitinib 3 mg BID			Tofacitinib 5 mg BID		
	n (%)	n1*	n2**	n (%)	n1*	n2**	n (%)	n1*	n2**
Number (%) of Subjects: Evaluable for adverse events	**53**			**53**			**52**		
With adverse events	**0**			**3 (5.7)**			**2 (3.8)**		
Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v13.0) Preferred Term									
Gastrointestinal disorders	0	0	0	1 (1.9)	1	1	0	0	0
Gastric ulcer perforation	0	0	0	1 (1.9)	1	1	0	0	0
Infections and infestations	0	0	0	0	0	0	1 (1.9)	1	1
Herpes zoster	0	0	0	0	0	0	1 (1.9)	1	1
Herpes zoster oticus	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	1 (1.9)	2	0
Fibula fracture	0	0	0	0	0	0	1 (1.9)	1	0
Spinal compression fracture	0	0	0	0	0	0	0	0	0
Tendon rupture	0	0	0	0	0	0	0	0	0
Tibia fracture	0	0	0	0	0	0	1 (1.9)	1	0
Investigations	0	0	0	1 (1.9)	3	3	0	0	0
Alanine aminotransferase increased	0	0	0	1 (1.9)	1	1	0	0	0
Aspartate aminotransferase increased	0	0	0	1 (1.9)	1	1	0	0	0
Blood creatine phosphokinase increased	0	0	0	1 (1.9)	1	1	0	0	0
Nervous system disorders	0	0	0	0	0	0	1 (1.9)	1	1
Post herpetic neuralgia	0	0	0	0	0	0	1 (1.9)	1	1
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	0	0	0
Atelectasis	0	0	0	0	0	0	0	0	0
Vascular disorders	0	0	0	1 (1.9)	1	1	0	0	0
Rheumatoid vasculitis	0	0	0	1 (1.9)	1	1	0	0	0

	Tofacitinib 10 mg BID			Tofacitinib 15 mg BID			Placebo		
	n (%)	n1*	n2**	n (%)	n1*	n2**	n (%)	n1*	n2**
Number (%) of Subjects: Evaluable for adverse events	**53**			**54**			**52**		
With adverse events	**2 (3.8)**			**1 (1.9)**			**1 (1.9)**		

Gastrointestinal disorders	0	0	0	0	0	0	0	0	0
Gastric ulcer perforation	0	0	0	0	0	0	0	0	0
Infections and infestations	1 (1. 9)	1	1	1 (1.9)	1	1	0	0	0
Herpes zoster	1 (1. 9)	1	1	0	0	0	0	0	0
Herpes zoster oticus	0	0	0	1 (1.9)	1	1	0	0	0
Injury, poisoning and procedural complications	1 (1. 9)	2	0	1 (1.9)	1	0	0	0	0
Fibula fracture	0	0	0	0	0	0	0	0	0
Spinal compression fracture	0	0	0	1 (1.9)	1	0	0	0	0
Tendon rupture	1 (1. 9)	2	0	0	0	0	0	0	0
Tibia fracture	0	0	0	0	0	0	0	0	0
Investigations	0	0	0	0	0	0	0	0	0
Alanine aminotransferase increased	0	0	0	0	0	0	0	0	0
Aspartate aminotransferase increased	0	0	0	0	0	0	0	0	0
Blood creatine phosphokinase increased	0	0	0	0	0	0	0	0	0
Nervous system disorders	0	0	0	0	0	0	0	0	0
Post herpetic neuralgia	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	1 (1.9)	1	0
Atelectasis	0	0	0	0	0	0	1 (1.9)	1	0
Vascular disorders	0	0	0	0	0	0	0	0	0
Rheumatoid vasculitis	0	0	0	0	0	0	0	0	0

Except for 'n1' and 'n2' Subjects are only counted once per treatment for each row. Includes data up to 999 days after last dose of study drug. Percentages of gender specific events are calculated using the corresponding gender count as denominator.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities (Version 13.0), n = the number of subjects in this reporting group affected by any occurrence of this adverse event, all Causalities; n1 = the number of occurrences of treatment emergent all causalities adverse events; n2 (optional) = the number of occurrences of treatment emergent causally related to treatment adverse events.

Treatment emergent adverse events occurring at the incidence of ≥2 % subjects in any treatment Group for treatment related adverse events are presented in Table 23.

Table 23. Treatment-Emergent Treatment Related Adverse Events Occurring at an Incidence of ≥2% or Greater Subjects by Preferred Term in any Treatment Group

System Organ Class / Preferred Term (MedDRA)	Tofacitinib										Placebo	
	1 mg BID		3 mg BID		5 mg BID		10 mg BID		15 mg BID			
	N=53		N=53		N=52		N=53		N=54		N=52	
	n	%	n	%	n	%	n	%	n	%	n	%
Gastrointestinal disorders	6	11.3	6	11.3	5	9.6	6	11.3	6	11.1	4	7.7
Dental caries	0	-	0	-	2	3.8	1	1.9	0	-	1	1.9
Gingivitis	0	-	0	-	0	-	0	-	2	3.7	1	1.9
Constipation	1	1.9	0	-	1	1.9	0	-	3	5.6	1	1.9
Infection and Infestations	5	9.4	5	9.4	9	17.3	15	28.3	11	20.4	8	15.4
Bronchitis	1	1.9	1	1.9	0	-	2	3.8	0	-	0	-
Nasopharyngitis	4	7.5	4	7.5	5	9.6	3	5.7	8	14.8	6	11.5
Pharyngitis	0	-	0	-	0	-	2	3.8	2	3.7	1	1.9
Upper respiratory tract infection	0	-	0	-	1	1.9	3	5.7	0	-	0	-
Herpes zoster	0	-	0	-	1	1.9	3	5.7	1	1.9	0	-
Investigations	0	-	3	5.7	2	3.8	3	5.7	7	13.0	3	5.8
Alanine aminotransferase increased	0	-	2	3.8	0	-	1	1.9	1	1.9	3	5.8
Aspartate aminotransferase increased	0	-	1	1.9	0	-	1	1.9	0	-	3	5.8
Blood Cholesterol Increased	0	-	1	1.9	1	1.9	1	1.9	2	3.7	0	-
Low density lipoprotein increased	0	-	1	1.9	0	-	1	1.9	5	9.3	0	-
Metabolism and nutrition disorders	1	1.9	2	3.8	4	7.7	9	17.0	3	5.6	0	-
Hypercholesterolaemia	0	-	2	3.8	0	-	3	5.7	0	-	0	-
Hyperlipidaemia	1	1.9	0	-	2	3.8	6	11.3	3	5.6	0	-
Nervous system disorders	2	3.8	2	3.8	3	5.8	1	1.9	0	-	1	1.9
Headache	1	1.9	2	3.8	2	3.8	0	-	0	-	1	1.9
Respiratory, thoracic and mediastinal disorders	2	3.8	1	1.9	0	-	1	1.9	0	-	3	5.8
Upper respiratory tract inflammation	0	-	0	-	0	-	0	-	0	-	2	3.8
Vascular Disorder	0	-	1	1.9	2	3.8	2	3.8	0	-	0	-
Hypertension	0	-	0	-	2	3.8	1	1.9	0	-	0	-

If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence is taken. Subjects are counted only once per treatment in each row. Includes data up to 999 days after last dose of study drug.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities (Version 13.0), N = total number of subjects, n = number of subjects per group.

Treatment-emergent significant infection adverse events by preferred term are listed in Table 24.

Table 24. Incidence and Severity of Treatment-Emergent Significant Infection Adverse Events by Preferred Term (All Causality)

Preferred Term (MedDRA v13.0)	Tofacitinib BID										Placebo
	1 mg BID	3 mg BID	5 mg BID		10 mg BID				15 mg BID		Placebo
	N=53	N=53	N=52		N=53				N=54		N=52
				Severity		Severity				Severity	
	n	n	n (%)	Mild	n (%)	Mild	Mod.	Sev.	n (%)	Mod.	n
Helicobacter infection	0	0	0	0	1 (1.9)	1	0	0	0	0	0
Herpes simplex	0	0	0	0	0	0	0	0	1 (1.9)	1	0
Herpes zoster	0	0	1 (1.9)	1	3 (5.7)	0	2	1	1 (1.9)	1	0
Herpes zoster oticus	0	0	0	0	0	0	0	0	1 (1.9)	1	0
Total preferred term events	0	0	1	1	4	1	2	1	3	3	0

BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (Version 13.0), Mod. = moderate, Sev. = severe.

Permanent discontinuations due to treatment emergent adverse events are presented in Table 25.

Table 25. Treatment-Emergent Adverse Events Leading to Permanent Discontinuation

MedDRA Preferred Term	Start Day/ Stop Day	Severity	Outcome	Relationship to Treatment
Tofacitinib 3 mg BID				
Rheumatoid vasculitis	15/ [>44]	Severe	Still present	Related
Tofacitinib 5 mg BID				
Fibula fracture	11/ 61	Severe	Resolved	Other[a]
Tibia facture	11/ 61	Severe	Resolved	Other[a]
Herpes zoster	33/ 71	Mild	Resolved	Related
Post herpetic neuralgia	38/ 204	Moderate	Resolved	Related
Tofacitinib 10 mg BID				
Tendon rupture	10/ 73	Moderate	Resolved	Disease under study
Herpes zoster	46/ 73	Severe	Resolved	Related
Ecchymosis	3/ 25	Mild	Resolved	Related
Placebo				
Alanine aminotransferase increased	15/ [>23]	Moderate	Still Present	Related
Aspartate aminotransferase increased	15/ [>23]	Moderate	Still Present	Related
Alanine aminotransferase increased	29/ 57	Mild	Resolved	Related
Aspartate aminotransferase increased	29/ 57	Mild	Resolved	Related

BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (Version 13.0)
a. Accidental fall

There were no deaths among subjects who participated in this study. Nine subjects (three subjects in 3 mg BID, two subjects in 5 mg BID, two subjects in 10 mg BID, one subject in 15 mg BID and one subject in placebo) reported serious adverse events for study treatment.

Tofacitinib was associated with decreases in neutrophils and platelet counts, increases in hemoglobin, serum lipids (HDL cholesterol, LDL cholesterol and total cholesterol), serum creatinine.

Most of the adverse events were mild in severity. Six severe adverse events that were gastric ulcer perforation and rheumatoid vasculitis in 3 mg BID, fibula fracture, tibia fracture and fall in 5 mg BID, and herpes zoster in 10 mg BID

There were no notable differences between treatment groups in the numbers of subjects with laboratory abnormalities after dosing (Table 26).

Table 26. Summary of Incidence of Laboratory Test Abnormalities

	Tofacitinib 1 mg BID		Tofacitinib 3 mg BID		Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Tofacitinib 15 mg BID		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects evaluable for laboratory abnormalities	53		53		52		53		54		52	
Number with laboratory abnormalities												
When normal baseline	26	(49)	19	(36)	29	(56)	31	(58)	35	(65)	27	(52)
When abnormal baseline	30	(57)	18	(34)	10	(19)	22	(42)	13	(24)	43	(83)
Without regard to baseline abnormality	52	(98)	49	(92)	51	(98)	47	(89)	48	(89)	52	(100)

BID = twice daily, n = number of subjects.

Table 27 summarizes the incidence of postbaseline vital signs that met the pre-defined reporting criteria of clinical concern.

Table 27. Incidence of Postbaseline Vital Signs of Clinical Concern

		Tofacitinib 1 mg BID			Tofacitinib 3 mg BID			Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Tofacitinib 15 mg BID			Placebo		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Sitting Systolic BP	≥30 mm Hg increase	53	3	5.7	53	2	3.8	52	6	11.5	53	4	7.5	54	3	5.6	52	2	3.8
	≥30 mm Hg decrease	53	4	7.5	53	1	1.9	52	5	9.6	53	3	5.7	54	5	9.3	52	4	7.7
	<90 mm Hg	53	1	1.9	53	0		52	2	3.8	53	1	1.9	54	1	1.9	52	0	1.9
Diastolic BP	≥20 mm Hg increase	53	6	11.3	53	2	3.8	52	2	3.8	53	4	7.5	54	4	7.4	52	1	5.8
	≥20 mm Hg decrease	53	6	11.3	53	2	3.8	52	5	9.6	53	3	5.7	54	4	7.4	52	3	1.9
	<50 mm Hg	53	0	−	53	1	1.9	52	0	−	53	2	3.8	54	1	1.9	52	1	1.9
Pulse Rate	<40 bpm	53	0	−	53	0	−	52	0	−	53	0	−	54	0	−	52	0	−
	>120 bpm	53	0	−	53	0	−	52	0	−	53	0	−	54	0	−	52	1	1.9

BID = twice daily

Mean baseline and mean changes from Baseline in ECG data (heart rate and intervals) and the incidence of postbaseline ECG values of clinical concern. The changes were generally small and no notable trends were observed.

CONCLUSIONS:

Tofacitinib at all doses demonstrated statistically significant responses over placebo as measured by the ACR20 at Week 12. Statistically significant response rates in ACR20 were seen as early as Week 2 for all tofacitinib doses compared with placebo; these significant difference were maintained throughout the 12- week period. Tofacitinib at high doses (10 mg and 15 mg BID) kept higher ACR20 response rates over other doses throughout the

12-week period. The clear dose-response relationship was also observed on ACR20 at Week 12.

Tofacitinib at doses of ≥3 mg BID was statistically significant in ACR50 and ACR70 at Week 12 and highly efficacious at doses of 10 and 15 mg BID.

The dose-response relationship in tofacitinib doses including placebo was shown on ACR assessments and DAS assessments at Week 12 and tofacitinib at high doses kept higher response over other doses throughout the 12-week period.

The HAQ-DI values decreased over time and with increased dose of tofacitinib which was indicative of improved functional status.

Tofacitinib at doses of 1 mg BID, 3 mg BID, 5 mg BID, 10 mg BID, and 15 mg BID is well tolerated when compared to placebo over a treatment period of 12 weeks.

There were no deaths among subjects who participated in this study. Nine subjects (three subjects in 3 mg BID, two subjects in 5 mg BID, two subjects in 10 mg BID, one subject in 15 mg BID and one subject in placebo) reported serious adverse events for study treatment.

The most commonly observed all causality adverse events were nasopharyngitis, hyperlipidaemia and low density lipoprotein increased. Most of the adverse events were mild in severity. The most common treatment-emergent infections across all tofacitinib dose groups were nasopharyngitis, pharyngitis, and herpes zoster. No opportunistic infections were reported during this study.

Tofacitinib is associated with decreases in neutrophils and platelet counts, increases in hemoglobin, serum lipids (HDL cholesterol, LDL cholesterol and total cholesterol), serum creatinine.

Efficacy and safety were similar to those seen previously in Phase 2 studies. All tofacitinib treatment groups (1, 3, 5, 10, and 15 mg BID) were well tolerated in Japanese subjects with active RA who failed at least 1 DMARD.