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

PROTOCOL NO.: A3921069

PROTOCOL TITLE: Phase 3 Randomized, Double-Blind Study of the Efficacy and Safety of 2 Doses of CP-690,550 Compared to Methotrexate in Methotrexate-Naïve Patients With Rheumatoid Arthritis

Study Center(s): A total of 153 centers in 30 countries in regions of Europe, Canada, Latin America, Asia/other, and the United States took part in the study and enrolled subjects; 3 centers in Argentina, 3 centers in Australia, 1 center in Belgium, 5 centers in Brazil, 6 centers in Bulgaria, 10 centers in Canada, 5 centers in Chile, 3 centers in Colombia, 2 centers in Costa Rica, 6 centers in the Czech Republic, 1 center in the Dominican Republic, 8 centers in Germany, 5 centers in Hungary, 7 centers in India, 3 centers in the Republic of Korea, 3 centers in Malaysia, 4 centers in Mexico, 3 centers in New Zealand, 4 centers in Peru, 3 centers in the Philippines, 3 centers in Poland, 1 center in Puerto Rico, 12 centers in the Russian Federation, 5 centers in Slovakia, 5 centers in Spain, 3 centers in Sweden, 3 centers in Taiwan, 3 centers in Thailand, 6 centers in the Ukraine, and 27 centers in the United States.

Study Initiation and Final Completion Dates: 25 January 2010 to 13 March 2013

Phase of Development: Phase 3

Study Objective(s):

Primary Objective:

- To compare evidence of preservation of joint structure after administration of tofacitinib in doses of 5 mg twice daily (BID) and 10 mg BID versus methotrexate (MTX) alone in MTX-naïve subjects with active rheumatoid arthritis (RA), as measured by changes from Baseline using a standardized, validated method, such as the van der Heijde modified Total Sharp Score (mTSS) at Month 6.

- To compare the efficacy of tofacitinib in doses of 5 mg BID and 10 mg BID versus MTX alone for the treatment of signs and symptoms of RA in MTX-naïve subjects with active RA, as measured by American College of Rheumatology (ACR) 70 response rates at Month 6.

- To evaluate the safety and tolerability of tofacitinib in doses of 5 mg BID and 10 mg BID versus MTX alone in MTX-naïve subjects with active RA for 24 months.

Secondary Objectives:

- To compare the efficacy of tofacitinib in doses of 5 mg BID and 10 mg BID versus MTX for the treatment of signs and symptoms of RA in subjects with active RA, as measured by ACR20, ACR50 and Disease Activity Score (DAS) 28 response rates at all timepoints and by ACR70 response rates at all other time points versus MTX alone in MTX-naïve subjects with active RA.

- To compare physical function status of subjects after administration of tofacitinib in doses of 5 mg BID and 10 mg BID versus MTX alone using the Health Assessment Questionnaire-Disability Index (HAQ-DI) at all time points compared to Baseline in MTX-naïve subjects with active RA.

- To compare the durability of ACR20, ACR50, and ACR70 and DAS28 response rates after administration of tofacitinib in doses of 5 mg BID and 10 mg BID versus MTX alone in MTX-naïve subjects with active RA.

- To compare the incidence of DAS28 <2.6 and DAS28 ≤3.2 at each visit after administration of tofacitinib in doses of 5 mg BID and 10 mg BID versus MTX alone in MTX-naïve subjects with active RA.

- To compare the incidence of major clinical response, defined as maintaining an ACR70 response for at least 6 months, after administration of tofacitinib in doses of 5 mg BID and 10 mg BID versus MTX alone in MTX naïve subjects with active RA.

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

- To characterize the pharmacokinetics (PK) of tofacitinib in subjects who are MTX-naïve.

METHODS

Study Design: This was a Phase 3 randomized, 24 month, double-blind, parallel group study. Subjects were randomized in a 2:2:1 ratio to 1 of 3 parallel treatment arms and sequences:

- Tofacitinib 5 mg BID, tablets;

- Tofacitinib 10 mg BID, tablets; and

- MTX 10 mg/week to 20 mg/week, capsules.

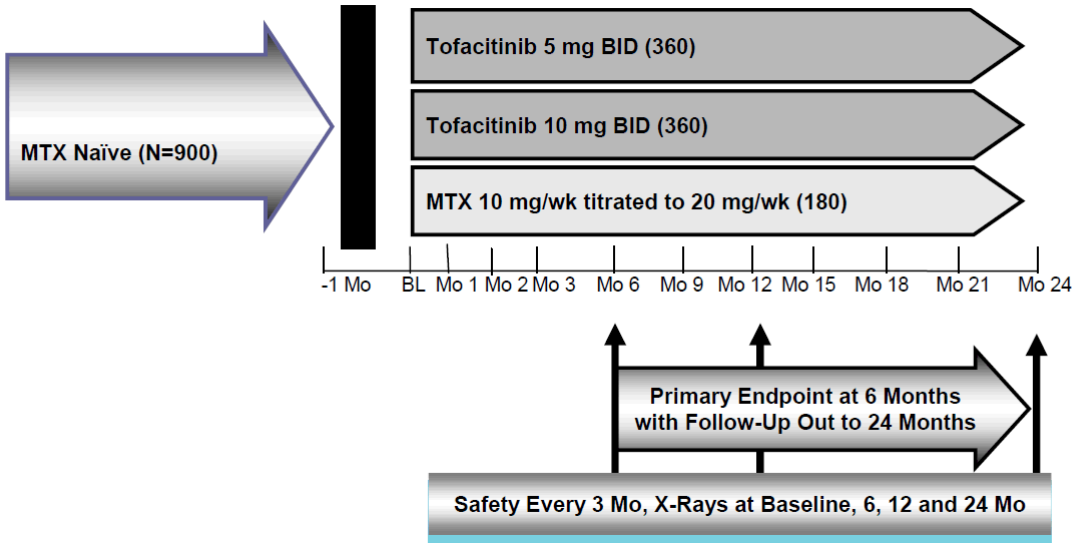
The MTX titration was as follows:

- 10 mg once weekly for 4 weeks; if well tolerated, then

- Titrate up to; 15 mg once weekly for 4 weeks, if well tolerated, then
- Titrate up to; 20 mg once weekly for duration of study.

One dose reduction of 5 mg/week MTX was allowed for lack of tolerance. Division of weekly doses into 2 or 3 fractions, delivered approximately 12 hours apart, were allowed after Visit 3 (Month 2) for lack of tolerance. The study design is presented in Figure 1 and study schedule of activities is presented in Table 1.

Figure 1. Overview of Study Design



*MTX dose started at 10 mg/week and was titrated by 5 mg/week every 4 weeks as tolerated to 20 mg/week by Week 8; then maintained at the titrated dose throughout study, with one 5 mg/week dose reduction allowed for MTX intolerance.
BID = twice daily, BL = Baseline, MTX = methotrexate, N = number of subjects, mo = month, wk = week.

Table 1. Schedule of Activities

		Screening[a]	Visits										
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
			Baseline Day 0	1 Mo	2 Mo	3 Mo	6 Mo	9 Mo	12 Mo	15 Mo	18 Mo	21 Mo	24 Mo/ EOS
Informed consent, RA diagnosis, medical history[b]		X											
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination		X	X						X				X
Targeted physical examination[c]				X	X	X	X	X		X	X	X	
Vital signs, temperature		X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON-Gold®™		X											
Radiograph of chest[d]		X											
12-lead Electrocardiogram		X							X				X
Radiograph of hands & feet[e]			X				X		X				X
Blood/Urine	Rheumatoid factor, anti-CCP	X	X										X
	Hematology[f], chemistry panel[g]	X	X	X	X	X	X	X	X	X	X	X	X
	Lipid profile (fasting)[h]	X	X			X	X	X	X		X		X
	CBC with differential & chemistry labs[i]						As appropriate for MTX local label						
	Urine pregnancy test (HCG) (done locally)[j]	X	X	X	X	X	X	X	X	X	X	X	X
	Urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X
	Stool examination for parasites (Brazil only)	X											
	Molecular profiling sampling[k]		X				X		X				X
	Tofacitinib pharmacokinetics[l]			X					X				
	HIV Serology, HBsAg, HCV Ab	X											
ACR/ DAS	C-reactive protein (CRP)	X	X	X	X	X	X	X	X	X	X	X	X
	Erythrocyte sedimentation rate (ESR)[m]	X	X	X	X	X	X	X	X	X	X	X	X
	Tender/painful joint count, swollen joint count	X	X	X	X	X	X	X	X	X	X	X	X
	Patient Assessment of Arthritis Pain		X	X	X	X	X	X	X	X	X	X	X
	Patient Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X	X	X
	Physician Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X	X	X
	Health Assessment Questionnaire – Disability Index		X	X	X	X	X	X	X	X	X	X	X

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	Screening[a]	Visits										
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
		Baseline Day 0	1 Mo	2 Mo	3 Mo	6 Mo	9 Mo	12 Mo	15 Mo	18 Mo	21 Mo	24 Mo/ EOS
SF-36 (Version 2, acute)		X	X	X	X	X	X	X	X	X	X	X
MOS Sleep Scale/FACIT- Fatigue Scale		X	X	X	X	X		X		X		X
EuroQol EQ-5D, Work Limitations Questionnaire		X			X	X		X		X		X
RA Healthcare Resource Utilization Questionnaire		X			X	X		X		X		X
Randomization		X										
Drug dispensing[n]		X	X	X	X	X	X	X	X	X	X	
Drug accountability			X	X	X	X	X	X	X	X	X	X
Adverse event reporting		X	X	X	X	X	X	X	X	X	X	X

ACR = American College of Rheumatology, CBC = complete blood count, CCP = cyclic citrullinated peptide, DAS = Disease Activity Score, EOS = end of study, EuroQol EQ-5D = European Quality of Life 5-dimension scale, ESR = erythrocyte sedimentation rate, FACIT = Functional Assessment of Chronic Illness Therapy, HBsAg = hepatitis B surface antigen, HCG = human chorionic gonadotropin, HCV Ab = hepatitis C virus antibody, HDL = high-density lipoprotein, HIV = human immunodeficiency virus, IEC = independent ethics committee, IRB = institutional review board, LDL = low-density lipoprotein, mo = month, MOS = Medical Outcomes Study, MTX = methotrexate, RA = rheumatoid arthritis, SF-36 = Short Form-36, V = volume.

a. Baseline visit was to occur within 1 month of the completion of the screening assessments within a +10 day window. Visits 2, 3 and 4 consisted of 28 day periods with a ±2 day window, all other study visits (5-11) consisted of 91 day periods with a ±7 day window.
b. Medical History included smoking status, average weekly alcohol consumption, family history of premature coronary heart disease.
c. Targeted physical examination consisted of weight, examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes.
d. Radiograph of chest was done unless performed and documented within 3 months of screening.
e. Hand and foot radiographs were read and scored centrally.
f. Hematology included RBC, WBC with differential, hemoglobin, hematocrit and platelet count
g. Chemistry panel included urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin, creatine kinase (CK).
h. Lipid profile included fasting total cholesterol, LDL, HDL, and triglycerides; apolipoprotein A-1 and B and other lipoprotein tests potentially including particle size measurements were obtained at Screening (only LDL and HDL), Baseline, Month 3, 6, 9, 12, 18 and 24. The blood draws for laboratory parameters requiring a fasting state was separated by -48 hours from the Baseline visit and ±48 hours for the other visits requiring fasting laboratory parameters.
i. Chemistry procedures as appropriate for local label in subjects receiving MTX; included hematology, creatinine, albumin and liver function tests.
j. Urinalysis included specific gravity, pH, protein, glucose, ketones, and blood and leukocyte esterase. Urinary pregnancy testing (HCG) was required only for women who were of childbearing potential; could be repeated more frequently if required by local practices, IRB/IECs or local regulations if a

Table 1. Schedule of Activities

	Screening[a]	Visits										
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
		Baseline Day 0	1 Mo	2 Mo	3 Mo	6 Mo	9 Mo	12 Mo	15 Mo	18 Mo	21 Mo	24 Mo/ EOS

menstrual cycle was missed, or if potential pregnancy was otherwise suspected. Pregnancy tests were repeated as per request of IRB/IECs or local regulations regulatory authority every month. (Bulgaria only).

k. Only at sites participating in the molecular profiling research component.

l. PK at participating sites only.

m. All ESR tests performed after screening were done blinded. This was done only at sites where the local laboratory had the capability of reporting results only to the central laboratory and maintaining the blind.

n. Folate supplementation prescription at V1 and V7.

Number of Subjects (Planned and Analyzed): Approximately 900 subjects were planned to participate in this study in a 2:2:1 ratio to treatment arm 1 (360 subjects), treatment arm 2 (360 subjects), or treatment arm 3 (180 subjects), respectively. The study enrolled 958 subjects: 12 in Argentina, 15 in Australia, 3 in Belgium, 43 in Brazil, 33 in Bulgaria, 44 in Canada, 44 in Chile, 48 in Colombia, 6 in Costa Rica, 44 in Czech Republic, 9 in Dominican Republic, 36 in Germany, 9 in Hungary, 92 in India, 19 in Republic of Korea, 5 in Malaysia, 25 in Mexico, 9 in New Zealand, 15 in Peru, 23 in Philippines, 11 in Poland, 3 in Puerto Rico, 134 in Russian Federation, 16 in Slovakia, 13 in Spain, 9 in Sweden, 8 in Taiwan, 15 in Thailand, 82 in Ukraine, 133 in the United States. A total of 1543 subjects were screened and 958 subjects randomized to treatment.

Diagnosis and Main Criteria for Inclusion: In order to enroll in the study subjects had to have moderately to severely active RA (and met Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA) with joint erosions or positive immunoglobulin M (IgM) Rheumatoid Factor or antibodies to cyclic citrullinated peptide and not have received more than 3 weekly doses of MTX. Subjects must have had active disease at both Screening and Baseline as defined by having both ≥6 tender or painful joints on motion and ≥6 joints swollen together with either an erythrocyte sedimentation rate (ESR) >28 mm or a C-reactive protein (CRP) concentration >7 mg/dL.

Exclusion criteria:

- Blood dyscrasias including confirmed: hemoglobin <9 g/dL or Hematocrit <30%; white blood cell count <3.0 x 10^9/L; absolute neutrophil count <1.2 x 10^9/L; platelet count <100 x 10^9/L.
- History of any other rheumatic autoimmune disease other than Sjogren's syndrome.
- No malignancy or history of malignancy.
- History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study drug.
- No chronic liver disease, recent or active hepatitis or other contraindication to methotrexate therapy.

Study Treatment: Subjects were randomized in a 2:2:1 ratio to 1 of the following 3 parallel treatment arms:

- **Treatment Arm 1**: tofacitinib 5 mg BID (tablets)
- **Treatment Arm 2:** tofacitinib 10 mg BID (tablets)
- **Treatment Arm 3**: MTX 10 mg/week to 20 mg/week (capsules), titrated as follows:
    - 10 mg/once weekly for 4 weeks; if well tolerated, then titrate up to;

- 15 mg/once weekly for 4 weeks, if well tolerated, then titrate up;
- 20 mg/once weekly for duration of study.

One dose reduction of 5 mg/week was allowed for lack of tolerance. Division of weekly doses into 2 or 3 fractions, delivered approximately 12 hours apart, were allowed after Visit 3 (Month 2) for lack of tolerance.

Efficacy Endpoints:

Primary Endpoints:

- Structure preservation as measured by a modified mTSS at Month 6.
- Signs and symptoms as measured by ACR 70 at Month 6.

Secondary Endpoints:

- Actual and change from Baseline of mTSS at Months 12 and 24.
- Actual and change from Baseline of 2 individual components of mTSS (Erosion and Joint Space Narrowing [JSN] Scores) at Months 6, 12, and 24.
- The rate of non progression in mTSS change from Baseline. The non progression was defined as mTSS change ≤0.5.
- The rate of no new erosion. The no new erosion is defined as erosion change ≤0.5.
- ACR70 responder rates analyzed at all time points other than Month 6.
- ACR20 and ACR50 responder rates.
- Actual and change from Baseline of the 7 individual components (Tender Joint Count, Swollen Joint Count, Patient Assessment of Arthritis Pain, Physician Global Assessment of Arthritis, Patient Global Assessment of Arthritis, CRP, and HAQ-DI) of the ACR criteria variables (separate analyses at all time points where collected).
- Actual and change from Baseline in disease activity score (DAS28) which included the following DAS: DAS28-3 (CRP) and DAS28-4(ESR), that is, separate endpoints, analyzed separately.
- Incidences of DAS28-3 (CRP) ≤3.2, and DAS28-4 (ESR) ≤3.2 (separate endpoints, analyzed separately).
- Incidences of DAS28-3 (ESR) <2.6.
- Incidences of DAS28-4 (CRP) <2.6.

- DAS28 response rates (no improvement vs improvement (moderate improvement or good improvement)), based on DAS28-3 (CRP) and DAS28-4 (ESR), (separate endpoints, analyzed separately).

- ACR70 response for at least 6 Months (MCR).

- Durability of ACR20, ACR50, ACR70, DAS28 response rates.

- Actual and change from Baseline in HAQ-DI.

- Rates of clinically meaningful decrease in the HAQ-DI (decrease of at least 0.22, 0.3, or 0.5 units) "HAQ-DI (0.22)", "HAQ-DI (0.30)", "HAQ-DI (0.5)", respectively will be analyzed at all time points.

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

- Actual and change from Baseline in Work Limitations Questionnaire (WLQ) 4° domain scores and the Work Loss Index (separate analyses).

- Actual and change from Baseline in the EuroQol EQ-5D (a self-report questionnaire developed by the European Quality of Life [EuroQoL] Group) and the utility score (separate analyses).

- RA Healthcare Resource Utilization Questionnaire (RA-HCRU).

- Actual and change from Baseline in the Medical Outcomes Study (MOS)-Sleep Scale and the Sleep Problem Index (separate analyses).

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

Safety Evaluations:

- Incidence and severity of adverse events

- Incidence and severity of clinical laboratory abnormalities

- Summary of changes in physical examination compared to baseline by subject

- Mean change from baseline in vital signs (blood pressure and weight) measurements

- Categorical summary of absolute vital signs and vital sign changes compared to baseline by subject

Statistical Methods:

The full analysis set (FAS) included all subjects who were randomized to the study and received at least 1 dose of the randomized study drug (tofacitinib) or MTX. This was the primary analysis population for the study. For each endpoint the subject was required to have a baseline and at least 1 nonmissing on-study assessment of that endpoint to be included the analysis.

FAS subjects who had a protocol deviation thought to affect the efficacy analysis were excluded from the Per Protocol (PP) efficacy analysis.

The safety analysis set was defined as those subjects who received at least 1 dose of the study drug (tofacitinib) or MTX. For laboratory data, only those subjects who had laboratory data were included in the analyses. For vital signs data, only those subjects who had vital signs data were included in the analyses.

Two primary endpoints, the mTSS and ACR70 at Month 6, were analyzed for both dose groups of tofacitinib and the MTX group. Both of these analyses were based on the FAS.

For the change from Baseline in the mTSS at Month 6, the analysis of covariance model was used. Missing values were imputed by linear extrapolation.

The change of mTSS from Baseline to Month 12 and Month 24 was analyzed using the same method as the analysis for the change of mTSS from Baseline to Month 6.

For ACR70 at Month 6, the normal approximation for the difference in binomial proportions was used. For Erosion score and JSN score, missing values due to patient withdraw were linearly extrapolated based on the Baseline value and post Baseline value prior to withdraw. The binary variables (eg, progression or not progression) were derived from the linearly extrapolated imputation data.

For ACR20, 50, 70, DAS28-4 (ESR) <2.6, HAQ-DI change from Baseline, and mTSS change from Baseline, subgroup analysis was performed by geographic region, gender, Baseline weight, Baseline age, Baseline rheumatoid factor, Baseline Anti-cyclic citrullinated peptide, prior disease-modifying antirheumatic drugexposure, Baseline disease duration, and Baseline DAS28-4 (ESR). For mTSS change from Baseline, subgroup analysis was also be performed by Baseline radiographic annual progression rate and combined erosions and serological status.

The endpoint that determines the sample size for this trial was the preservation of joint structure as measured by mTSS. The given sample size provided a 90% power, assuming a difference in mTSS of at least 0.9 unit (with a standard deviation of 2.8). For ACR70 analysis, the given sample size yielded over 90% power assuming a difference in response rates of at least 15% (with a MTX response of approximately 20%). All the secondary analyses were based on the FAS.

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

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2. Of 1543 subjects screened for entry into the study, 958 were randomized to treatment, and 956 received at least 1 dose of study medication. Two subjects in the tofacitinib 10 mg group were randomized but not treated.

Table 2. Subject Disposition by Treatment (2-Year Analysis)

No. (%) of Subjects	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Methotrexate
Screened: 1543			
Assigned to study treatment	373	399	186
Treated	373	397	186
Completed	266 (71.3)	286 (71.7)	106 (57.0)
Discontinued	107 (28.7)	111 (27.8)	80 (43.0)
Subject died	2 (0.5)	0	0
Related to study drug	43 (11.5)	36 (9.1)	44 (23.7)
Adverse event	23 (6.2)	25 (6.3)	18 (9.7)
Lack of efficacy	20 (5.4)	11 (2.8)	26 (14.0)
Not related to study drug	62 (16.6)	75 (18.9)	36 (19.4)
Adverse event	15 (4.0)	14 (3.5)	6 (3.2)
Lost to follow-up	11 (2.9)	9 (2.3)	5 (2.7)
Other	13(3.5)	25 (6.3)	12 (6.5)
Subject no longer willing to participate in study	23 (6.2)	27 (6.8)	13 (7.0)

BID = twice daily, No. = number.

The demographic and baseline characteristics are summarized in Table 3. The majority of the treated subjects were female (758 subjects [79.3%]) and the most frequent race reported was white (632 subjects, 66.1%). The mean age of subjects ranged from 48.8 years (MTX) to 50.3 years (tofacitinib 5 mg BID) across the 3 treatment groups (overall range 18 years to 83 years). The mean weight ranged from 70.6 kg (tofacitinib 5 mg BID) to 71.3 kg (tofacitinib 10 mg BID) (overall range 31.4 kg to 183.2 kg).

Table 3. Demographic Characteristics by Treatment Group (2-Year Analysis)

	Tofacitinib 5 mg BID N = 373	Tofacitinib 10 mg BID N = 397	Methotrexate N = 186
Gender, n (%)			
Male	87 (23.3)	70 (17.6)	41 (22.0)
Female	286 (76.7)	327 (82.4)	145 (78.0)
Age (years), n (%)			
18-44	103 (27.6)	130 (32.7)	67 (36.0)
45-64	233 (62.5)	221 (55.7)	99 (53.2)
≥65	37 (9.9)	46 (11.6)	20 (10.8)
Mean	50.3	49.3	48.8
SD	12.2	12.8	13.3
Range	18-76	18-83	20-80
Race, n (%)			
White	239 (64.1)	266 (67.0)	127 (68.3)
Black	13 (3.5)	12 (3.0)	4 (2.2)
Asian	68 (18.2)	63 (15.9)	33 (17.7)
Other	53 (14.2)	56 (14.1)	22 (11.8)
Weight (kg)			
Mean	70.6	71.3	70.9
SD	16.5	18.6	18.2
Range	33.0–143.0	34.1-183.2	31.4-129.0
Height (cm)			
Mean	163.0	162.5	162.8
SD	9.4	9.5	10.4
Range	142.5-198.0	136.0-190.0	127.0-198.0
BMI (kg/m^2)			
Mean	26.5	26.8	26.7
SD	5.4	6.0	6.1
Range	15.1-50.7	12.1-63.3	14.9-49.4

BID = twice daily, BMI = body mass index, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoints: These were structure preservation as measured by mTSS at Month 6, signs and symptoms as measured by ACR70 at Month 6.

mTSS at Month 6 (1-Year Analysis): Both tofacitinib treatment groups demonstrated statistically significant structural preservation compared with MTX as measured by the least squares (LS) mean change from Baseline in mTSS at Month 6 ($p \leq 0.0006$; Table 4).

Table 4. Summary of LS Mean Changes From Baseline in mTSSat Month 6 (FAS, LEP, 1-Year Analysis)

Treatment	N	LS Mean	Differences From MTX			
			LS Mean Difference	95% CI for Difference		p-Value
				Lower	Upper	
Tofacitinib 5 mg BID	346	0.18	-0.66	-1.03	-0.28	0.0006
Tofacitinib 10 mg BID	369	0.04	-0.81	-1.18	-0.44	<0.0001
Methotrexate	166	0.84				

If subjects did not have any valid postbaseline radiographs, they were not included in this summary.
BID = twice daily, CI = confidence interval, FAS = full analysis set, LEP = linear extrapolation, LS = least squares, mTSS = Modified Total Sharp Scores, MTX = methotrexate, N = number of subjects.

ACR70 at Month 6 (1-Year Analysis): Both tofacitinib doses demonstrated statistically significant ($p<0.0001$ for both doses) and clinically meaningful reductions in signs and symptoms of RA over MTX as measured by ACR70 response rates at Month 6 (Table 5).

Table 5. Normal Approximation to ACR70 Response Rates at Month 6 (FAS, NRI, Differences From MTX, 1-Year Analysis)

Treatment	N	n	%	Difference From MTX			
				Difference of %	95% CI for Difference		p-Value
					Lower	Upper	
Tofacitinib 5 mg BID	369	94	25.47	13.51	7.05	19.97	<0.0001
Tofacitinib 10 mg BID	393	148	37.66	25.70	18.99	32.40	<0.0001
Methotrexate	184	22	11.96				

ACR70 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, MTX = methotrexate, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation.

The results of the primary endpoint for mTSS were slightly different for the Month 6 timepoint when comparing data reported at the Year 1 interim analysis. However, the slight difference in the mTSS did not affect the overall conclusions of the primary endpoints. No difference was observed in the ACR70. There were an additional 6 subjects for whom 6 month efficacy data were provided for the 2 Year analysis (tofacitinib 5 mg BID: 2 subjects; tofacitinib 10 mg BID: 3 subjects; MTX: 1 subject). The results of the study with the addition of data from these subjects did not change the conclusions from the 1 Year analysis.

Secondary Endpoints:

Change From Baseline in mTTS:

Change from Baseline in mTSS at Months 12 and 24 from the 2 Year analysis are presented in Table 6. Both tofacitinib treatment groups demonstrated statistically significant structural preservation compared with MTX as measured by the LSmean change from Baseline in mTSS at Months 12 and 24 ($p \leq 0.0004$).

Table 6. Statistical Analysis of Change From Baseline mTSS at Month 12 and 24, Comparisons to MTX Using the Non-Longitudinal Linear Mixed Model (FAS, LEP, 2 Year Analysis)

Time Point/ Treatment	N	LS Mean	SE	Difference From MTX			
				Difference in % (SE)	95% CI for Difference		p-Value
					Lower	Upper	
Month 12							
Tofacitinib 5 mg BID	347	0.36	0.14	-0.82 (0.23)	-1.27	-0.36	0.0004
Tofacitinib 10 mg BID	373	0.16	0.14	-1.02 (0.23)	-1.47	-0.57	<0.0001
Methotrexate	171	1.18	0.20				
Month 24							
Tofacitinib 5 mg BID	348	0.55	0.25	-1.52 (0.41)	-2.33	-0.72	0.0002
Tofacitinib 10 mg BID	373	0.28	0.24	-1.80 (0.40)	-2.60	-1.01	<0.0001
Methotrexate	171	2.08	0.34				

If subjects did not have a valid post-Baseline radiographs, they were not included in this summary.
BID = twice daily, CI = confidence interval, FAS = full analysis set, LEP = linear extrapolation, LS = least squares, mTSS = modified Total Sharp Score, MTX = methotrexate, N = number of subjects, SE = standard error.

Change From Baseline in Components of mTSS (Erosion and JSN Scores):

Summaries of LS mean changes from Baseline in components of mTSS (erosion and JSN scores) are presented in Table 7. Treatment with tofacitinib (5 mg and 10 mg BID) resulted in significantly less progression from Baseline in erosion score compared to MTX at Months 12 and 24 ($p \leq 0.0001$).

Table 7. Statistical Analysis of Change From Baseline Erosion Scores and Joint Space Narrowing at Month 6, 12 and 24, Comparisons to Methotrexate Using the Non-Longitudinal Linear Mixed Model – 2 Year Analysis (FAS, Imputation Using Linear Extrapolation)

Visit	Treatment	N	LS Mean	SE	Difference From Methotrexate				
					Diff	SE Diff	95% CI Lower	95% CI Upper	p-Value
Erosion Scores									
Month 6 (LEP)	Tofacitinib 5 mg BID	348	0.14	0.04	-0.21	0.07	-0.35	-0.07	0.0029
	Tofacitinib 10 mg BID	372	0.1	0.04	-0.25	0.07	-0.39	-0.12	0.0003
	Methotrexate	167	0.35	0.06					
Month 12 (LEP)	Tofacitinib 5 mg BID	347	0.13	0.07	-0.45	0.11	-0.66	-0.24	<0.0001
	Tofacitinib 10 mg BID	373	0.12	0.06	-0.47	0.11	-0.68	-0.25	<0.0001
	Methotrexate	171	0.58	0.09					
Month 24 (LEP)	Tofacitinib 5 mg BID	348	0.16	0.11	-0.82	0.18	-1.17	-0.47	<0.0001
	Tofacitinib 10 mg BID	373	0.16	0.1	-0.83	0.18	-1.17	-0.48	<0.0001
	Methotrexate	171	0.98	0.15					
Joint Space Narrowing									
Month 6 (LEP)	Tofacitinib 5 mg BID	348	0.06	0.06	-0.23	0.1	-0.44	-0.03	0.0249
	Tofacitinib 10 mg BID	372	0.05	0.06	-0.24	0.1	-0.44	-0.04	0.0203
	Methotrexate	167	0.29	0.09					
Month 12 (LEP)	Tofacitinib 5 mg BID	347	0.23	0.1	-0.37	0.17	-0.7	-0.04	0.0302
	Tofacitinib 10 mg BID	373	0.05	0.1	-0.55	0.17	-0.88	-0.22	0.001
	Methotrexate	171	0.6	0.14					
Month 24 (LEP)	Tofacitinib 5 mg BID	348	0.39	0.18	-0.71	0.3	-1.29	-0.12	0.0176
	Tofacitinib 10 mg BID	373	0.12	0.17	-0.97	0.29	-1.55	-0.4	0.0009
	Methotrexate	171	1.1	0.25					

BID = twice daily, CI = confidence interval, Diff = difference, FAS = full analysis set, LEP = linear extrapolation, LS = least square, N = number of subjects, SE = standard error.

Rate of Non-Progression in mTSS from Baseline:

A normal approximation of rates of subjects with no progression in mTSS at Months 12 and 24 is presented in Table 8. The tofacitinib 5 mg and 10 mg BID groups had similar rates of subjects with no progression in mTSS from Baseline to Months 12 and 24; the rates were statistically significantly greater than the rates for the MTX group at Months 12 and 24 ($p \leq 0.0010$).

Table 8. Normal Approximation of Rates (%) of Subjects With No Progression in mTSS at Months 12 and 24 (FAS, LEP, Comparisons to MTX, 2 Year Analysis)

Time point/ Treatment	N	n	%	Difference From MTX			
				Difference in %	95% CI for Difference		p-Value
					Lower	Upper	
Month 12							
Tofacitinib 5 mg BID	347	286	82.42	13.41	5.40	21.42	0.0010
Tofacitinib 10 mg BID	373	327	87.67	18.66	10.96	26.35	<0.0001
Methotrexate	171	118	69.01				
Month 24							
Tofacitinib 5 mg BID	348	278	79.89	14.97	6.67	23.27	0.0004
Tofacitinib 10 mg BID	373	312	83.65	18.73	10.65	26.81	<0.0001
Methotrexate	171	111	64.91				

If subject did not have any valid postbaseline radiographs, they were not included in this summary.
No progression in mTSS was defined as a change from Baseline ≤0.5 units.
BID = twice daily, CI = confidence interval, FAS = full analysis set, LEP = linear extrapolation, mTSS = modified Total Sharp Score, MTX = methotrexate, N = number of subjects, n = number of subjects meeting prespecified criteria.

Rate of No New Erosion:

A normal approximation of rates of subjects with no new erosion at Months 12 and 24 in mTSS is presented in Table 9. The rates of subjects with no new erosions at Month 12 and 24 were statistically significantly greater in the tofacitinib groups compared to MTX (p≤0.0002).

Table 9. Normal Approximation of 'no new Erosions' in Erosion Score (Change ≤0.5) per Visit at Months 12 and 24 (FAS, LEP, Comparisons to MTX, 2 Year Analysis)

Time point/ Treatment	N	n	%	Difference From MTX			
				Difference in %	95% CI for Difference		p-Value
					Lower	Upper	
Month 12							
Tofacitinib 5 mg BID	347	307	88.47	13.61	6.29	20.93	0.0002
Tofacitinib 10 mg BID	373	339	90.88	16.03	8.90	23.15	<0.0001
Methotrexate	171	128	74.85				
Month 24							
Tofacitinib 5 mg BID	348	297	85.34	15.16	7.37	22.96	0.0001
Tofacitinib 10 mg BID	373	329	88.20	18.02	10.42	25.62	<0.0001
Methotrexate	171	120	70.18				

If subject did not have any valid postbaseline radiographs, they were not included in this summary.
BID = twice daily, CI = confidence interval, FAS = full analysis set, LEP = linear extrapolation, MTX = methotrexate, N = number of subjects, n = number of subjects meeting prespecified criteria.

ACR20 Response Rates at All Time Points:

ACR20 response rates (FAS, NRI, comparisons to MTX) for the tofacitinib groups are presented by treatment in Table 10. ACR20 response rates were higher for subjects in the tofacitinib 5 mg and 10 mg BID groups compared with subjects in the MTX group at Months 12 through 24.

Table 10. Normal Approximation to ACR 20 Response Rates per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	367	181	49.32	2.6	28.12	3.98	20.31	35.93	<0.0001
	Tofacitinib 10 mg BID	393	229	58.27	2.48	37.07	3.9	29.41	44.73	<0.0001
	Methotrexate	184	39	21.2	3.01					
Month 2 (NRI)	Tofacitinib 5 mg BID	368	234	63.59	2.5	21.19	4.42	12.52	29.86	<0.0001
	Tofacitinib 10 mg BID	394	282	71.57	2.27	29.18	4.29	20.76	37.59	<0.0001
	Methotrexate	184	78	42.39	3.64					
Month 3 (NRI)	Tofacitinib 5 mg BID	369	258	69.92	2.38	18.28	4.39	9.68	26.89	<0.0001
	Tofacitinib 10 mg BID	394	307	77.92	2.08	26.28	4.23	17.98	34.58	<0.0001
	Methotrexate	184	95	51.63	3.68					
Month 6 (NRI)	Tofacitinib 5 mg BID	369	263	71.27	2.35	20.73	4.37	12.15	29.3	<0.0001
	Tofacitinib 10 mg BID	394	300	76.14	2.14	25.59	4.26	17.23	33.95	<0.0001
	Methotrexate	184	93	50.54	3.68					
Month 9 (NRI)	Tofacitinib 5 mg BID	369	266	72.09	2.33	16.65	4.34	8.13	25.16	0.0001
	Tofacitinib 10 mg BID	394	290	73.6	2.22	18.16	4.28	9.77	26.56	<0.0001
	Methotrexate	184	102	55.43	3.66					
Month 12 (NRI)	Tofacitinib 5 mg BID	369	250	67.75	2.43	16.66	4.41	8	25.31	0.0001
	Tofacitinib 10 mg BID	394	282	71.57	2.27	20.48	4.32	12	28.97	<0.0001
	Methotrexate	184	94	51.09	3.68					
Month 15 (NRI)	Tofacitinib 5 mg BID	369	254	68.83	2.41	21.55	4.4	12.92	30.17	<0.0001
	Tofacitinib 10 mg BID	394	261	66.24	2.38	18.96	4.38	10.36	27.55	<0.0001
	Methotrexate	184	87	47.28	3.68					
Month 18 (NRI)	Tofacitinib 5 mg BID	369	237	64.23	2.49	17.48	4.44	8.77	26.2	<0.0001
	Tofacitinib 10 mg BID	394	260	65.99	2.38	19.25	4.38	10.65	27.84	<0.0001
	Methotrexate	184	86	46.74	3.67					
Month 21 (NRI)	Tofacitinib 5 mg BID	369	240	65.04	2.48	19.93	4.42	11.25	28.61	<0.0001
	Tofacitinib 10 mg BID	394	245	62.18	2.44	17.07	4.4	8.43	25.71	0.0001
	Methotrexate	184	83	45.11	3.66					
Month 24 (NRI)	Tofacitinib 5 mg BID	369	237	64.23	2.49	21.83	4.41	13.18	30.49	<0.0001
	Tofacitinib 10 mg BID	394	253	64.21	2.41	21.82	4.37	13.25	30.38	<0.0001
	Methotrexate	184	78	42.39	3.64					

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

ACR50 Response Rates at All Time Points:

Table 11 presents a summary of ACR50 response rates (FAS, NRI, comparisons to MTX) for the tofacitinib groups. ACR50 response rates were higher for subjects in the tofacitinib 5 mg and 10 mg BID groups compared with subjects in the MTX group at Months 12 through 24.

Table 11. Normal Approximation to ACR50 Response Rates per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	367	66	17.98	2	14.17	2.45	9.37	18.98	<0.0001
	Tofacitinib 10 mg BID	393	110	27.99	2.26	24.18	2.66	18.95	29.41	<0.0001
	Methotrexate	184	7	3.8	1.41					
Month 2 (NRI)	Tofacitinib 5 mg BID	368	120	32.61	2.44	21.19	3.38	14.55	27.83	<0.0001
	Tofacitinib 10 mg BID	394	158	40.1	2.46	28.68	3.4	22.01	35.36	<0.0001
	Methotrexate	184	21	11.41	2.34					
Month 3 (NRI)	Tofacitinib 5 mg BID	369	148	40.11	2.55	19.99	3.9	12.34	27.65	<0.0001
	Tofacitinib 10 mg BID	394	197	50	2.51	29.89	3.88	22.28	37.5	<0.0001
	Methotrexate	184	37	20.11	2.95					
Month 6 (NRI)	Tofacitinib 5 mg BID	369	172	46.61	2.59	19.98	4.16	11.81	28.14	<0.0001
	Tofacitinib 10 mg BID	394	222	56.35	2.49	29.71	4.1	21.66	37.76	<0.0001
	Methotrexate	184	49	26.63	3.25					
Month 9 (NRI)	Tofacitinib 5 mg BID	369	184	49.86	2.6	14.53	4.38	5.95	23.12	0.0009
	Tofacitinib 10 mg BID	394	224	56.85	2.49	21.52	4.31	13.06	29.98	<0.0001
	Methotrexate	184	65	35.33	3.52					
Month 12 (NRI)	Tofacitinib 5 mg BID	369	184	49.86	2.6	16.16	4.34	7.64	24.69	0.0002
	Tofacitinib 10 mg BID	394	219	55.58	2.5	21.88	4.29	13.47	30.29	<0.0001
	Methotrexate	184	62	33.7	3.48					
Month 15 (NRI)	Tofacitinib 5 mg BID	369	187	50.68	2.6	17.52	4.33	9.02	26.02	<0.0001
	Tofacitinib 10 mg BID	394	214	54.31	2.5	21.16	4.28	12.76	29.55	<0.0001
	Methotrexate	184	61	33.15	3.47					
Month 18 (NRI)	Tofacitinib 5 mg BID	369	177	47.97	2.6	17.53	4.27	9.15	25.91	<0.0001
	Tofacitinib 10 mg BID	394	204	51.78	2.51	21.34	4.22	13.06	29.62	<0.0001
	Methotrexate	184	56	30.43	3.39					
Month 21 (NRI)	Tofacitinib 5 mg BID	369	181	49.05	2.6	18.61	4.27	10.23	26.99	<0.0001
	Tofacitinib 10 mg BID	394	199	50.51	2.51	20.07	4.22	11.79	28.35	<0.0001
	Methotrexate	184	56	30.43	3.39					
Month 24 (NRI)	Tofacitinib 5 mg BID	369	182	49.32	2.6	21.06	4.21	12.79	29.32	<0.0001
	Tofacitinib 10 mg BID	394	194	49.24	2.51	20.97	4.16	12.81	29.14	<0.0001
	Methotrexate	184	52	28.26	3.31					

ACR50 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, NRI = nonresponder imputation, N = number of subjects, n = number of subjects meeting prespecified criteria, SE = standard error.

ACR70 Response Rates at All Time Points:

Table 12 presents a summary of ACR70 response rates (FAS, NRI, comparisons to MTX) for the tofacitinib groups. ACR70 response rates were higher for subjects in the tofacitinib 5 mg and 10 mg BID groups compared with subjects in the MTX group at Months 12 through 24.

Table 12. Normal Approximation to ACR70 Response Rates per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	367	19	5.18	1.15	4.63	1.27	2.13	7.13	0.0002
	Tofacitinib 10 mg BID	393	36	9.16	1.45	8.61	1.55	5.57	11.66	<0.0001
	Methotrexate	184	1	0.54	0.54					
Month 2 (NRI)	Tofacitinib 5 mg BID	368	59	16.03	1.91	12.77	2.31	8.22	17.31	<0.0001
	Tofacitinib 10 mg BID	394	91	23.1	2.12	19.83	2.49	14.94	24.72	<0.0001
	Methotrexate	184	6	3.26	1.3					
Month 3 (NRI)	Tofacitinib 5 mg BID	369	74	20.05	2.08	14.61	2.67	9.38	19.85	<0.0001
	Tofacitinib 10 mg BID	394	105	26.65	2.22	21.21	2.78	15.75	26.67	<0.0001
	Methotrexate	184	10	5.43	1.67					
Month 6 (NRI)	Tofacitinib 5 mg BID	369	94	25.47	2.26	13.51	3.29	7.05	19.97	<0.0001
	Tofacitinib 10 mg BID	394	148	37.56	2.43	25.6	3.41	18.91	32.3	<0.0001
	Methotrexate	184	22	11.96	2.39					
Month 9 (NRI)	Tofacitinib 5 mg BID	369	108	29.27	2.36	16.22	3.43	9.49	22.95	<0.0001
	Tofacitinib 10 mg BID	394	150	38.07	2.44	25.02	3.48	18.19	31.85	<0.0001
	Methotrexate	184	24	13.04	2.48					
Month 12 (NRI)	Tofacitinib 5 mg BID	369	106	28.73	2.35	13.5	3.54	6.56	20.45	0.0001
	Tofacitinib 10 mg BID	394	150	38.07	2.44	22.85	3.6	15.78	29.91	<0.0001
	Methotrexate	184	28	15.22	2.64					
Month 15 (NRI)	Tofacitinib 5 mg BID	369	111	30.08	2.38	13.23	3.64	6.08	20.38	0.0002
	Tofacitinib 10 mg BID	394	149	37.82	2.44	20.96	3.68	13.74	28.19	<0.0001
	Methotrexate	184	31	16.85	2.75					
Month 18 (NRI)	Tofacitinib 5 mg BID	369	119	32.25	2.43	16.48	3.62	9.38	23.59	<0.0001
	Tofacitinib 10 mg BID	394	145	36.8	2.42	21.04	3.62	13.94	28.14	<0.0001
	Methotrexate	184	29	15.76	2.68					
Month 21 (NRI)	Tofacitinib 5 mg BID	369	119	32.25	2.43	14.85	3.7	7.59	22.12	<0.0001
	Tofacitinib 10 mg BID	394	146	37.06	2.43	19.66	3.7	12.4	26.92	<0.0001
	Methotrexate	184	32	17.39	2.79					
Month 24 (NRI)	Tofacitinib 5 mg BID	369	127	34.42	2.47	19.19	3.62	12.09	26.3	<0.0001
	Tofacitinib 10 mg BID	394	148	37.56	2.43	22.34	3.6	15.28	29.4	<0.0001
	Methotrexate	184	28	15.22	2.64					

ACR70 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, NRI = nonresponder imputation, N = number of subjects, n = number of subjects meeting prespecified criteria, SE = standard error.

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

Table 13 presents the mean changes from Baseline in HAQ-DI. The mean change from Baseline was statistically significantly higher in the tofacitinib groups (5 mg and 10 mg BID) than the MTX groups at all timepoints ($p \leq 0.0033$), indicating a greater increase in functional ability.

Table 13. Statistical Analysis of Change From Baseline in HAQ-DI per Visit (FAS, Longitudinal Model), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	LS mean	SE	Difference	SE Difference	95% CI		p-Value
							Lower	Upper	
Month 1	Tofacitinib 5 mg BID	365	-0.48	0.03	-0.26	0.05	-0.35	-0.16	<0.0001
	Tofacitinib 10 mg BID	391	-0.62	0.03	-0.4	0.05	-0.49	-0.3	<0.0001
	Methotrexate	184	-0.23	0.04					
Month 2	Tofacitinib 5 mg BID	361	-0.65	0.03	-0.3	0.05	-0.4	-0.21	<0.0001
	Tofacitinib 10 mg BID	387	-0.77	0.03	-0.42	0.05	-0.52	-0.33	<0.0001
	Methotrexate	178	-0.35	0.04					
Month 3	Tofacitinib 5 mg BID	354	-0.75	0.03	-0.28	0.05	-0.38	-0.18	<0.0001
	Tofacitinib 10 mg BID	382	-0.85	0.03	-0.39	0.05	-0.48	-0.29	<0.0001
	Methotrexate	171	-0.47	0.04					
Month 6	Tofacitinib 5 mg BID	340	-0.83	0.03	-0.25	0.05	-0.35	-0.15	<0.0001
	Tofacitinib 10 mg BID	365	-0.94	0.03	-0.36	0.05	-0.46	-0.26	<0.0001
	Methotrexate	158	-0.58	0.04					
Month 9	Tofacitinib 5 mg BID	328	-0.85	0.03	-0.2	0.05	-0.3	-0.09	0.0002
	Tofacitinib 10 mg BID	348	-0.95	0.03	-0.3	0.05	-0.4	-0.2	<0.0001
	Methotrexate	143	-0.65	0.04					
Month 12	Tofacitinib 5 mg BID	315	-0.87	0.03	-0.19	0.05	-0.3	-0.09	0.0003
	Tofacitinib 10 mg BID	330	-0.98	0.03	-0.3	0.05	-0.4	-0.2	<0.0001
	Methotrexate	135	-0.68	0.04					
Month 15	Tofacitinib 5 mg BID	293	-0.9	0.03	-0.24	0.05	-0.35	-0.14	<0.0001
	Tofacitinib 10 mg BID	311	-0.98	0.03	-0.32	0.05	-0.42	-0.22	<0.0001
	Methotrexate	127	-0.65	0.05					
Month 18	Tofacitinib 5 mg BID	284	-0.9	0.03	-0.16	0.05	-0.27	-0.05	0.0033
	Tofacitinib 10 mg BID	294	-1.01	0.03	-0.27	0.05	-0.37	-0.16	<0.0001
	Methotrexate	116	-0.74	0.05					
Month 21	Tofacitinib 5 mg BID	273	-0.9	0.03	-0.18	0.05	-0.28	-0.07	0.0013
	Tofacitinib 10 mg BID	290	-1	0.03	-0.28	0.05	-0.38	-0.17	<0.0001
	Methotrexate	111	-0.72	0.05					
Month 24	Tofacitinib 5 mg BID	264	-0.9	0.03	-0.2	0.06	-0.31	-0.09	0.0004
	Tofacitinib 10 mg BID	280	-1.01	0.03	-0.31	0.05	-0.42	-0.2	<0.0001
	Methotrexate	106	-0.7	0.05					

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

Rates of at Least 0.22 Improvement in the HAQ-DI:

Rates of at least 0.22 improvement in the HAQ-DI are summarized in Table 14.

Table 14. Normal Approximation to Rates of at Least 0.22 Improvement in HAQ-DI per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	365	235	64.38	2.5	18.73	4.44	10.01	27.44	<0.0001
	Tofacitinib 10 mg BID	391	289	73.91	2.22	28.26	4.29	19.84	36.67	<0.0001
	Methotrexate	184	84	45.65	3.67					
Month 2 (NRI)	Tofacitinib 5 mg BID	366	253	69.13	2.41	7.71	4.32	-0.76	16.19	0.0745
	Tofacitinib 10 mg BID	392	313	79.85	2.02	18.43	4.12	10.35	26.51	<0.0001
	Methotrexate	184	113	61.41	3.58					
Month 3 (NRI)	Tofacitinib 5 mg BID	366	267	72.95	2.32	7.73	4.2	-0.51	15.98	0.0661
	Tofacitinib 10 mg BID	392	315	80.36	2	15.13	4.04	7.21	23.06	0.0001
	Methotrexate	184	120	65.22	3.51					
Month 6 (NRI)	Tofacitinib 5 mg BID	366	272	74.32	2.28	11.27	4.22	2.98	19.56	0.0076
	Tofacitinib 10 mg BID	392	305	77.81	2.09	14.76	4.13	6.66	22.85	0.0003
	Methotrexate	184	116	63.04	3.55					
Month 9 (NRI)	Tofacitinib 5 mg BID	366	269	73.5	2.3	12.08	4.26	3.72	20.44	0.0046
	Tofacitinib 10 mg BID	392	287	73.21	2.23	11.8	4.22	3.51	20.08	0.0052
	Methotrexate	184	113	61.41	3.58					
Month 12 (NRI)	Tofacitinib 5 mg BID	366	249	68.03	2.43	9.33	4.37	0.76	17.9	0.0327
	Tofacitinib 10 mg BID	392	280	71.43	2.28	12.73	4.28	4.32	21.13	0.0029
	Methotrexate	184	108	58.7	3.62					
Month 15 (NRI)	Tofacitinib 5 mg BID	366	239	65.3	2.48	13.67	4.44	4.95	22.38	0.0021
	Tofacitinib 10 mg BID	392	266	67.86	2.35	16.22	4.37	7.65	24.8	0.0002
	Methotrexate	184	95	51.63	3.68					
Month 18 (NRI)	Tofacitinib 5 mg BID	366	235	64.21	2.5	15.29	4.45	6.56	24.02	0.0005
	Tofacitinib 10 mg BID	392	254	64.8	2.41	15.88	4.4	7.25	24.51	0.0003
	Methotrexate	184	90	48.91	3.68					
Month 21 (NRI)	Tofacitinib 5 mg BID	366	228	62.3	2.53	15.55	4.46	6.8	24.3	0.0004
	Tofacitinib 10 mg BID	392	255	65.05	2.4	18.31	4.39	9.69	26.92	<0.0001
	Methotrexate	184	86	46.74	3.67					
Month 24 (NRI)	Tofacitinib 5 mg BID	366	220	60.11	2.55	13.37	4.48	4.58	22.15	0.0028
	Tofacitinib 10 mg BID	392	255	65.05	2.4	18.31	4.39	9.69	26.92	<0.0001
	Methotrexate	184	86	46.74	3.67					

BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire-Disability Index, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation, SE = standard error.

Rates of at Least 0.3 Improvement in the HAQ-DI:

Rates of at least 0.3 improvement in the HAQ-DI are summarized in Table 15.

Table 15. Normal Approximation to Rates of at Least 0.3 Improvement in HAQ-DI per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE OF Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	365	200	54.79	2.6	22.18	4.32	13.7	30.66	<0.0001
	Tofacitinib 10 mg BID	391	257	65.73	2.4	33.12	4.2	24.87	41.36	<0.0001
	Methotrexate	184	60	32.61	3.45					
Month 2 (NRI)	Tofacitinib 5 mg BID	366	228	62.3	2.53	14.46	4.46	5.7	23.22	0.0012
	Tofacitinib 10 mg BID	392	287	73.21	2.23	25.38	4.3	16.94	33.83	<0.0001
	Methotrexate	184	88	47.83	3.68					
Month 3 (NRI)	Tofacitinib 5 mg BID	366	240	65.57	2.48	10.68	4.42	1.99	19.36	0.0158
	Tofacitinib 10 mg BID	392	291	74.23	2.2	19.34	4.28	10.95	27.73	<0.0001
	Methotrexate	184	101	54.89	3.66					
Month 6 (NRI)	Tofacitinib 5 mg BID	366	255	69.67	2.4	15.86	4.39	7.26	24.47	0.0003
	Tofacitinib 10 mg BID	392	287	73.21	2.23	19.4	4.3	10.97	27.84	<0.0001
	Methotrexate	184	99	53.8	3.67					
Month 9 (NRI)	Tofacitinib 5 mg BID	366	253	69.13	2.41	15.86	4.4	7.24	24.48	0.0003
	Tofacitinib 10 mg BID	392	272	69.39	2.32	16.12	4.35	7.59	24.65	0.0002
	Methotrexate	184	98	53.26	3.67					
Month 12 (NRI)	Tofacitinib 5 mg BID	366	238	65.03	2.49	12.3	4.44	3.59	21.02	0.0056
	Tofacitinib 10 mg BID	392	264	67.35	2.36	14.62	4.37	6.05	23.2	0.0008
	Methotrexate	184	97	52.72	3.68					
Month 15 (NRI)	Tofacitinib 5 mg BID	366	224	61.2	2.54	13.37	4.47	4.59	22.15	0.0028
	Tofacitinib 10 mg BID	392	256	65.31	2.4	17.48	4.39	8.86	26.09	<0.0001
	Methotrexate	184	88	47.83	3.68					
Month 18 (NRI)	Tofacitinib 5 mg BID	366	219	59.84	2.56	13.64	4.48	4.85	22.42	0.0023
	Tofacitinib 10 mg BID	392	248	63.27	2.43	17.06	4.4	8.42	25.71	0.0001
	Methotrexate	184	85	46.2	3.67					
Month 21 (NRI)	Tofacitinib 5 mg BID	366	215	58.74	2.57	14.72	4.47	5.95	23.48	0.0009
	Tofacitinib 10 mg BID	392	240	61.22	2.46	17.2	4.41	8.55	25.84	<0.0001
	Methotrexate	184	81	44.02	3.65					
Month 24 (NRI)	Tofacitinib 5 mg BID	366	208	56.83	2.58	13.35	4.47	4.57	22.13	0.0028
	Tofacitinib 10 mg BID	392	246	62.76	2.44	19.27	4.39	10.66	27.89	<0.0001
	Methotrexate	184	80	43.48	3.65					

BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire-Disability Index, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation, SE = standard error.

Rates of at Least 0.5 Improvement in the HAQ-DI:

Rates of at least 0.5 improvement in the HAQ-DI are summarized in Table 16.

Table 16. Normal Approximation to Rates of at Least 0.5 Improvement in HAQ-DI per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Diffeence	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	365	175	47.95	2.61	21.85	4.16	13.7	30.01	<0.0001
	Tofacitinib 10 mg BID	391	218	55.75	2.51	29.66	4.09	21.63	37.69	<0.0001
	Methotrexate	184	48	26.09	3.23					
Month 2 (NRI)	Tofacitinib 5 mg BID	366	203	55.46	2.59	15.79	4.44	7.07	24.5	0.0003
	Tofacitinib 10 mg BID	392	266	67.86	2.35	28.18	4.3	19.73	36.62	<0.0001
	Methotrexate	184	73	39.67	3.6					
Month 3 (NRI)	Tofacitinib 5 mg BID	366	222	60.66	2.55	17.17	4.45	8.43	25.91	0.0001
	Tofacitinib 10 mg BID	392	273	69.64	2.32	26.16	4.33	17.67	34.65	<0.0001
	Methotrexate	184	80	43.48	3.65					
Month 6 (NRI)	Tofacitinib 5 mg BID	366	231	63.11	2.52	14.2	4.46	5.44	22.95	0.0014
	Tofacitinib 10 mg BID	392	270	68.88	2.33	19.96	4.36	11.41	28.51	<0.0001
	Methotrexate	184	90	48.91	3.68					
Month 9 (NRI)	Tofacitinib 5 mg BID	366	239	65.3	2.48	18.01	4.44	9.31	26.72	<0.0001
	Tofacitinib 10 mg BID	392	255	65.05	2.4	17.76	4.39	9.14	26.38	<0.0001
	Methotrexate	184	87	47.28	3.68					
Month 12 (NRI)	Tofacitinib 5 mg BID	366	218	59.56	2.56	13.91	4.47	5.13	22.69	0.0018
	Tofacitinib 10 mg BID	392	247	63.01	2.43	17.35	4.4	8.71	25.99	<0.0001
	Methotrexate	184	84	45.65	3.67					
Month 15 (NRI)	Tofacitinib 5 mg BID	366	213	58.2	2.57	13.63	4.48	4.85	22.41	0.0023
	Tofacitinib 10 mg BID	392	238	60.71	2.46	16.14	4.41	7.49	24.8	0.0002
	Methotrexate	184	82	44.57	3.66					
Month 18 (NRI)	Tofacitinib 5 mg BID	366	206	56.28	2.59	14.97	4.46	6.23	23.72	0.0007
	Tofacitinib 10 mg BID	392	238	60.71	2.46	19.4	4.38	10.8	28.01	<0.0001
	Methotrexate	184	76	41.3	3.62					
Month 21 (NRI)	Tofacitinib 5 mg BID	366	202	55.19	2.59	13.34	4.47	4.58	22.1	0.0028
	Tofacitinib 10 mg BID	392	228	58.16	2.49	16.31	4.4	7.67	24.95	0.0002
	Methotrexate	184	77	41.85	3.63					
Month 24 (NRI)	Tofacitinib 5 mg BID	366	195	53.28	2.6	15.77	4.42	7.11	24.44	0.0003
	Tofacitinib 10 mg BID	392	233	59.44	2.47	21.93	4.34	13.42	30.45	<0.0001
	Methotrexate	184	69	37.5	3.56					

BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire-Disability Index, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation, SE = standard error.

DAS28-4 (ESR):

Table 17 presents mean changes from Baseline in DAS28-4 (ESR) during the study (FAS, comparisons to MTX). The mean change from Baseline was statistically significantly greater in the tofacitinib groups (5 mg and 10 mg BID) than the MTX groups at all timepoints ($p \leq 0.0001$); indicating a greater reduction in the tofacitinib groups in a composite disease activity index calculated from the number of tender and swollen joints, ESR and global assessment.

Table 17. Statistical Analysis of Change From Baseline in DAS28-4 ESR) per Visit (FAS, Longitudinal Model), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	LS Mean	SE	Difference	SE Difference	95% CI		p-Value
							Lower	Upper	
Month 1	Tofacitinib 5 mg BID	338	-1.4	0.07	-0.68	0.12	-0.91	-0.45	<0.0001
	Tofacitinib 10 mg BID	369	-1.83	0.07	-1.11	0.11	-1.34	-0.89	<0.0001
	Methotrexate	167	-0.72	0.1					
Month 2	Tofacitinib 5 mg BID	333	-2.03	0.07	-0.86	0.12	-1.09	-0.63	<0.0001
	Tofacitinib 10 mg BID	366	-2.36	0.07	-1.19	0.12	-1.42	-0.96	<0.0001
	Methotrexate	163	-1.17	0.1					
Month 3	Tofacitinib 5 mg BID	329	-2.34	0.07	-0.81	0.12	-1.04	-0.58	<0.0001
	Tofacitinib 10 mg BID	360	-2.59	0.07	-1.06	0.12	-1.29	-0.83	<0.0001
	Methotrexate	159	-1.53	0.1					
Month 6	Tofacitinib 5 mg BID	319	-2.47	0.07	-0.6	0.12	-0.84	-0.36	<0.0001
	Tofacitinib 10 mg BID	345	-2.88	0.07	-1.01	0.12	-1.24	-0.78	<0.0001
	Methotrexate	146	-1.87	0.1					
Month 9	Tofacitinib 5 mg BID	305	-2.64	0.07	-0.45	0.12	-0.69	-0.21	0.0003
	Tofacitinib 10 mg BID	329	-2.93	0.07	-0.74	0.12	-0.98	-0.51	<0.0001
	Methotrexate	132	-2.19	0.1					
Month 12	Tofacitinib 5 mg BID	292	-2.78	0.07	-0.58	0.13	-0.83	-0.34	<0.0001
	Tofacitinib 10 mg BID	309	-3.05	0.07	-0.85	0.12	-1.09	-0.61	<0.0001
	Methotrexate	123	-2.2	0.11					
Month 15	Tofacitinib 5 mg BID	276	-2.87	0.07	-0.62	0.13	-0.87	-0.37	<0.0001
	Tofacitinib 10 mg BID	293	-3.08	0.07	-0.84	0.13	-1.08	-0.59	<0.0001
	Methotrexate	116	-2.25	0.11					
Month 18	Tofacitinib 5 mg BID	264	-2.92	0.07	-0.58	0.13	-0.83	-0.32	<0.0001
	Tofacitinib 10 mg BID	272	-3.09	0.07	-0.75	0.13	-1	-0.5	<0.0001
	Methotrexate	106	-2.34	0.11					
Month 21	Tofacitinib 5 mg BID	254	-2.96	0.08	-0.65	0.13	-0.91	-0.39	<0.0001
	Tofacitinib 10 mg BID	269	-3.1	0.07	-0.8	0.13	-1.06	-0.54	<0.0001
	Methotrexate	100	-2.3	0.11					
Month 24	Tofacitinib 5 mg BID	238	-2.99	0.08	-0.59	0.14	-0.86	-0.33	<0.0001
	Tofacitinib 10 mg BID	254	-3.16	0.07	-0.76	0.13	-1.02	-0.5	<0.0001
	Methotrexate	92	-2.4	0.12					

DAS = Disease Activity Score, BID = twice daily, CI = confidence interval, ESR = erythrocyte sedimentation rate, FAS = full analysis set, LS = least square, N = number of subjects, SE = standard error.

DAS28-4 (ESR) <2.6:

Table 18 presents the proportions of subjects with DAS28-4 (ESR) <2.6 classified by the number of active joints (ie, tender or swollen) per visit. The proportion of subjects in the tofacitinib groups (5 mg and 10 mg BID) with DAS28-4 (ESR) <2.6 and 0 active joints increased from Month 12 to Month 24.

Table 18. Number (%) of Subjects With Active Joints per Visit Who Achieved DAS28-4 (ESR) <2.6 (FAS, No Imputation, Comparisons to MTX, 2 Year Analysis)

Visit	Treatment	N	Active Joints (Tender or Swollen)			
			0 Joints n (%)	1 Joint n (%)	2 Joints n (%)	≥3 Joints n (%)
Month 12	Tofacitinib 5 mg BID	63	33 (52.4)	9 (14.3)	4 (6.3)	17 (27.0)
	Tofacitinib 10 mg BID	85	47 (55.3)	14 (16.5)	8 (9.4)	16 (18.8)
	Methotrexate	19	10 (52.6)	0	0	9 (47.4)
Month 15	Tofacitinib 5 mg BID	58	28 (48.3)	11 (19.0)	5 (8.6)	14 (24.1)
	Tofacitinib 10 mg BID	92	59 (64.1)	16 (17.4)	5 (5.4)	12 (13.0)
	Methotrexate	22	13 (59.1)	1 (4.5)	4 (18.2)	4 (18.2)
Month 18	Tofacitinib 5 mg BID	60	38 (63.3)	4 (6.7)	4 (6.7)	14 (23.3)
	Tofacitinib 10 mg BID	76	43 (56.6)	13 (17.1)	5 (6.6)	15 (19.7)
	Methotrexate	20	6 (30.0)	5 (25.0)	4 (20.0)	5 (25.0)
Month 21	Tofacitinib 5 mg BID	64	45 (70.3)	7 (10.9)	4 (6.3)	8 (12.5)
	Tofacitinib 10 mg BID	79	54 (68.4)	8 (10.1)	6 (7.6)	11 (13.9)
	Methotrexate	15	8 (53.3)	2 (13.3)	2 (13.3)	3 (20.0)
Month 24	Tofacitinib 5 mg BID	70	45 (64.3)	8 (11.4)	7 (10.0)	10 (14.3)
	Tofacitinib 10 mg BID	81	59 (72.8)	9 (11.1)	8 (9.9)	5 (6.2)
	Methotrexate	17	9 (52.9)	4 (23.5)	2 (11.8)	2 (11.8)

At each month, N was the number of subjects with DAS <2.6.
BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, n = number of subjects meeting prespecified criteria, MTX = methotrexate.

DAS28-4 (ESR) ≤3.2:

Table 19 presents the proportions of subjects with DAS28-4 (ESR) ≤3.2.

Table 19. Normal Approximation to DAS 28-4 (ESR) ≤3.2 Rates per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	338	25	7.4	1.42	4.4	1.94	0.59	8.2	0.0232
	Tofacitinib 10 mg BID	369	52	14.09	1.81	11.09	2.24	6.7	15.48	<0.0001
	Methotrexate	167	5	2.99	1.31					
Month 2 (NRI)	Tofacitinib 5 mg BID	342	63	18.42	2.09	13.71	2.65	8.51	18.91	<0.0001
	Tofacitinib 10 mg BID	372	96	25.81	2.26	21.1	2.79	15.63	26.56	<0.0001
	Methotrexate	170	8	4.71	1.62					
Month 3 (NRI)	Tofacitinib 5 mg BID	342	86	25.15	2.34	15.2	3.27	8.78	21.62	<0.0001
	Tofacitinib 10 mg BID	372	113	30.38	2.38	20.43	3.3	13.95	26.91	<0.0001
	Methotrexate	171	17	9.94	2.28					
Month 6 (NRI)	Tofacitinib 5 mg BID	342	95	27.78	2.42	13.74	3.59	6.69	20.78	0.0001
	Tofacitinib 10 mg BID	372	142	38.17	2.51	24.13	3.66	16.96	31.31	<0.0001
	Methotrexate	171	24	14.04	2.65					
Month 9 (NRI)	Tofacitinib 5 mg BID	342	100	29.24	2.45	11.11	3.83	3.58	18.63	0.0037
	Tofacitinib 10 mg BID	372	148	39.78	2.53	21.65	3.88	14.03	29.27	<0.0001
	Methotrexate	171	31	18.13	2.94					
Month 12 (NRI)	Tofacitinib 5 mg BID	342	114	33.33	2.54	14.61	3.92	6.92	22.3	0.0001
	Tofacitinib 10 mg BID	372	153	41.13	2.55	22.41	3.92	14.72	30.1	<0.0001
	Methotrexate	171	32	18.71	2.98					
Month 15 (NRI)	Tofacitinib 5 mg BID	342	113	33.04	2.54	14.91	3.89	7.28	22.54	0.0001
	Tofacitinib 10 mg BID	372	152	40.86	2.54	22.73	3.89	15.09	30.36	<0.0001
	Methotrexate	171	31	18.13	2.94					
Month 18 (NRI)	Tofacitinib 5 mg BID	342	110	32.16	2.52	15.78	3.79	8.35	23.22	<0.0001
	Tofacitinib 10 mg BID	372	131	35.22	2.47	18.84	3.76	11.47	26.21	<0.0001
	Methotrexate	171	28	16.37	2.82					
Month 21 (NRI)	Tofacitinib 5 mg BID	342	117	34.21	2.56	17.83	3.81	10.35	25.32	<0.0001
	Tofacitinib 10 mg BID	372	142	38.17	2.51	21.79	3.78	14.37	29.22	<0.0001
	Methotrexate	171	28	16.37	2.82					
Month 24 (NRI)	Tofacitinib 5 mg BID	342	119	34.8	2.57	19	3.79	11.56	26.44	<0.0001
	Tofacitinib 10 mg BID	372	134	36.02	2.48	20.23	3.73	12.9	27.55	<0.0001
	Methotrexate	171	27	15.79	2.78					

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

DAS28-3 (CRP)

Table 20 presents analysis of change from Baseline in DAS28-3 (CRP) (FAS, comparisons to MTX). The mean change from Baseline was statistically significantly improved in the tofacitinib groups (5 mg and 10 mg BID) compared to the MTX groups at all timepoints ($p < 0.0001$). Subjects who received tofacitinib 10 mg BID experienced numerically greater improvement compared with tofacitinib 5 mg BID.

Table 20. Statistical Analysis of Change From Baseline in DAS28-3 (CRP) per Visit (FAS, Longitudinal Model), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	LS Mean	SE	Difference	SE Difference	95% CI		p-Value
							Lower	Upper	
Month 1	Tofacitinib 5 mg BID	366	-1.3	0.06	-0.72	0.1	-0.92	-0.53	<0.0001
	Tofacitinib 10 mg BID	389	-1.71	0.06	-1.13	0.1	-1.32	-0.93	<0.0001
	Methotrexate	184	-0.58	0.08					
Month 2	Tofacitinib 5 mg BID	359	-1.85	0.06	-0.83	0.1	-1.02	-0.63	<0.0001
	Tofacitinib 10 mg BID	386	-2.16	0.06	-1.14	0.1	-1.33	-0.94	<0.0001
	Methotrexate	176	-1.02	0.08					
Month 3	Tofacitinib 5 mg BID	353	-2.09	0.06	-0.73	0.1	-0.93	-0.54	<0.0001
	Tofacitinib 10 mg BID	383	-2.42	0.06	-1.06	0.1	-1.26	-0.87	<0.0001
	Methotrexate	171	-1.36	0.08					
Month 6	Tofacitinib 5 mg BID	339	-2.27	0.06	-0.64	0.1	-0.84	-0.44	<0.0001
	Tofacitinib 10 mg BID	366	-2.68	0.06	-1.06	0.1	-1.26	-0.86	<0.0001
	Methotrexate	158	-1.62	0.09					
Month 9	Tofacitinib 5 mg BID	327	-2.4	0.06	-0.45	0.11	-0.66	-0.24	<0.0001
	Tofacitinib 10 mg BID	349	-2.72	0.06	-0.77	0.1	-0.98	-0.57	<0.0001
	Methotrexate	143	-1.95	0.09					
Month 12	Tofacitinib 5 mg BID	313	-2.52	0.06	-0.53	0.11	-0.75	-0.32	<0.0001
	Tofacitinib 10 mg BID	330	-2.85	0.06	-0.87	0.11	-1.07	-0.66	<0.0001
	Methotrexate	135	-1.99	0.09					
Month 15	Tofacitinib 5 mg BID	289	-2.65	0.06	-0.63	0.11	-0.84	-0.41	<0.0001
	Tofacitinib 10 mg BID	311	-2.85	0.06	-0.83	0.11	-1.04	-0.61	<0.0001
	Methotrexate	128	-2.03	0.09					
Month 18	Tofacitinib 5 mg BID	279	-2.72	0.06	-0.67	0.11	-0.89	-0.45	<0.0001
	Tofacitinib 10 mg BID	291	-2.91	0.06	-0.86	0.11	-1.07	-0.64	<0.0001
	Methotrexate	116	-2.05	0.1					
Month 21	Tofacitinib 5 mg BID	272	-2.75	0.06	-0.7	0.11	-0.92	-0.47	<0.0001
	Tofacitinib 10 mg BID	288	-2.89	0.06	-0.84	0.11	-1.06	-0.62	<0.0001
	Methotrexate	111	-2.05	0.1					
Month 24	Tofacitinib 5 mg BID	263	-2.76	0.07	-0.64	0.12	-0.86	-0.41	<0.0001
	Tofacitinib 10 mg BID	279	-2.94	0.06	-0.82	0.11	-1.05	-0.6	<0.0001
	Methotrexate	104	-2.12	0.1					

DAS = Disease Activity Score, CI = confidence interval, CRP = C-reactive protein, BID = twice daily, FAS = full analysis set, LS = least square, N = number of subjects, SE = standard error.

DAS28-3 (CRP) <2.6:

Table 21 presents the proportions of subjects with DAS28-3 (CRP) <2.6.

Table 21. Normal Approximation to DAS 28-3 (CRP) <2.6 Rates per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	366	27	7.38	1.36	4.65	1.81	1.09	8.22	0.0103
	Tofacitinib 10 mg BID	389	55	14.14	1.76	11.42	2.13	7.23	15.6	<0.0001
	Methotrexate	184	5	2.72	1.19					
Month 2 (NRI)	Tofacitinib 5 mg BID	367	75	20.44	2.1	15	2.68	9.73	20.26	<0.0001
	Tofacitinib 10 mg BID	394	113	28.68	2.27	23.24	2.82	17.7	28.78	<0.0001
	Methotrexate	184	10	5.43	1.67					
Month 3 (NRI)	Tofacitinib 5 mg BID	367	95	25.89	2.28	16.1	3.16	9.89	22.3	<0.0001
	Tofacitinib 10 mg BID	394	149	37.82	2.44	28.03	3.28	21.6	34.46	<0.0001
	Methotrexate	184	18	9.78	2.19					
Month 6 (NRI)	Tofacitinib 5 mg BID	367	115	31.34	2.42	16.11	3.58	9.08	23.15	<0.0001
	Tofacitinib 10 mg BID	394	186	47.21	2.51	31.99	3.65	24.83	39.14	<0.0001
	Methotrexate	184	28	15.22	2.64					
Month 9 (NRI)	Tofacitinib 5 mg BID	367	133	36.24	2.5	18.84	3.75	11.48	26.2	<0.0001
	Tofacitinib 10 mg BID	394	180	45.69	2.5	28.29	3.75	20.93	35.65	<0.0001
	Methotrexate	184	32	17.39	2.79					
Month 12 (NRI)	Tofacitinib 5 mg BID	367	134	36.51	2.51	15.86	3.9	8.21	23.5	<0.0001
	Tofacitinib 10 mg BID	394	195	49.49	2.51	28.84	3.9	21.18	36.49	<0.0001
	Methotrexate	184	38	20.65	2.98					
Month 15 (NRI)	Tofacitinib 5 mg BID	367	138	37.6	2.52	18.03	3.86	10.45	25.61	<0.0001
	Tofacitinib 10 mg BID	394	194	49.24	2.51	29.67	3.85	22.1	37.23	<0.0001
	Methotrexate	184	36	19.57	2.92					
Month 18 (NRI)	Tofacitinib 5 mg BID	367	141	38.42	2.53	19.39	3.84	11.85	26.94	<0.0001
	Tofacitinib 10 mg BID	394	176	44.67	2.5	25.64	3.82	18.14	33.14	<0.0001
	Methotrexate	184	35	19.02	2.89					
Month 21 (NRI)	Tofacitinib 5 mg BID	367	136	37.06	2.52	19.66	3.76	12.28	27.04	<0.0001
	Tofacitinib 10 mg BID	394	176	44.67	2.5	27.27	3.75	19.92	34.63	<0.0001
	Methotrexate	184	32	17.39	2.79					
Month 24 (NRI)	Tofacitinib 5 mg BID	367	141	38.42	2.53	19.94	3.82	12.44	27.43	<0.0001
	Tofacitinib 10 mg BID	394	173	43.91	2.5	25.43	3.79	17.98	32.87	<0.0001
	Methotrexate	184	34	18.48	2.86					

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

DAS28-3 (CRP) ≤3.2:

Table 22 presents the proportions of subjects with DAS28-3 (CRP) ≤3.2.

Table 22. Normal Approximation to DAS 28-3(CRP) ≤3.2 Rates per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	366	61	16.67	1.94	10.68	2.61	5.55	15.81	<0.0001
	Tofacitinib 10 mg BID	389	129	33.16	2.38	27.18	2.95	21.38	32.98	<0.0001
	Methotrexate	184	11	5.98	1.74					
Month 2 (NRI)	Tofacitinib 5 mg BID	367	130	35.42	2.49	21.29	3.58	14.27	28.31	<0.0001
	Tofacitinib 10 mg BID	394	189	47.97	2.51	33.83	3.59	26.79	40.88	<0.0001
	Methotrexate	184	26	14.13	2.56					
Month 3 (NRI)	Tofacitinib 5 mg BID	367	148	40.33	2.56	20.76	3.88	13.14	28.38	<0.0001
	Tofacitinib 10 mg BID	394	224	56.85	2.49	37.28	3.84	29.75	44.82	<0.0001
	Methotrexate	184	36	19.57	2.92					
Month 6 (NRI)	Tofacitinib 5 mg BID	367	175	47.68	2.6	19.96	4.2	11.72	28.2	<0.0001
	Tofacitinib 10 mg BID	394	247	62.69	2.43	34.97	4.1	26.93	43.01	<0.0001
	Methotrexate	184	51	27.72	3.29					
Month 9 (NRI)	Tofacitinib 5 mg BID	367	191	52.04	2.6	18.89	4.34	10.38	27.39	<0.0001
	Tofacitinib 10 mg BID	394	238	60.41	2.46	27.25	4.25	18.91	35.59	<0.0001
	Methotrexate	184	61	33.15	3.47					
Month 12 (NRI)	Tofacitinib 5 mg BID	367	193	52.59	2.6	19.97	4.32	11.49	28.46	<0.0001
	Tofacitinib 10 mg BID	394	256	64.97	2.4	32.36	4.2	24.11	40.61	<0.0001
	Methotrexate	184	60	32.61	3.45					
Month 15 (NRI)	Tofacitinib 5 mg BID	367	196	53.41	2.6	23.51	4.26	15.16	31.86	<0.0001
	Tofacitinib 10 mg BID	394	232	58.88	2.47	28.99	4.18	20.78	37.19	<0.0001
	Methotrexate	184	55	29.89	3.37					
Month 18 (NRI)	Tofacitinib 5 mg BID	367	193	52.59	2.6	27.58	4.12	19.51	35.66	<0.0001
	Tofacitinib 10 mg BID	394	221	56.09	2.5	31.09	4.05	23.14	39.03	<0.0001
	Methotrexate	184	46	25	3.19					
Month 21 (NRI)	Tofacitinib 5 mg BID	367	193	52.59	2.6	24.32	4.22	16.05	32.59	<0.0001
	Tofacitinib 10 mg BID	394	220	55.84	2.5	27.57	4.15	19.42	35.72	<0.0001
	Methotrexate	184	52	28.26	3.31					
Month 24 (NRI)	Tofacitinib 5 mg BID	367	192	52.32	2.6	22.96	4.25	14.63	31.29	<0.0001
	Tofacitinib 10 mg BID	394	224	56.85	2.49	27.5	4.18	19.3	35.7	<0.0001
	Methotrexate	184	54	29.35	3.35					

BID = twice daily, CI = confidence interval, DAS = Disease Activity Score, CRP = C-reactive protein, FAS = full analysis set, N = number of subjects, n = number of subjects meeting prespecified criteria, NRI = nonresponder imputation, SE = standard error.

Good or Moderate Improvement in the DAS28-4 (ESR):

Rates of at least good or moderate improvement in the DAS28-4 (ESR) are summarized in Table 23.

Table 23. Normal Approximation to DAS 28-4 (ESR) Response (Good or Moderate Improvement) Rates per Visit (FAS, NRI), comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	338	211	62.43	2.63	28.89	4.5	20.06	37.72	<0.0001
	Tofacitinib 10 mg BID	369	274	74.25	2.27	40.72	4.3	32.28	49.15	<0.0001
	Methotrexate	167	56	33.53	3.65					
Month 2 (NRI)	Tofacitinib 5 mg BID	342	254	74.27	2.36	24.26	4.5	15.43	33.09	<0.0001
	Tofacitinib 10 mg BID	372	306	82.26	1.98	32.25	4.31	23.79	40.71	<0.0001
	Methotrexate	170	85	50	3.83					
Month 3 (NRI)	Tofacitinib 5 mg BID	342	275	80.41	2.14	13.74	4.19	5.51	21.96	0.001
	Tofacitinib 10 mg BID	372	328	88.17	1.67	21.5	3.97	13.71	29.29	<0.0001
	Methotrexate	171	114	66.67	3.6					
Month 6 (NRI)	Tofacitinib 5 mg BID	342	270	78.95	2.2	18.12	4.33	9.63	26.62	<0.0001
	Tofacitinib 10 mg BID	372	313	84.14	1.89	23.32	4.18	15.11	31.52	<0.0001
	Methotrexate	171	104	60.82	3.73					
Month 9 (NRI)	Tofacitinib 5 mg BID	342	268	78.36	2.22	16.95	4.33	8.45	25.46	<0.0001
	Tofacitinib 10 mg BID	372	304	81.72	2	20.31	4.22	12.03	28.6	<0.0001
	Methotrexate	171	105	61.4	3.72					
Month 12 (NRI)	Tofacitinib 5 mg BID	342	262	76.61	2.28	16.95	4.39	8.34	25.57	0.0001
	Tofacitinib 10 mg BID	372	296	79.57	2.09	19.92	4.29	11.5	28.33	<0.0001
	Methotrexate	171	102	59.65	3.75					
Month 15 (NRI)	Tofacitinib 5 mg BID	342	256	74.85	2.34	18.12	4.45	9.39	26.86	<0.0001
	Tofacitinib 10 mg BID	372	272	73.12	2.29	16.39	4.43	7.7	25.07	0.0002
	Methotrexate	171	97	56.73	3.78					
Month 18 (NRI)	Tofacitinib 5 mg BID	342	240	70.18	2.47	18.12	4.55	9.2	27.04	<0.0001
	Tofacitinib 10 mg BID	372	264	70.97	2.35	18.92	4.48	10.12	27.71	<0.0001
	Methotrexate	171	89	52.05	3.82					
Month 21 (NRI)	Tofacitinib 5 mg BID	342	239	69.88	2.48	21.34	4.55	12.41	30.27	<0.0001
	Tofacitinib 10 mg BID	372	260	69.89	2.37	21.35	4.5	12.53	30.17	<0.0001
	Methotrexate	171	83	48.54	3.82					
Month 24 (NRI)	Tofacitinib 5 mg BID	342	235	68.71	2.5	19.59	4.57	10.62	28.55	<0.0001
	Tofacitinib 10 mg BID	372	259	69.62	2.38	20.5	4.5	11.66	29.33	<0.0001
	Methotrexate	171	84	49.12	3.82					

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

Good or Moderate Improvement in the DAS28-3 (CRP):

Rates of at least good or moderate improvement in the DAS28-3 (CRP) are summarized in Table 24.

Table 24. Normal Approximation to DAS 28-3 (CRP) Response (Good or Moderate Improvement) Rates per Visit (FAS, NRI), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	n	Response Rate	SE	Difference	SE of Difference	95% CI Interval		p-Value
								Lower	Upper	
Month 1 (NRI)	Tofacitinib 5 mg BID	366	263	71.86	2.35	34.35	4.27	25.98	42.73	<0.0001
	Tofacitinib 10 mg BID	389	313	80.46	2.01	42.96	4.09	34.93	50.99	<0.0001
	Methotrexate	184	69	37.5	3.56					
Month 2 (NRI)	Tofacitinib 5 mg BID	367	294	80.11	2.08	21.95	4.19	13.74	30.17	<0.0001
	Tofacitinib 10 mg BID	394	338	85.79	1.75	27.63	4.03	19.71	35.55	<0.0001
	Methotrexate	184	107	58.15	3.63					
Month 3 (NRI)	Tofacitinib 5 mg BID	367	307	83.65	1.93	15.17	3.93	7.46	22.87	0.0001
	Tofacitinib 10 mg BID	394	352	89.34	1.55	20.86	3.76	13.48	28.23	<0.0001
	Methotrexate	184	126	68.48	3.42					
Month 6 (NRI)	Tofacitinib 5 mg BID	367	304	82.83	1.96	18.7	4.04	10.77	26.63	<0.0001
	Tofacitinib 10 mg BID	394	335	85.03	1.79	20.89	3.96	13.12	28.66	<0.0001
	Methotrexate	184	118	64.13	3.53					
Month 9 (NRI)	Tofacitinib 5 mg BID	367	295	80.38	2.07	16.25	4.09	8.21	24.28	<0.0001
	Tofacitinib 10 mg BID	394	326	82.74	1.9	18.61	4.01	10.73	26.48	<0.0001
	Methotrexate	184	118	64.13	3.53					
Month 12 (NRI)	Tofacitinib 5 mg BID	367	280	76.29	2.21	15.42	4.22	7.13	23.71	0.0002
	Tofacitinib 10 mg BID	394	310	78.68	2.06	17.81	4.14	9.68	25.93	<0.0001
	Methotrexate	184	112	60.87	3.59					
Month 15 (NRI)	Tofacitinib 5 mg BID	367	276	75.2	2.25	15.96	4.26	7.6	24.32	0.0001
	Tofacitinib 10 mg BID	394	289	73.35	2.22	14.11	4.25	5.77	22.44	0.0009
	Methotrexate	184	109	59.24	3.62					
Month 18 (NRI)	Tofacitinib 5 mg BID	367	268	73.02	2.31	17.04	4.33	8.55	25.53	<0.0001
	Tofacitinib 10 mg BID	394	282	71.57	2.27	15.59	4.3	7.15	24.03	0.0002
	Methotrexate	184	103	55.98	3.65					
Month 21 (NRI)	Tofacitinib 5 mg BID	367	255	69.48	2.4	18.93	4.4	10.31	27.56	<0.0001
	Tofacitinib 10 mg BID	394	273	69.29	2.32	18.74	4.35	10.2	27.28	<0.0001
	Methotrexate	184	93	50.54	3.68					
Month 24 (NRI)	Tofacitinib 5 mg BID	367	253	68.94	2.41	19.48	4.4	10.84	28.11	<0.0001
	Tofacitinib 10 mg BID	394	275	69.8	2.31	20.34	4.35	11.81	28.86	<0.0001
	Methotrexate	184	91	49.46	3.68					

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

CRP:

Table 25 presents mean changes from Baseline in CRP concentrations (FAS, comparisons to MTX). In the 1-Year report it was reported that treatment with tofacitinib (5 mg and 10 mg BID) resulted in statistically significant decreases (improvements) from Baseline in CRP concentrations compared with MTX from Months 1 through 12. Between the Months 12 and 24 timepoints the mean change from Baseline CRP remained statistically significantly improved in the tofacitinib groups compared to the MTX group ($p \leq 0.003$).

Table 25. Statistical Analysis of Change From Baseline in C-Reactive Protein (mg/L) per Visit (FAS, Longitudinal Model), Comparisons to Methotrexate, 2 Year Analysis

Visit	Treatment	N	LS Mean	SE	Diff	SE diff	95% CI		p-Value
							Lower	Upper	
Month 1	Tofacitinib 5 mg BID	366	-15.64	0.68	-10.09	1.14	-12.33	-7.86	<0.0001
	Tofacitinib 10 mg BID	390	-18.84	0.66	-13.29	1.13	-15.51	-11.08	<0.0001
	Methotrexate	184	-5.55	0.95					
Month 2	Tofacitinib 5 mg BID	360	-16.02	0.69	-9.19	1.15	-11.45	-6.93	<0.0001
	Tofacitinib 10 mg BID	386	-18.59	0.66	-11.75	1.14	-13.99	-9.51	<0.0001
	Methotrexate	176	-6.83	0.97					
Month 3	Tofacitinib 5 mg BID	353	-15.69	0.69	-5.83	1.16	-8.11	-3.55	<0.0001
	Tofacitinib 10 mg BID	384	-19.01	0.66	-9.15	1.15	-11.4	-6.9	<0.0001
	Methotrexate	172	-9.86	0.97					
Month 6	Tofacitinib 5 mg BID	339	-16.98	0.7	-7.31	1.19	-9.64	-4.97	<0.0001
	Tofacitinib 10 mg BID	366	-18.76	0.67	-9.08	1.18	-11.39	-6.77	<0.0001
	Methotrexate	158	-9.68	1					
Month 9	Tofacitinib 5 mg BID	327	-16.03	0.71	-3.28	1.22	-5.67	-0.89	0.0072
	Tofacitinib 10 mg BID	349	-18.48	0.68	-5.73	1.21	-8.1	-3.36	<0.0001
	Methotrexate	143	-12.75	1.03					
Month 12	Tofacitinib 5 mg BID	314	-16.58	0.72	-5.46	1.24	-7.89	-3.03	<0.0001
	Tofacitinib 10 mg BID	330	-19.16	0.69	-8.03	1.23	-10.45	-5.62	<0.0001
	Methotrexate	135	-11.12	1.05					
Month 15	Tofacitinib 5 mg BID	290	-16.1	0.73	-3.75	1.26	-6.23	-1.27	0.003
	Tofacitinib 10 mg BID	311	-18.8	0.7	-6.45	1.25	-8.91	-4	<0.0001
	Methotrexate	128	-12.35	1.07					
Month 18	Tofacitinib 5 mg BID	280	-17.06	0.74	-5.44	1.3	-7.98	-2.9	<0.0001
	Tofacitinib 10 mg BID	291	-18.17	0.72	-6.55	1.29	-9.07	-4.02	<0.0001
	Methotrexate	116	-11.62	1.1					
Month 21	Tofacitinib 5 mg BID	272	-16.83	0.75	-5.75	1.31	-8.33	-3.18	<0.0001
	Tofacitinib 10 mg BID	288	-17.67	0.72	-6.59	1.3	-9.15	-4.04	<0.0001
	Methotrexate	111	-11.07	1.11					
Month 24	Tofacitinib 5 mg BID	262	-15.97	0.75	-5.66	1.34	-8.29	-3.03	<0.0001
	Tofacitinib 10 mg BID	279	-17.96	0.73	-7.65	1.33	-10.25	-5.04	<0.0001
	Methotrexate	103	-10.31	1.14					

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

Rates of Subjects With ACR70 Response Sustained at Least 6 Months (MCR):

The number of subjects with ACR70 response sustained for at least 6 months is presented in Table 26. The tofacitinib 10 mg BID group had the highest proportion of subjects with ACR70 response sustained at least 6 months (153 [38.54%]). The proportion of subjects in the tofacitinib 5 mg BID group (106 [28.42%]) was also greater than in the MTX group (26 [13.98%]).

Table 26. Number (%) of Subjects With ACR70 Response Sustained at Least 6 Months (FAS, No Imputation, 2 Year Analysis)

	N	n (%)	Exact 95% CI for %
Tofacitinib 5 mg BID	373	106 (28.42)	23.89 - 33.29
Tofacitinib 10 mg BID	397	153 (38.54)	33.73 - 43.52
Methotrexate	186	26 (13.98)	9.34 - 19.81

ACR70 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of subjects, n = number of subjects meeting prespecified criteria.

Durability of ACR20 Responses:

A summary of the percentage of subjects who had ACR20 response at 2 or more consecutive visits is presented in Table 27. There was a greater proportion of subjects with ACR20 response for 10 consecutive visits in the tofacitinib groups (5 mg BID: 88 [23.6%]; 10 mg BID: 121 [30.5%]) compared with the MTX group (9 [4.8%]).

Table 27. Rates (%) of Subjects With Consecutive Visits With ACR20 Response (FAS, No Imputation, Comparisons to MTX, 2 Year Analysis)

	N	Most Consecutive Visits With Response								
		2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	8 n (%)	9 n (%)	10 n (%)
Tofacitinib 5 mg BID	373	32 (8.6)	32 (8.6)	21 (5.6)	26 (7.0)	25 (6.7)	25 (6.7)	35 (9.4)	36 (9.7)	88 (23.6)
Tofacitinib 10 mg BID	397	26 (6.5)	44 (11.1)	27 (6.8)	17 (4.3)	24 (6.0)	27 (6.8)	18 (4.5)	46 (11.6)	121 (30.5)
Methotrexate	186	14 (7.5)	27 (14.5)	19 (10.2)	10 (5.4)	9 (4.8)	11 (5.9)	10 (5.4)	18 (9.7)	9 (4.8)

A subject was represented only once in each row.
ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, MTX = methotrexate, N = number of subjects in each treatment at Baseline, with Percent = 100×(n/N), n = number of subjects meeting pre-specified criteria.

Durability of ACR50 Responses:

A summary of the percentage of subjects who had ACR50 response at 2 or more consecutive visits is presented in Table 28. There was a greater proportion of subjects with ACR50 response for 10 consecutive visits in the tofacitinib groups (5 mg BID: 22 [5.9%]; 10 mg BID: 47 [11.8%]) compared with the MTX group (2 [1.1%]).

Table 28. Rates (%) of Subjects With Consecutive Visits With ACR50 Response (FAS, No Imputation, Comparisons to MTX, 2 Year Analysis)

	N	Most Consecutive Visits With Response								
		2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	8 n (%)	9 n (%)	10 n (%)
Tofacitinib 5 mg BID	373	37 (9.9)	40 (10.7)	24 (6.4)	36 (9.7)	17 (4.6)	23 (6.2)	21 (5.6)	21 (5.6)	22 (5.9)
Tofacitinib 10 mg BID	397	39 (9.8)	36 (9.1)	29 (7.3)	21 (5.3)	19 (4.8)	24 (6.0)	28 (7.1)	33 (8.3)	47 (11.8)
Methotrexate	186	17 (9.1)	15 (8.1)	10 (5.4)	6 (3.2)	10 (5.4)	11 (5.9)	4 (2.2)	3 (1.6)	2 (1.1)

A subject was represented only once in each row.
ACR50 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, MTX = methotrexate, N = number of subjects in each treatment at Baseline, with Percent = 100×(n/N), n = number of subjects meeting pre-specified criteria.

Durability of ACR70 Responses:

A summary of the percentage of subjects who had ACR70 response at 2 or more consecutive visits is presented in Table 29. There were no subjects with ACR70 response for 10 consecutive visits in the MTX group; however, subjects with response for 10 consecutive visits were observed in both tofacitinib groups (5 mg BID: 5 [1.3%]; 10 mg BID: 11 [2.8%]).

Table 29. Rates (%) of Subjects With Consecutive Visits With ACR70 Response (FAS, No Imputation, Comparisons to MTX, 2 Year Analysis)

	N	Most Consecutive Visits With Response								
		2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	8 n (%)	9 n (%)	10 n (%)
Tofacitinib 5 mg BID	373	40 (10.7)	22 (5.9)	20 (5.4)	16 (4.3)	14 (3.8)	11 (2.9)	11 (2.9)	12 (3.2)	5 (1.3)
Tofacitinib 10 mg BID	397	35 (8.8)	31 (7.8)	24 (6.0)	23 (5.8)	13 (3.3)	19 (4.8)	16 (4.0)	23 (5.8)	11 (2.8)
Methotrexate	186	11 (5.9)	7 (3.8)	8 (4.3)	3 (1.6)	2 (1.1)	5 (2.7)	1 (<1.0)	2 (1.1)	0

A subject was represented only once in each row.
ACR70 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, MTX = methotrexate, N = number of subjects in each treatment at Baseline, with Percent = 100×(n/N), n = number of subjects meeting pre-specified criteria.

Durability of DAS28-3 (CRP) <2.6 Response:

A summary of the percentage of subjects who had DAS28-3 (CRP) <2.6 response at 2 or more consecutive visit is presented in Table 30. There were a greater proportion of subjects in the tofacitinib groups (5 mg and 10 mg BID) than the MTX group with 6 to 10 consecutive visits with DAS28-3 response.

Table 30. Rates (%) of Subjects With Consecutive Visits With DAS28-3 (CRP) <2.6 (FAS, No Imputation, Comparisons to MTX, 2 Year Analysis)

	N	Most Consecutive Visits With Response								
		2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	8 n (%)	9 n (%)	10 n (%)
Tofacitinib 5 mg BID	373	38 (10.2)	32 (8.6)	24 (6.4)	19 (5.1)	20 (5.4)	15 (4.0)	12 (3.2)	15 (4.0)	5 (1.3)
Tofacitinib 10 mg BID	397	42 (10.6)	34 (8.6)	29 (7.3)	22 (5.5)	16 (4.0)	29 (7.3)	26 (6.5)	30 (7.6)	11 (2.8)
Methotrexate	186	13 (7.0)	13 (7.0)	7 (3.8)	8 (4.3)	2 (1.1)	3 (1.6)	2 (1.1)	1 (<1.0)	1 (<1.0)

A subject was represented only once in each row.
BID = twice daily, CRP = C-reactive protein, DAS = Disease Activity Score, FAS = full analysis set, MTX = methotrexate, N = number of subjects in each treatment at Baseline, with Percent = 100×(n/N), n = number of subjects meeting pre-specified criteria.

Durability of DAS28-4 (ESR) <2.6 Response:

A summary of the percentage of subjects who had DAS28-4 (ESR) <2.6 response at 2 or more consecutive visits is presented in Table 31. Across all study groups, ≤8% of subjects reported consecutive visits with DAS28-4 response. Despite the overall number of consecutive responders being low, there were generally a greater proportion of subjects reporting responses in the tofacitinib groups (5 mg and 10 mg BID) than in the MTX group across all responses.

Table 31. Rates (%) of Subjects With Consecutive Visits With DAS28-4 (ESR) <2.6 Response (FAS, No Imputation, Comparisons to MTX, 2 Year Analysis)

	N	Most Consecutive Visits With Response								
		2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	8 n (%)	9 n (%)	10 n (%)
Tofacitinib 5 mg BID	373	23 (6.2)	20 (5.4)	15 (4.0)	2 (<1.0)	9 (2.4)	7 (1.9)	2 (<1.0)	2 (<1.0)	2 (<1.0)
Tofacitinib 10 mg BID	397	30 (7.6)	21 (5.3)	16 (4.0)	5 (1.3)	8 (2.0)	12 (3.0)	8 (2.0)	10 (2.5)	3 (<1.0)
Methotrexate	186	8 (4.3)	5 (2.7)	6 (3.2)	3 (1.6)	1 (<1.0)	1 (<1.0)	0	2 (1.1)	0

A subject was represented only once in each row.
BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, MTX = methotrexate, N = number of subjects in each treatment at Baseline, with Percent = 100×(n/N), n = number of subjects meeting pre-specified criteria.

RA Healthcare Resource Utilization (RA-HCRU) Questionnaire:

The RA-HCRU is summarized in Table 32.

Table 32. Descriptive Statistics of Change From Baseline of RA-HCRU (RA Healthcare Resource Utilization Questionnaire) Seen any Doctor/Healthcare Professional in Past 3 Months, 2 Year Analysis

Visit	Treatment	N	Mean	SD
Month 3	Tofacitinib 5 mg BID	349	0.24	0.49
	Tofacitinib 10 mg BID	380	0.18	0.48
	Methotrexate	171	0.18	0.46
Month 6	Tofacitinib 5 mg BID	338	0.28	0.53
	Tofacitinib 10 mg BID	362	0.26	0.5
	Methotrexate	158	0.22	0.47
Month 12	Tofacitinib 5 mg BID	314	0.34	0.51
	Tofacitinib 10 mg BID	326	0.31	0.52
	Methotrexate	135	0.26	0.46
Month 18	Tofacitinib 5 mg BID	283	0.32	0.54
	Tofacitinib 10 mg BID	292	0.36	0.55
	Methotrexate	116	0.28	0.54
Month 24	Tofacitinib 5 mg BID	262	0.34	0.53
	Tofacitinib 10 mg BID	278	0.36	0.55
	Methotrexate	105	0.34	0.5

BID = twice daily, N = number of subjects, RA-HCRU = Rheumatoid Arthritis – Healthcare Resource Utilization, SD = standard deviation.

Patient Global Assessment of Arthritis:

Table 33 presents analysis of change from Baseline in Patient Global Assessment of Arthritis. The mean reduction from Baseline was statistically significantly greater in the tofacitinib groups (5 mg and 10 mg BID) than the MTX groups at all timepoints ($p \leq 0.0221$, or lesser at all timpoints).

Table 33. Descriptive Statistics of Change From Baseline of Patient Global Assessment (mm) per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	-21.95	28.35
	Tofacitinib 10 mg BID	392	-28.14	28.2
	Methotrexate	183	-11.23	25.91
Month 2	Tofacitinib 5 mg BID	361	-28.38	27.35
	Tofacitinib 10 mg BID	388	-31.88	28.12
	Methotrexate	178	-16.08	28.29
Month 3	Tofacitinib 5 mg BID	353	-29.82	28.52
	Tofacitinib 10 mg BID	383	-32.19	28.72
	Methotrexate	172	-19.28	28.56
Month 6	Tofacitinib 5 mg BID	340	-31.64	28.77
	Tofacitinib 10 mg BID	366	-36.26	28.98
	Methotrexate	158	-24.17	30.43
Month 9	Tofacitinib 5 mg BID	328	-33.01	28.51
	Tofacitinib 10 mg BID	349	-35.73	30.65
	Methotrexate	143	-23.41	27.85
Month 12	Tofacitinib 5 mg BID	315	-32.35	27.83
	Tofacitinib 10 mg BID	330	-36.06	29.31
	Methotrexate	135	-23.37	30.87
Month 15	Tofacitinib 5 mg BID	293	-33.4	28.94
	Tofacitinib 10 mg BID	312	-36.61	30.34
	Methotrexate	128	-24.41	30.57
Month 18	Tofacitinib 5 mg BID	284	-34.03	28.47
	Tofacitinib 10 mg BID	294	-35.75	28.85
	Methotrexate	116	-27.68	27.64
Month 21	Tofacitinib 5 mg BID	273	-34.25	28.74
	Tofacitinib 10 mg BID	290	-36.35	29.26
	Methotrexate	111	-27.64	30.67
Month 24	Tofacitinib 5 mg BID	264	-34.88	29.45
	Tofacitinib 10 mg BID	280	-36.69	28.64
	Methotrexate	106	-28.51	30.24

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

Physician Global Assessment of Arthritis:

Table 34 presents mean changes from Baseline in the physician global assessment of arthritis. Reductions represent improvement.

Table 34. Descriptive Statistics of Change From Baseline of Physician Global Assessment (mm) per Visit, 2 Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	362	-25.17	20.84
	Tofacitinib 10 mg BID	390	-27.52	20.75
	Methotrexate	183	-13.54	17.79
Month 2	Tofacitinib 5 mg BID	357	-34.18	20.59
	Tofacitinib 10 mg BID	385	-34.66	21.63
	Methotrexate	177	-21.87	20.19
Month 3	Tofacitinib 5 mg BID	351	-36.97	21.08
	Tofacitinib 10 mg BID	380	-37.76	21.3
	Methotrexate	171	-26.43	22.1
Month 6	Tofacitinib 5 mg BID	336	-39.63	21.04
	Tofacitinib 10 mg BID	363	-42.07	20.67
	Methotrexate	157	-31.54	22.21
Month 9	Tofacitinib 5 mg BID	324	-42.97	20.14
	Tofacitinib 10 mg BID	345	-43.51	21.48
	Methotrexate	142	-35.09	22.97
Month 12	Tofacitinib 5 mg BID	312	-43.75	21.56
	Tofacitinib 10 mg BID	328	-46.07	19.83
	Methotrexate	133	-36.05	23.76
Month 15	Tofacitinib 5 mg BID	291	-44.82	19.7
	Tofacitinib 10 mg BID	309	-45.1	19.55
	Methotrexate	126	-35.24	23.73
Month 18	Tofacitinib 5 mg BID	281	-44.78	20.24
	Tofacitinib 10 mg BID	292	-46.4	19.13
	Methotrexate	114	-38.08	22.41
Month 21	Tofacitinib 5 mg BID	270	-45.79	20.18
	Tofacitinib 10 mg BID	288	-45.78	20.38
	Methotrexate	109	-38.77	22.81
Month 24	Tofacitinib 5 mg BID	261	-46.28	22.09
	Tofacitinib 10 mg BID	279	-46.18	20.74
	Methotrexate	105	-39.23	24.67

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

Patient Assessment of Arthritis Pain:

Table 35 presents mean changes from Baseline in the patient assessment of arthritis pain. The mean reduction from Baseline was statistically significantly greater in the tofacitinib groups (5 mg and 10 mg BID) than the MTX groups at all timepoints ($p \leq 0.037$, or lesser at all timpoints).

Table 35. Descriptive Statistics of Change From Baseline of Pain VAS (mm) per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	-22.5	27.06
	Tofacitinib 10 mg BID	392	-28.5	27.96
	Methotrexate	183	-12.1	25.45
Month 2	Tofacitinib 5 mg BID	361	-27	27.47
	Tofacitinib 10 mg BID	388	-30.9	28
	Methotrexate	178	-19	25.02
Month 3	Tofacitinib 5 mg BID	352	-29.4	29.9
	Tofacitinib 10 mg BID	383	-34.1	27.67
	Methotrexate	172	-21.1	27.96
Month 6	Tofacitinib 5 mg BID	340	-31.4	29.19
	Tofacitinib 10 mg BID	366	-37.1	29.07
	Methotrexate	158	-27	29.87
Month 9	Tofacitinib 5 mg BID	328	-32	29.43
	Tofacitinib 10 mg BID	349	-37.1	29.89
	Methotrexate	143	-26	28.48
Month 12	Tofacitinib 5 mg BID	315	-31.5	28.43
	Tofacitinib 10 mg BID	331	-38.2	27.95
	Methotrexate	135	-27.1	29.29
Month 15	Tofacitinib 5 mg BID	293	-32.7	29.27
	Tofacitinib 10 mg BID	312	-37.3	29.51
	Methotrexate	128	-27.6	30.59
Month 18	Tofacitinib 5 mg BID	284	-33.3	29.1
	Tofacitinib 10 mg BID	294	-38.1	28.27
	Methotrexate	116	-30.4	28.29
Month 21	Tofacitinib 5 mg BID	273	-34	28.63
	Tofacitinib 10 mg BID	290	-38.1	28.86
	Methotrexate	111	-29.8	28.18
Month 24	Tofacitinib 5 mg BID	264	-34.8	29.73
	Tofacitinib 10 mg BID	280	-39.9	27.06
	Methotrexate	106	-31.5	28.95

BID = twice daily, N = number of subjects, SD = standard deviation, VAS = Visual Analog Scale.

Tender Joint Counts:

Table 36 presents mean change from Baseline in Tender Joint Counts. The mean reduction from Baseline was numerically greater in the tofacitinib groups (5 mg and 10 mg BID) than the MTX groups at all timepoints.

Table 36. Descriptive Statistics of Change From Baseline of Tender-Joint Counts per Visit, 2 Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	367	-9.97	11.73
	Tofacitinib 10 mg BID	393	-11.52	11.38
	Methotrexate	184	-5.3	10.35
Month 2	Tofacitinib 5 mg BID	361	-13.6	12.19
	Tofacitinib 10 mg BID	388	-14.45	11.7
	Methotrexate	177	-8.93	11.13
Month 3	Tofacitinib 5 mg BID	356	-15.54	13.58
	Tofacitinib 10 mg BID	383	-16.52	11.73
	Methotrexate	172	-11.08	11.96
Month 6	Tofacitinib 5 mg BID	340	-16.66	12.65
	Tofacitinib 10 mg BID	367	-18.41	13.27
	Methotrexate	158	-13.06	13.18
Month 9	Tofacitinib 5 mg BID	328	-17.94	13.5
	Tofacitinib 10 mg BID	350	-18.73	13.35
	Methotrexate	143	-15.73	14.27
Month 12	Tofacitinib 5 mg BID	315	-18.5	13.47
	Tofacitinib 10 mg BID	332	-18.96	14.29
	Methotrexate	136	-15.24	15.07
Month 15	Tofacitinib 5 mg BID	294	-19.3	13.75
	Tofacitinib 10 mg BID	313	-19.23	15.25
	Methotrexate	129	-16.14	15.2
Month 18	Tofacitinib 5 mg BID	284	-19.52	13.31
	Tofacitinib 10 mg BID	295	-20.26	13.96
	Methotrexate	116	-17.39	14.33
Month 21	Tofacitinib 5 mg BID	273	-20.06	13.06
	Tofacitinib 10 mg BID	290	-20.61	13.69
	Methotrexate	111	-17.49	14.42
Month 24	Tofacitinib 5 mg BID	264	-20.09	13.17
	Tofacitinib 10 mg BID	281	-20.2	14.31
	Methotrexate	106	-18.56	14.01

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

Swollen Joint Counts (SJC):

Table 37 presents mean changes from Baseline in SJC. From Baseline until Month 6 a greater reduction in SJC was observed in the tofacitinib groups (5 mg and 10 mg BID) compared to the MTX group, indicating an improvement in the mean number of swollen joints in the tofacitinib groups.

Table 37. Descriptive Statistics of Change From Baseline of Swollen-Joint Counts per Visit, 2 Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	367	-6.43	9.25
	Tofacitinib 10 mg BID	393	-7.59	7.9
	Methotrexate	184	-4.16	9.19
Month 2	Tofacitinib 5 mg BID	361	-9.47	8.82
	Tofacitinib 10 mg BID	388	-9.88	7.67
	Methotrexate	177	-6.65	9.87
Month 3	Tofacitinib 5 mg BID	356	-10.43	9.47
	Tofacitinib 10 mg BID	383	-11.32	7.92
	Methotrexate	172	-8.62	9.61
Month 6	Tofacitinib 5 mg BID	340	-11.34	9.18
	Tofacitinib 10 mg BID	367	-11.9	8.29
	Methotrexate	158	-10.27	10.3
Month 9	Tofacitinib 5 mg BID	328	-12.04	8.67
	Tofacitinib 10 mg BID	350	-12.31	9.03
	Methotrexate	143	-11.9	10.3
Month 12	Tofacitinib 5 mg BID	315	-12.3	9.04
	Tofacitinib 10 mg BID	332	-12.69	9.13
	Methotrexate	136	-11.54	12.6
Month 15	Tofacitinib 5 mg BID	294	-12.81	9.85
	Tofacitinib 10 mg BID	313	-12.57	10.6
	Methotrexate	129	-11.83	12
Month 18	Tofacitinib 5 mg BID	284	-12.89	8.7
	Tofacitinib 10 mg BID	295	-13.56	9.32
	Methotrexate	116	-12.7	10.77
Month 21	Tofacitinib 5 mg BID	273	-13.08	8.84
	Tofacitinib 10 mg BID	290	-13.73	8.79
	Methotrexate	111	-13.38	10.67
Month 24	Tofacitinib 5 mg BID	264	-13.26	8.79
	Tofacitinib 10 mg BID	281	-13.63	10.09
	Methotrexate	106	-13.33	10.97

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

Short Form-36 (SF-36):

Physical Functioning: Table 38 presents mean changes from Baseline in SF-36 physical functioning.

Table 38. Descriptive Statistics of Change From Baseline of SF-36 Physical Functioning per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	6.19	9.49
	Tofacitinib 10 mg BID	390	7.17	9.17
	Methotrexate	184	0.82	7.04
Month 2	Tofacitinib 5 mg BID	361	8.04	10.55
	Tofacitinib 10 mg BID	387	8.99	9.83
	Methotrexate	178	3.16	8.39
Month 3	Tofacitinib 5 mg BID	354	9.76	10.18
	Tofacitinib 10 mg BID	382	9.97	10.33
	Methotrexate	172	3.94	9.2
Month 6	Tofacitinib 5 mg BID	340	10.32	11.47
	Tofacitinib 10 mg BID	366	11.42	10.93
	Methotrexate	158	5.26	9.9
Month 9	Tofacitinib 5 mg BID	328	10.73	11.44
	Tofacitinib 10 mg BID	349	12.23	11.14
	Methotrexate	143	6.07	10.59
Month 12	Tofacitinib 5 mg BID	315	11.4	11.7
	Tofacitinib 10 mg BID	330	13.21	11.1
	Methotrexate	135	7.35	10.58
Month 15	Tofacitinib 5 mg BID	293	11.9	11.79
	Tofacitinib 10 mg BID	312	13.06	12.04
	Methotrexate	128	6.94	10.86
Month 18	Tofacitinib 5 mg BID	284	12.37	11.36
	Tofacitinib 10 mg BID	294	13.72	11.63
	Methotrexate	116	7.32	11.58
Month 21	Tofacitinib 5 mg BID	273	12.23	11.52
	Tofacitinib 10 mg BID	290	13.68	11.45
	Methotrexate	111	7.66	11.58
Month 24	Tofacitinib 5 mg BID	264	12.81	11.4
	Tofacitinib 10 mg BID	280	13.9	11.72
	Methotrexate	106	8.3	12.07

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form -36.

Role Physical:

Table 39 presents mean changes from Baseline in the SF-36 role physical domain.

Table 39. Descriptive Statistics of Change From Baseline of SF-36 Role Physical Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	5.48	9.29
	Tofacitinib 10 mg BID	391	7.21	9.35
	Methotrexate	184	2.37	7.27
Month 2	Tofacitinib 5 mg BID	361	7.75	10.61
	Tofacitinib 10 mg BID	387	8.72	9.81
	Methotrexate	178	4.29	7.47
Month 3	Tofacitinib 5 mg BID	354	8.87	10.74
	Tofacitinib 10 mg BID	382	9.46	10.01
	Methotrexate	172	4.92	8.68
Month 6	Tofacitinib 5 mg BID	340	9.73	10.78
	Tofacitinib 10 mg BID	366	10.44	10.77
	Methotrexate	158	6.57	9
Month 9	Tofacitinib 5 mg BID	328	9.22	11.5
	Tofacitinib 10 mg BID	349	11.01	10.68
	Methotrexate	143	6.56	10.43
Month 12	Tofacitinib 5 mg BID	315	10.18	11.3
	Tofacitinib 10 mg BID	331	11.8	10.88
	Methotrexate	135	7.09	10.44
Month 15	Tofacitinib 5 mg BID	293	10.9	11.63
	Tofacitinib 10 mg BID	312	11.91	11.58
	Methotrexate	128	7.16	10.89
Month 18	Tofacitinib 5 mg BID	284	10.8	10.93
	Tofacitinib 10 mg BID	294	11.58	11.03
	Methotrexate	116	8.5	11.29
Month 21	Tofacitinib 5 mg BID	273	10.74	11.2
	Tofacitinib 10 mg BID	290	12.06	11.05
	Methotrexate	111	9.07	10.12
Month 24	Tofacitinib 5 mg BID	264	11.25	11.35
	Tofacitinib 10 mg BID	280	12.45	10.86
	Methotrexate	106	8.1	10.81

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

Social Functioning:

Table 40 presents mean changes from Baseline in the SF-36 social functioning domain.

Table 40. Descriptive Statistics of Change From Baseline of SF-36 Social Functioning Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	4.91	11.35
	Tofacitinib 10 mg BID	391	7.41	10.69
	Methotrexate	184	2.48	9.39
Month 2	Tofacitinib 5 mg BID	361	7.14	11.48
	Tofacitinib 10 mg BID	387	7.11	11.19
	Methotrexate	178	3.56	9.82
Month 3	Tofacitinib 5 mg BID	354	8.34	11.9
	Tofacitinib 10 mg BID	382	7.95	12.04
	Methotrexate	172	4.47	10.27
Month 6	Tofacitinib 5 mg BID	340	8.83	11.96
	Tofacitinib 10 mg BID	366	9.58	12.28
	Methotrexate	158	6.19	11.24
Month 9	Tofacitinib 5 mg BID	328	8.84	11.83
	Tofacitinib 10 mg BID	349	9.89	12.25
	Methotrexate	143	7.07	11.37
Month 12	Tofacitinib 5 mg BID	315	8.79	11.92
	Tofacitinib 10 mg BID	331	10.27	12.48
	Methotrexate	135	5.1	11.99
Month 15	Tofacitinib 5 mg BID	293	9.23	12.19
	Tofacitinib 10 mg BID	312	10.34	11.97
	Methotrexate	128	5.34	12.25
Month 18	Tofacitinib 5 mg BID	284	9.43	11.93
	Tofacitinib 10 mg BID	294	10.59	12.04
	Methotrexate	116	7.05	12.99
Month 21	Tofacitinib 5 mg BID	273	9.14	11.56
	Tofacitinib 10 mg BID	290	11.05	11.76
	Methotrexate	111	7.32	12.43
Month 24	Tofacitinib 5 mg BID	264	9.57	11.85
	Tofacitinib 10 mg BID	280	11.52	11.5
	Methotrexate	106	6.75	12.24

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

Bodily Pain:

Table 41 presents mean changes from Baseline in the SF-36 bodily pain domain.

Table 41. Descriptive Statistics of Change From Baseline of SF-36 Bodily Pain Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	7.31	9.18
	Tofacitinib 10 mg BID	390	9.65	9.36
	Methotrexate	183	3.73	7.97
Month 2	Tofacitinib 5 mg BID	361	9.5	9.43
	Tofacitinib 10 mg BID	387	10.97	9.87
	Methotrexate	177	5.05	8.02
Month 3	Tofacitinib 5 mg BID	354	10.84	9.77
	Tofacitinib 10 mg BID	382	11.59	10.42
	Methotrexate	171	6.41	9.16
Month 6	Tofacitinib 5 mg BID	340	11.07	10.45
	Tofacitinib 10 mg BID	366	12.92	10.95
	Methotrexate	157	7.92	9.66
Month 9	Tofacitinib 5 mg BID	328	10.92	10.02
	Tofacitinib 10 mg BID	349	13.29	11.3
	Methotrexate	142	8.36	9.51
Month 12	Tofacitinib 5 mg BID	315	11.85	10.39
	Tofacitinib 10 mg BID	331	13.98	10.68
	Methotrexate	134	8.03	10.42
Month 15	Tofacitinib 5 mg BID	293	12.21	10.91
	Tofacitinib 10 mg BID	312	14.02	11.2
	Methotrexate	127	8.71	11.23
Month 18	Tofacitinib 5 mg BID	284	11.87	10.4
	Tofacitinib 10 mg BID	294	14.39	11.11
	Methotrexate	115	9.36	11.15
Month 21	Tofacitinib 5 mg BID	273	12.51	10.59
	Tofacitinib 10 mg BID	290	14.46	11.17
	Methotrexate	110	9.86	11.26
Month 24	Tofacitinib 5 mg BID	264	12.43	10.96
	Tofacitinib 10 mg BID	280	14.6	10.96
	Methotrexate	106	9.56	10.72

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

Mental Health:

Table 42 presents mean changes from Baseline in the SF-36 mental health domain.

Table 42. Descriptive Statistics of Change From Baseline of SF-36 Mental Health Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	4.58	10.22
	Tofacitinib 10 mg BID	390	6.07	9.55
	Methotrexate	184	3.09	9.31
Month 2	Tofacitinib 5 mg BID	361	5.46	10.82
	Tofacitinib 10 mg BID	386	5.71	9.28
	Methotrexate	178	3.5	10.38
Month 3	Tofacitinib 5 mg BID	354	6.62	10.99
	Tofacitinib 10 mg BID	381	6.08	10.64
	Methotrexate	172	4.27	10.66
Month 6	Tofacitinib 5 mg BID	340	7.06	11.55
	Tofacitinib 10 mg BID	365	6.75	11
	Methotrexate	158	4.31	12.24
Month 9	Tofacitinib 5 mg BID	328	6.48	11.42
	Tofacitinib 10 mg BID	349	7.43	10.43
	Methotrexate	143	5.89	11.95
Month 12	Tofacitinib 5 mg BID	315	7.28	11.55
	Tofacitinib 10 mg BID	331	7.57	11.43
	Methotrexate	135	5.17	11.65
Month 15	Tofacitinib 5 mg BID	293	7.05	11.42
	Tofacitinib 10 mg BID	312	7.21	11.55
	Methotrexate	128	4.98	12.97
Month 18	Tofacitinib 5 mg BID	284	7.35	12.11
	Tofacitinib 10 mg BID	294	8.33	10.85
	Methotrexate	116	5.45	13.98
Month 21	Tofacitinib 5 mg BID	273	6.9	11.96
	Tofacitinib 10 mg BID	290	8.38	10.74
	Methotrexate	111	6.66	12.92
Month 24	Tofacitinib 5 mg BID	264	7.24	12.52
	Tofacitinib 10 mg BID	280	8.5	10.45
	Methotrexate	106	6.48	11.62

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

Role Emotional:

Table 43 presents mean changes from Baseline in the SF-36 role emotional domain.

Table 43. Descriptive Statistics of Change From Baseline of SF-36 Role Emotional Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	5.07	12.63
	Tofacitinib 10 mg BID	391	6.54	11.18
	Methotrexate	184	2.2	10.81
Month 2	Tofacitinib 5 mg BID	361	6.37	13.13
	Tofacitinib 10 mg BID	387	6.94	11.57
	Methotrexate	178	3.25	11.49
Month 3	Tofacitinib 5 mg BID	354	7.28	12.85
	Tofacitinib 10 mg BID	382	7.31	11.98
	Methotrexate	172	3.98	10.91
Month 6	Tofacitinib 5 mg BID	340	7.63	13.38
	Tofacitinib 10 mg BID	366	8.95	12.85
	Methotrexate	158	5.44	12.58
Month 9	Tofacitinib 5 mg BID	328	7.42	14.02
	Tofacitinib 10 mg BID	349	9.29	12.43
	Methotrexate	143	6.25	12.88
Month 12	Tofacitinib 5 mg BID	315	7.78	14.05
	Tofacitinib 10 mg BID	331	9.55	12.61
	Methotrexate	135	5.97	13.29
Month 15	Tofacitinib 5 mg BID	293	8.39	14.39
	Tofacitinib 10 mg BID	312	10.11	13.64
	Methotrexate	128	5.21	13.08
Month 18	Tofacitinib 5 mg BID	284	8.77	13.82
	Tofacitinib 10 mg BID	294	9.85	12.89
	Methotrexate	116	7.73	13.41
Month 21	Tofacitinib 5 mg BID	273	7.75	14.03
	Tofacitinib 10 mg BID	290	10.34	12.37
	Methotrexate	111	6.62	13.94
Month 24	Tofacitinib 5 mg BID	264	9.03	14.77
	Tofacitinib 10 mg BID	280	11.14	13.58
	Methotrexate	106	6.82	12.73

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

Vitality:

Table 44 presents mean changes from Baseline in the SF-36 vitality domain.

Table 44. Descriptive Statistics of Change From Baseline of SF-36 Vitality Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	6.08	9.49
	Tofacitinib 10 mg BID	390	7.39	9.07
	Methotrexate	184	3.11	8.34
Month 2	Tofacitinib 5 mg BID	361	7.32	10.7
	Tofacitinib 10 mg BID	386	8.1	9.64
	Methotrexate	178	3.78	9.65
Month 3	Tofacitinib 5 mg BID	354	8.24	10.44
	Tofacitinib 10 mg BID	381	9.04	10.33
	Methotrexate	172	5.29	9.38
Month 6	Tofacitinib 5 mg BID	340	8.52	10.64
	Tofacitinib 10 mg BID	365	8.91	10.48
	Methotrexate	158	6.29	10.62
Month 9	Tofacitinib 5 mg BID	328	8.47	11.02
	Tofacitinib 10 mg BID	349	9.51	10.63
	Methotrexate	143	6.7	10.59
Month 12	Tofacitinib 5 mg BID	315	8.42	10.98
	Tofacitinib 10 mg BID	331	9.97	10.67
	Methotrexate	135	6.94	9.29
Month 15	Tofacitinib 5 mg BID	293	9.14	11.05
	Tofacitinib 10 mg BID	312	9.22	10.8
	Methotrexate	128	6.38	11.15
Month 18	Tofacitinib 5 mg BID	284	8.91	11
	Tofacitinib 10 mg BID	294	10.24	10.73
	Methotrexate	116	7.17	11.23
Month 21	Tofacitinib 5 mg BID	273	8.76	11.61
	Tofacitinib 10 mg BID	290	10.14	11.05
	Methotrexate	111	7.66	11.15
Month 24	Tofacitinib 5 mg BID	264	8.51	11.54
	Tofacitinib 10 mg BID	280	10.43	10.41
	Methotrexate	106	7.4	10.14

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

General Health Perception:

Table 45 presents mean changes from Baseline in the SF-36 general health perception domain.

Table 45. Descriptive Statistics of Change From Baseline of SF-36 General Health Perception Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	3.64	7.11
	Tofacitinib 10 mg BID	391	5.21	6.95
	Methotrexate	184	1.96	7.1
Month 2	Tofacitinib 5 mg BID	361	5.03	7.42
	Tofacitinib 10 mg BID	387	6.01	7.72
	Methotrexate	178	3.17	7.21
Month 3	Tofacitinib 5 mg BID	354	5.74	7.83
	Tofacitinib 10 mg BID	382	6.53	8.1
	Methotrexate	172	3.79	8.03
Month 6	Tofacitinib 5 mg BID	340	5.82	8.59
	Tofacitinib 10 mg BID	366	7.03	8.91
	Methotrexate	158	4.9	7.93
Month 9	Tofacitinib 5 mg BID	328	5.81	8.55
	Tofacitinib 10 mg BID	349	7.21	9.17
	Methotrexate	143	4.74	9.36
Month 12	Tofacitinib 5 mg BID	315	5.89	8.82
	Tofacitinib 10 mg BID	331	7.69	8.89
	Methotrexate	135	5.54	8.89
Month 15	Tofacitinib 5 mg BID	293	6.3	8.66
	Tofacitinib 10 mg BID	312	7.81	9.27
	Methotrexate	128	4.76	9.35
Month 18	Tofacitinib 5 mg BID	284	6.42	8.69
	Tofacitinib 10 mg BID	294	7.74	9.22
	Methotrexate	116	4.98	10.25
Month 21	Tofacitinib 5 mg BID	273	6.57	9.09
	Tofacitinib 10 mg BID	290	7.79	9.35
	Methotrexate	111	5.62	9.86
Month 24	Tofacitinib 5 mg BID	264	6.4	9.46
	Tofacitinib 10 mg BID	280	8.05	9.26
	Methotrexate	106	5.42	9.61

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

Mental Component:

Table 46 presents mean changes from Baseline in the SF-36 mental component score.

Table 46. Descriptive Statistics of Change From Baseline of SF-36 Mental Component Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	4.31	10.83
	Tofacitinib 10 mg BID	389	5.95	9.41
	Methotrexate	183	2.97	9.34
Month 2	Tofacitinib 5 mg BID	361	5.25	11.14
	Tofacitinib 10 mg BID	386	5.29	9.4
	Methotrexate	177	3.13	10.47
Month 3	Tofacitinib 5 mg BID	354	6.08	11.14
	Tofacitinib 10 mg BID	381	5.71	10.53
	Methotrexate	171	4.05	10.33
Month 6	Tofacitinib 5 mg BID	340	6.37	11.26
	Tofacitinib 10 mg BID	365	6.54	11.22
	Methotrexate	157	4.73	11.87
Month 9	Tofacitinib 5 mg BID	328	5.98	11.55
	Tofacitinib 10 mg BID	349	6.96	10.52
	Methotrexate	142	5.93	10.82
Month 12	Tofacitinib 5 mg BID	315	6.14	11.81
	Tofacitinib 10 mg BID	330	6.99	11.33
	Methotrexate	134	4.65	11.33
Month 15	Tofacitinib 5 mg BID	293	6.33	11.82
	Tofacitinib 10 mg BID	312	6.88	11.66
	Methotrexate	127	4.2	12.47
Month 18	Tofacitinib 5 mg BID	284	6.57	11.71
	Tofacitinib 10 mg BID	294	7.48	11.33
	Methotrexate	115	5.9	13.03
Month 21	Tofacitinib 5 mg BID	273	5.78	12.1
	Tofacitinib 10 mg BID	290	7.75	10.48
	Methotrexate	110	5.92	12.47
Month 24	Tofacitinib 5 mg BID	264	6.37	12.94
	Tofacitinib 10 mg BID	280	8.24	10.5
	Methotrexate	106	5.74	11.17

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

Physical Component: Table 47 presents mean changes from Baseline in the SF-36 physical component score.

Table 47. Descriptive Statistics of Change From Baseline of SF-36 Physical Component Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	5.93	7.72
	Tofacitinib 10 mg BID	389	7.51	7.92
	Methotrexate	183	1.82	5.94
Month 2	Tofacitinib 5 mg BID	361	8.13	8.53
	Tofacitinib 10 mg BID	386	9.43	8.58
	Methotrexate	177	3.96	6.52
Month 3	Tofacitinib 5 mg BID	354	9.45	8.34
	Tofacitinib 10 mg BID	381	10.32	9.05
	Methotrexate	171	4.76	7.6
Month 6	Tofacitinib 5 mg BID	340	9.92	9.02
	Tofacitinib 10 mg BID	365	11.41	9.46
	Methotrexate	157	6.37	7.95
Month 9	Tofacitinib 5 mg BID	328	10.03	9
	Tofacitinib 10 mg BID	349	11.85	10.05
	Methotrexate	142	6.42	8.01
Month 12	Tofacitinib 5 mg BID	315	10.72	9.17
	Tofacitinib 10 mg BID	330	12.84	9.59
	Methotrexate	134	7.47	8.75
Month 15	Tofacitinib 5 mg BID	293	11.35	9.54
	Tofacitinib 10 mg BID	312	12.78	10.09
	Methotrexate	127	7.53	9.48
Month 18	Tofacitinib 5 mg BID	284	11.29	9.18
	Tofacitinib 10 mg BID	294	12.87	10.16
	Methotrexate	115	7.86	9.37
Month 21	Tofacitinib 5 mg BID	273	11.74	9.28
	Tofacitinib 10 mg BID	290	12.95	10.24
	Methotrexate	110	8.45	8.96
Month 24	Tofacitinib 5 mg BID	264	11.76	9.82
	Tofacitinib 10 mg BID	280	13.11	9.71
	Methotrexate	106	8.17	9.34

BID = twice daily, N = number of subjects, SD = standard deviation, SF-36 = Short Form-36.

Medical Outcomes Study Sleep Scale (MOS-SS):

Overall, consistently differences between the tofacitinib groups (5 mg and 10 mg BID) and MTX were not observed between Month 12 and 24 in the majority of MOS sleep scores. For all scores, the differences from MTX were similar in both tofacitinib groups.

Overall Sleep Problem: Table 48 presents mean changes from Baseline in MOS scores, overall sleep problem.

Table 48. Descriptive Statistics of Change From Baseline of Medical Outcome Study (MOS) Overall Sleep Problem Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	364	-8.86	17.61
	Tofacitinib 10 mg BID	392	-9.12	15.37
	Methotrexate	184	-4.7	15.56
Month 2	Tofacitinib 5 mg BID	359	-10.93	18.95
	Tofacitinib 10 mg BID	388	-10.14	17.4
	Methotrexate	178	-7.82	15.93
Month 3	Tofacitinib 5 mg BID	352	-12.44	19.27
	Tofacitinib 10 mg BID	382	-11.19	18.28
	Methotrexate	172	-8.91	17.85
Month 6	Tofacitinib 5 mg BID	339	-11.76	19.81
	Tofacitinib 10 mg BID	366	-12.38	18.77
	Methotrexate	158	-9.77	17.53
Month 12	Tofacitinib 5 mg BID	314	-12.1	19.14
	Tofacitinib 10 mg BID	330	-12.41	17.89
	Methotrexate	135	-9.35	17.89
Month 18	Tofacitinib 5 mg BID	284	-11.51	19.56
	Tofacitinib 10 mg BID	293	-14.02	19.28
	Methotrexate	116	-12.51	18.73
Month 24	Tofacitinib 5 mg BID	264	-11.5	21.42
	Tofacitinib 10 mg BID	278	-12.86	19.77
	Methotrexate	106	-11.95	18.81

BID = twice daily, N = number of subjects, MOS = Medical Outcome Study, SD = standard deviation.

Sleep Problem Summary:

Table 49 presents mean changes from Baseline in MOS scores, sleep problem summary.

Table 49. Descriptive Statistics of Change From Baseline of Medical Outcome Study (MOS) Sleep Problem Summary Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	364	-7.49	18.39
	Tofacitinib 10 mg BID	392	-8.15	16.19
	Methotrexate	184	-3.8	16.26
Month 2	Tofacitinib 5 mg BID	360	-9.44	19.56
	Tofacitinib 10 mg BID	388	-8.81	18.25
	Methotrexate	178	-6.55	16.52
Month 3	Tofacitinib 5 mg BID	352	-10.68	19.44
	Tofacitinib 10 mg BID	382	-9.66	19.12
	Methotrexate	172	-7.36	18.53
Month 6	Tofacitinib 5 mg BID	339	-9.93	20.12
	Tofacitinib 10 mg BID	366	-11.27	19.49
	Methotrexate	158	-8.4	18.42
Month 12	Tofacitinib 5 mg BID	314	-10.22	19.93
	Tofacitinib 10 mg BID	330	-11.27	18.59
	Methotrexate	135	-7.41	18.58
Month 18	Tofacitinib 5 mg BID	284	-9.69	20
	Tofacitinib 10 mg BID	293	-13.21	19.66
	Methotrexate	116	-10.34	19.65
Month 24	Tofacitinib 5 mg BID	264	-9.39	21.65
	Tofacitinib 10 mg BID	278	-11.7	20.46
	Methotrexate	106	-10.22	19.36

BID = twice daily, N = number of subjects, MOS = Medical Outcome Study, SD = standard deviation.

Somnolence:

Table 50 presents mean changes from Baseline in MOS scores, somnolence.

Table 50. Descriptive Statistics of Change From Baseline of Medical Outcome Study (MOS) Somnolence Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	364	-5.84	19.71
	Tofacitinib 10 mg BID	392	-7.35	18.69
	Methotrexate	184	-3.19	19.55
Month 2	Tofacitinib 5 mg BID	360	-7.74	19.97
	Tofacitinib 10 mg BID	388	-7.66	20.62
	Methotrexate	178	-6.59	22.42
Month 3	Tofacitinib 5 mg BID	352	-8.37	20.56
	Tofacitinib 10 mg BID	383	-7.42	21.32
	Methotrexate	172	-7.36	21.5
Month 6	Tofacitinib 5 mg BID	339	-8.53	22.7
	Tofacitinib 10 mg BID	366	-8.96	20.58
	Methotrexate	158	-8.02	22.05
Month 12	Tofacitinib 5 mg BID	314	-7.83	21.05
	Tofacitinib 10 mg BID	330	-8.65	21.41
	Methotrexate	135	-6.96	23.09
Month 18	Tofacitinib 5 mg BID	284	-8.17	22.42
	Tofacitinib 10 mg BID	293	-9.42	21.63
	Methotrexate	116	-10.06	21.31
Month 24	Tofacitinib 5 mg BID	264	-8.26	22.52
	Tofacitinib 10 mg BID	278	-8.97	23.68
	Methotrexate	106	-10.75	21.25

BID = twice daily, N = number of subjects, MOS = Medical Outcome Study, SD = standard deviation.

Snoring:

Table 51 presents mean changes from Baseline in MOS scores, snoring.

Table 51. Descriptive Statistics of Change From Baseline of Medical Outcome Study (MOS) Snoring Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	364	-3.96	23.93
	Tofacitinib 10 mg BID	392	-3.52	22.64
	Methotrexate	184	-1.96	24.93
Month 2	Tofacitinib 5 mg BID	359	-3.01	25.59
	Tofacitinib 10 mg BID	388	-3.04	24.02
	Methotrexate	178	-4.94	25.21
Month 3	Tofacitinib 5 mg BID	352	-4.26	25.15
	Tofacitinib 10 mg BID	383	-4.23	24.68
	Methotrexate	172	-3.49	23.13
Month 6	Tofacitinib 5 mg BID	339	-3.89	25.12
	Tofacitinib 10 mg BID	365	-1.1	23.74
	Methotrexate	157	-4.59	23.08
Month 12	Tofacitinib 5 mg BID	314	-2.04	26.19
	Tofacitinib 10 mg BID	330	0.06	26.67
	Methotrexate	135	-1.93	24.66
Month 18	Tofacitinib 5 mg BID	283	-1.48	24.57
	Tofacitinib 10 mg BID	293	-0.68	24.82
	Methotrexate	115	-5.04	22.45
Month 24	Tofacitinib 5 mg BID	262	-1.83	26.31
	Tofacitinib 10 mg BID	278	-1.58	27.88
	Methotrexate	106	-4.72	27.82

BID = twice daily, N = number of subjects, MOS = Medical Outcome Study, SD = standard deviation.

Quantity:

Table 52 presents mean changes from Baseline in MOS scores, quantity.

Table 52. Descriptive Statistics of Change From Baseline of Medical Outcome Study (MOS) Quantity Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	364	0.46	1.33
	Tofacitinib 10 mg BID	391	0.43	1.55
	Methotrexate	183	0.27	1.49
Month 2	Tofacitinib 5 mg BID	359	0.48	1.32
	Tofacitinib 10 mg BID	388	0.48	1.69
	Methotrexate	177	0.33	1.48
Month 3	Tofacitinib 5 mg BID	352	0.5	1.38
	Tofacitinib 10 mg BID	383	0.53	1.7
	Methotrexate	171	0.37	1.41
Month 6	Tofacitinib 5 mg BID	339	0.51	1.52
	Tofacitinib 10 mg BID	366	0.52	1.76
	Methotrexate	157	0.39	1.46
Month 12	Tofacitinib 5 mg BID	314	0.54	1.49
	Tofacitinib 10 mg BID	329	0.47	1.76
	Methotrexate	134	0.14	1.36
Month 18	Tofacitinib 5 mg BID	284	0.52	1.39
	Tofacitinib 10 mg BID	293	0.48	1.92
	Methotrexate	115	0.45	1.61
Month 24	Tofacitinib 5 mg BID	264	0.48	1.5
	Tofacitinib 10 mg BID	278	0.5	1.75
	Methotrexate	104	0.43	1.47

BID = twice daily, N = number of subjects, MOS = Medical Outcome Study, SD = standard deviation.

Sleep Disturbance:

Table 53 presents mean changes from Baseline in MOS scores, sleep disturbance.

Table 53. Descriptive Statistics of Change From Baseline of Medical Outcome Study (MOS) Sleep Disturbance Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	364	-11.88	22.82
	Tofacitinib 10 mg BID	392	-11.04	19.73
	Methotrexate	184	-7.17	21.51
Month 2	Tofacitinib 5 mg BID	359	-14.72	24.52
	Tofacitinib 10 mg BID	388	-12.62	22.47
	Methotrexate	178	-10.06	21.88
Month 3	Tofacitinib 5 mg BID	352	-16.22	26
	Tofacitinib 10 mg BID	382	-14.68	-23.71
	Methotrexate	172	-11.61	23.94
Month 6	Tofacitinib 5 mg BID	339	-16.21	24.88
	Tofacitinib 10 mg BID	366	-15.76	-24.82
	Methotrexate	158	-12.18	23.45
Month 12	Tofacitinib 5 mg BID	314	-16.66	25.3
	Tofacitinib 10 mg BID	330	-15.9	23.4
	Methotrexate	135	-12.08	24.57
Month 18	Tofacitinib 5 mg BID	284	-15.61	25.51
	Tofacitinib 10 mg BID	293	-17.35	-25.56
	Methotrexate	116	-16.95	25.99
Month 24	Tofacitinib 5 mg BID	264	-15.21	28.03
	Tofacitinib 10 mg BID	278	-16.75	-25.97
	Methotrexate	106	-15.25	25.95

BID = twice daily, N = number of subjects, MOS = Medical Outcome Study, SD = standard deviation.

Awaken Short of Breath:

Table 54 presents mean changes from Baseline in MOS scores, awaken short of breath.

Table 54. Descriptive Statistics of Change From Baseline of Medical Outcome Study (MOS) Awaken Short of Breath Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	364	-3.3	23.33
	Tofacitinib 10 mg BID	392	-1.99	22.46
	Methotrexate	184	-1.74	23.03
Month 2	Tofacitinib 5 mg BID	360	-4.56	23.54
	Tofacitinib 10 mg BID	388	-2.32	24.18
	Methotrexate	178	-3.26	22.51
Month 3	Tofacitinib 5 mg BID	352	-3.13	24.4
	Tofacitinib 10 mg BID	383	-2.77	24.59
	Methotrexate	172	-2.33	23.78
Month 6	Tofacitinib 5 mg BID	339	-3.13	26.93
	Tofacitinib 10 mg BID	366	-4.43	23.15
	Methotrexate	158	-2.78	23.07
Month 12	Tofacitinib 5 mg BID	314	-4.01	23.67
	Tofacitinib 10 mg BID	330	-4	23.67
	Methotrexate	135	0	21.72
Month 18	Tofacitinib 5 mg BID	284	-4.3	24.94
	Tofacitinib 10 mg BID	293	-5.32	23.03
	Methotrexate	116	0	23.29
Month 24	Tofacitinib 5 mg BID	264	-4.47	25.09
	Tofacitinib 10 mg BID	278	-2.95	22.25
	Methotrexate	106	0.19	23.66

BID = twice daily, N = number of subjects, MOS = Medical Outcome Study, SD = standard deviation.

Adequacy:

Table 55 presents mean changes from Baseline in MOS scores, adequacy.

Table 55. Descriptive Statistics of Change From Baseline of Medical Outcome Study (MOS) Adequacy Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	364	7.39	26.96
	Tofacitinib 10 mg BID	392	9.77	26.19
	Methotrexate	184	2.5	25.57
Month 2	Tofacitinib 5 mg BID	360	8.81	29.67
	Tofacitinib 10 mg BID	388	10.75	28.1
	Methotrexate	178	6.18	26.91
Month 3	Tofacitinib 5 mg BID	352	12.59	29.22
	Tofacitinib 10 mg BID	383	11.17	28.29
	Methotrexate	172	6.98	26.16
Month 6	Tofacitinib 5 mg BID	339	10.03	30
	Tofacitinib 10 mg BID	366	11.72	29.63
	Methotrexate	158	8.92	28.39
Month 12	Tofacitinib 5 mg BID	314	10.7	30.75
	Tofacitinib 10 mg BID	330	12.55	30.02
	Methotrexate	135	10.22	29.23
Month 18	Tofacitinib 5 mg BID	284	10.32	29.45
	Tofacitinib 10 mg BID	293	14.81	30.88
	Methotrexate	116	11.9	30.73
Month 24	Tofacitinib 5 mg BID	264	10.27	31.3
	Tofacitinib 10 mg BID	278	13.13	30.79
	Methotrexate	106	12.64	30.75

BID = twice daily, N = number of subjects, MOS = Medical Outcome Study, SD = standard deviation.

Work Limitations Questionnaire (WLQ):

Time Management: The WLQ, time management is summarized in Table 56.

Table 56. Descriptive Statistics of Change From Baseline of Work Limitation Questionnaire: Time Management Scale per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 3	Tofacitinib 5 mg BID	165	-15.02	30.52
	Tofacitinib 10 mg BID	174	-17.34	35.39
	Methotrexate	81	-12.73	23.37
Month 6	Tofacitinib 5 mg BID	155	-17.96	31.72
	Tofacitinib 10 mg BID	162	-21.92	33.76
	Methotrexate	72	-15.89	28.14
Month 12	Tofacitinib 5 mg BID	141	-18.61	31.93
	Tofacitinib 10 mg BID	143	-22.08	34.64
	Methotrexate	62	-19.96	29.75
Month 15	Tofacitinib 5 mg BID	1	-85	
	Tofacitinib 10 mg BID	2	-35	35.36
	Methotrexate	1	5	
Month 18	Tofacitinib 5 mg BID	124	-20.78	27.04
	Tofacitinib 10 mg BID	125	-24.36	31.33
	Methotrexate	53	-20.27	36.66
Month 21	Tofacitinib 5 mg BID	2	0	0
	Tofacitinib 10 mg BID	1	0	
	Methotrexate	1	-20	
Month 24	Tofacitinib 5 mg BID	117	-14.84	31.32
	Tofacitinib 10 mg BID	118	-24.7	28.91
	Methotrexate	46	-21.96	30.08

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

Physical Demands:

The WLQ, physical demands is summarized in Table 57.

Table 57. Descriptive Statistics of Change From Baseline of Work Limitation Questionnaire: Physical Demands Scale per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 3	Tofacitinib 5 mg BID	164	-4.69	34.42
	Tofacitinib 10 mg BID	172	-7.27	38.6
	Methotrexate	78	4.88	30.57
Month 6	Tofacitinib 5 mg BID	156	1.31	36.12
	Tofacitinib 10 mg BID	160	-8.35	41.81
	Methotrexate	71	-3.87	40.76
Month 12	Tofacitinib 5 mg BID	142	-2.28	38.31
	Tofacitinib 10 mg BID	142	-5.47	43.5
	Methotrexate	62	-9.18	40.59
Month 15	Tofacitinib 5 mg BID	1	-16.67	
	Tofacitinib 10 mg BID	3	-33.06	78.53
	Methotrexate	3	2.92	39.35
Month 18	Tofacitinib 5 mg BID	130	-0.1	37.41
	Tofacitinib 10 mg BID	119	-8.91	40.92
	Methotrexate	53	-1.07	45.86
Month 21	Tofacitinib 5 mg BID	3	7.64	30.92
	Tofacitinib 10 mg BID	1	-50	
	Methotrexate	1	62.5	
Month 24	Tofacitinib 5 mg BID	113	0.75	39.49
	Tofacitinib 10 mg BID	112	-6.78	37.96
	Methotrexate	46	-5.29	43.81

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

Mental/Interpersonal Demands:

The WLQ, mental/interpersonal demands is summarized in Table 58.

Table 58. Descriptive Statistics of Change From Baseline of Work Limitation Questionnaire: Mental/Interpersonal Demands Scale per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 3	Tofacitinib 5 mg BID	170	-7.46	25.07
	Tofacitinib 10 mg BID	177	-9.43	27.18
	Methotrexate	81	-5.59	23.73
Month 6	Tofacitinib 5 mg BID	160	-10.51	23.41
	Tofacitinib 10 mg BID	164	-13.17	23.09
	Methotrexate	73	-9.01	25.81
Month 12	Tofacitinib 5 mg BID	146	-10.46	23.26
	Tofacitinib 10 mg BID	145	-15.17	25.39
	Methotrexate	63	-12.22	29.44
Month 15	Tofacitinib 5 mg BID	1	-52.78	
	Tofacitinib 10 mg BID	3	-31.48	26.4
	Methotrexate	2	15.63	22.1
Month 18	Tofacitinib 5 mg BID	132	-10.71	20.33
	Tofacitinib 10 mg BID	125	-13.55	28.43
	Methotrexate	55	-12.74	30.25
Month 21	Tofacitinib 5 mg BID	3	-4.26	5.16
	Tofacitinib 10 mg BID	1	41.67	
	Methotrexate	1	-75	
Month 24	Tofacitinib 5 mg BID	121	-8.54	23.41
	Tofacitinib 10 mg BID	117	-13.7	23.81
	Methotrexate	49	-15.2	25.15

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

Output Demands:

The WLQ, output demands demands is summarized in Table 59.

Table 59. Descriptive Statistics of Change From Baseline of Work Limitation Questionnaire: Output Demands Scale per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 3	Tofacitinib 5 mg BID	167	-13.52	30.24
	Tofacitinib 10 mg BID	170	-13.25	31.65
	Methotrexate	74	-8.54	23.06
Month 6	Tofacitinib 5 mg BID	155	-16.51	25.4
	Tofacitinib 10 mg BID	154	-20.21	27.02
	Methotrexate	68	-14.19	23.79
Month 12	Tofacitinib 5 mg BID	145	-16.43	26.74
	Tofacitinib 10 mg BID	137	-21.2	29.44
	Methotrexate	59	-17.05	32.72
Month 15	Tofacitinib 5 mg BID	1	-80	
	Tofacitinib 10 mg BID	3	-11.67	25.17
	Methotrexate	2	15.83	34.18
Month 18	Tofacitinib 5 mg BID	134	-14.92	24.57
	Tofacitinib 10 mg BID	118	-19.29	30.39
	Methotrexate	51	-16.86	30.98
Month 21	Tofacitinib 5 mg BID	2	5	7.07
	Tofacitinib 10 mg BID	1	10	
	Methotrexate	1	-55	
Month 24	Tofacitinib 5 mg BID	120	-14.15	29
	Tofacitinib 10 mg BID	116	-21.2	26.51
	Methotrexate	47	-19.76	29.44

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

Work Loss Index:

The WLQ, work loss index is summarized in Table 60.

Table 60. Descriptive Statistics of Change From Baseline of Work Limitation Questionnaire: Work Loss Index per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 3	Tofacitinib 5 mg BID	176	-3.12	6.35
	Tofacitinib 10 mg BID	185	-3.36	6.98
	Methotrexate	83	-2	5.03
Month 6	Tofacitinib 5 mg BID	163	-3.54	5.66
	Tofacitinib 10 mg BID	168	-4.53	6.09
	Methotrexate	74	-3.23	5.51
Month 12	Tofacitinib 5 mg BID	149	-3.73	5.63
	Tofacitinib 10 mg BID	151	-5.24	6.35
	Methotrexate	64	-3.93	6.9
Month 15	Tofacitinib 5 mg BID	1	-18.2	
	Tofacitinib 10 mg BID	3	-6.6	2.19
	Methotrexate	3	1.13	4.86
Month 18	Tofacitinib 5 mg BID	137	-3.67	5.02
	Tofacitinib 10 mg BID	129	-5.13	7
	Methotrexate	55	-3.71	6.91
Month 21	Tofacitinib 5 mg BID	3	-0.3	2.76
	Tofacitinib 10 mg BID	1	3.2	
	Methotrexate	1	-11.7	
Month 24	Tofacitinib 5 mg BID	125	-3.07	5.92
	Tofacitinib 10 mg BID	121	-5.3	5.89
	Methotrexate	50	-4.66	6.34

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

EuroQoL EQ-5D Health State Profile – Utility Score:

Table 61 presents mean changes from Baseline in the EQ-5D utility score. Overall, the mean increase from Baseline was numerically greater in the tofacitinib groups (5 mg and 10 mg BID) than the MTX groups at the majority of timepoints, indicating an overall improvement in health state. The change from Baseline EQ-5D was similar in both tofacitinib groups.

Table 61. Descriptive Statistics of Change From Baseline of EuroQol EQ-5D Health State Profile-Utility Score per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 3	Tofacitinib 5 mg BID	352	0.28	0.34
	Tofacitinib 10 mg BID	381	0.27	0.33
	Methotrexate	170	0.16	0.32
Month 6	Tofacitinib 5 mg BID	338	0.29	0.34
	Tofacitinib 10 mg BID	364	0.3	0.34
	Methotrexate	158	0.16	0.34
Month 12	Tofacitinib 5 mg BID	315	0.29	0.32
	Tofacitinib 10 mg BID	330	0.32	0.34
	Methotrexate	135	0.18	0.31
Month 18	Tofacitinib 5 mg BID	284	0.31	0.32
	Tofacitinib 10 mg BID	293	0.35	0.33
	Methotrexate	116	0.2	0.32
Month 24	Tofacitinib 5 mg BID	262	0.31	0.34
	Tofacitinib 10 mg BID	279	0.35	0.35
	Methotrexate	105	0.26	0.3

BID = twice daily, EQ-5D = European Quality of Life 5-dimention, EuroQol = European Quality of Life, N = number of subjects, SD = standard deviation.

FACIT Fatigue Scale:

Table 62 presents mean changes from Baseline in the FACIT-fatigue scale (FAS, comparisons to MTX). The mean increase from Baseline was numerically greater in the tofacitinib groups (5 mg and 10 mg BID) than the MTX groups at all timepoints, indicating a more notable improvement in fatigue. The mean change from Baseline in FACIT-fatigue scale was similar in the 2 tofacitinib groups.

Table 62. Descriptive Statistics of Change From Baseline of FACIT - Fatigue Scale per Visit, 2-Year Analysis

Visit	Treatment	N	Mean	SD
Month 1	Tofacitinib 5 mg BID	365	5.82	9.71
	Tofacitinib 10 mg BID	391	6.92	8.99
	Methotrexate	183	3.15	8.78
Month 2	Tofacitinib 5 mg BID	358	7.42	10.24
	Tofacitinib 10 mg BID	386	7.67	9.31
	Methotrexate	177	4.29	9.7
Month 3	Tofacitinib 5 mg BID	352	8.26	10.41
	Tofacitinib 10 mg BID	382	8.53	10.04
	Methotrexate	170	5.18	9.98
Month 6	Tofacitinib 5 mg BID	340	8.88	10.87
	Tofacitinib 10 mg BID	365	9.14	10.41
	Methotrexate	158	6.36	10.57
Month 12	Tofacitinib 5 mg BID	315	8.87	11.18
	Tofacitinib 10 mg BID	329	9.52	10.49
	Methotrexate	135	6.94	10.81
Month 18	Tofacitinib 5 mg BID	284	9.03	10.85
	Tofacitinib 10 mg BID	292	10.13	10.62
	Methotrexate	116	7.7	11.43
Month 24	Tofacitinib 5 mg BID	264	9.17	11.19
	Tofacitinib 10 mg BID	279	10.2	10.69
	Methotrexate	106	6.83	12.13

BID = twice daily, FACIT = Functional Assessment Of Chronic Illness Therapy, N = number of subjects, SD = standard deviation.

Safety Results:

The proportions of subjects with treatment-emergent AEs (TEAEs), serious adverse events (SAEs), severe TEAEs, and subjects who were discontinued due to AEs were similar across the 3 treatments. The majority of subjects experienced AEs. The treatment-emergent non serious AEs at a threshold >5% (all causality and treatment-related) are summarized in Table 63. The System Organ Classes (SOCs) with the most common TEAEs were Infections and infestations, Gastrointestinal disorders and Investigations. The most frequently reported treatment-related TEAE in all 3 treatment groups was nausea.

Table 63. Treatment-Emergent Non Serious Adverse Events (Treatment Related) by System Organ Class and Preferred Term (All causalities) in >5 % of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v16.0) Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Methotrexate		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:									
Evaluable for adverse events	373			397			186		
With adverse events	169 (45.3)			204 (51.4)			88 (47.3)		
Gastrointestinal disorders	49 (13.1)	59	26	55 (13.9)	81	48	50 (26.9)	89	77
Diarrhoea	15 (4.0)	17	6	24 (6.0)	26	7	15 (8.1)	15	9
Nausea	27 (7.2)	31	17	30 (7.6)	39	31	40 (21.5)	57	54
Vomiting	11 (2.9)	11	3	13 (3.3)	16	10	11 (5.9)	17	14
Infections and infestations	85 (22.8)	123	38	107 (27.0)	170	56	35 (18.8)	46	18
Bronchitis	20 (5.4)	22	7	27 (6.8)	31	5	4 (2.2)	5	2
Nasopharyngitis	28 (7.5)	36	8	39 (9.8)	50	6	12 (6.5)	13	5
Upper respiratory tract infection	30 (8.0)	38	16	36 (9.1)	50	23	15 (8.1)	20	7
Urinary tract infection	17 (4.6)	27	7	26 (6.5)	39	22	7 (3.8)	8	4
Investigations	22 (5.9)	31	15	48 (12.1)	58	35	12 (6.5)	14	8
Alanine aminotransferase increased	8 (2.1)	9	4	15 (3.8)	17	12	11 (5.9)	12	8
Blood creatine phosphokinase increased	16 (4.3)	22	11	36 (9.1)	41	23	2 (1.1)	2	0
Musculoskeletal and connective tissue disorders	19 (5.1)	21	0	18 (4.5)	20	0	4 (2.2)	5	0
Back pain	19 (5.1)	21	0	18 (4.5)	20	0	4 (2.2)	5	0
Nervous system disorders	26 (7.0)	36	11	34 (8.6)	46	23	12 (6.5)	17	10
Headache	26 (7.0)	36	11	34 (8.6)	46	23	12 (6.5)	17	10
Vascular disorders	26 (7.0)	28	5	29 (7.3)	30	12	7 (3.8)	9	0
Hypertension	26 (7.0)	28	5	29 (7.3)	30	12	7 (3.8)	9	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v16.0) coding dictionary applied.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment emergent all causalities adverse events.
n2: The number of occurrences of treatment emergent causally related to treatment adverse events.
BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; v = version.

The treatment-emergent SAEs (all causality and treatment related) are summarized in Table 64. The most commonly reported SAEs across the treatment groups were gastroenteritis, pneumonia, humerus fracture, cerebrovascular accident, deep vein thrombosis and osteoarthritis.

Table 64. Treatment-Emergent Serious Adverse Events (Treatment Related) by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v16.0) Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Methotrexate		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:									
Evaluable for adverse events	373			397			186		
With adverse events	40 (10.7)			43 (10.8)			22 (11.8)		
Blood and lymphatic system disorders	0	0	0	1 (0.3)	1	0	0	0	0
Disseminated intravascular coagulation	0	0	0	1 (0.3)	1	0	0	0	0
Cardiac disorders	5 (1.3)	5	1	2 (0.5)	2	0	3 (1.6)	3	0
Angina pectoris	2 (0.5)	2	1	0	0	0	0	0	0
Angina unstable	1 (0.3)	1	0	0	0	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	1 (0.5)	1	0
Atrial flutter	0	0	0	0	0	0	1 (0.5)	1	0
Atrioventricular block first degree	0	0	0	0	0	0	1 (0.5)	1	0
Cardiac failure	1 (0.3)	1	0	0	0	0	0	0	0
Cardiac failure congestive	0	0	0	1 (0.3)	1	0	0	0	0
Myocardial ischaemia	1 (0.3)	1	0	1 (0.3)	1	0	0	0	0
Eye disorders	3 (0.8)	3	2	0	0	0	0	0	0
Cataract	2 (0.5)	2	1	0	0	0	0	0	0
Scleritis	1 (0.3)	1	1	0	0	0	0	0	0
Gastrointestinal disorders	5 (1.3)	5	2	6 (1.5)	6	0	4 (2.2)	4	0
Abdominal hernia	1 (0.3)	1	0	0	0	0	0	0	0
Abdominal pain	0	0	0	1 (0.3)	1	0	0	0	0
Abdominal wall haematoma	1 (0.3)	1	0	0	0	0	0	0	0
Colonic stenosis	0	0	0	1 (0.3)	1	0	0	0	0
Constipation	0	0	0	1 (0.3)	1	0	0	0	0
Diarrhoea	0	0	0	1 (0.3)	1	0	0	0	0
Enterocolitis	1 (0.3)	1	0	0	0	0	0	0	0
Gastric ulcer	1 (0.3)	1	1	0	0	0	0	0	0
Gastric ulcer perforation	1 (0.3)	1	1	0	0	0	0	0	0
Gastritis	0	0	0	1 (0.3)	1	0	0	0	0
Haemorrhoids	0	0	0	0	0	0	1 (0.5)	1	0
Inguinal hernia	0	0	0	0	0	0	1 (0.5)	1	0
Pancreatitis	0	0	0	0	0	0	1 (0.5)	1	0
Pancreatitis chronic	0	0	0	1 (0.3)	1	0	0	0	0
Salivary gland calculus	0	0	0	0	0	0	1 (0.5)	1	0
General disorders and administration site conditions	3 (0.8)	3	2	2 (0.5)	2	0	0	0	0
Chest pain	1 (0.3)	1	0	1 (0.3)	1	0	0	0	0
Death	1 (0.3)	1	1	0	0	0	0	0	0
Non-cardiac chest pain	0	0	0	1 (0.3)	1	0	0	0	0
Pyrexia	1 (0.3)	1	1	0	0	0	0	0	0
Hepatobiliary disorders	0	0	0	3 (0.8)	3	1	1 (0.5)	1	0
Biliary colic	0	0	0	1 (0.3)	1	0	0	0	0
Cholecystitis acute	0	0	0	1 (0.3)	1	0	0	0	0
Cholelithiasis	0	0	0	0	0	0	1 (0.5)	1	0
Hepatomegaly	0	0	0	1 (0.3)	1	1	0	0	0
Immune system disorders	1 (0.3)	1	1	0	0	0	0	0	0
Hypersensitivity	1 (0.3)	1	1	0	0	0	0	0	0

Table 64. Treatment-Emergent Serious Adverse Events (Treatment Related) by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v16.0) Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Methotrexate		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Infections and infestations	11 (2.9)	11	7	10 (2.5)	11	6	5 (2.7)	5	2
Bone tuberculosis	0	0	0	1 (0.3)	1	1	0	0	0
Bronchitis	0	0	0	1 (0.3)	1	1	0	0	0
Chronic hepatitis C	0	0	0	0	0	0	1 (0.5)	1	0
Dengue fever	1 (0.3)	1	0	0	0	0	0	0	0
Diverticulitis	0	0	0	1 (0.3)	1	0	0	0	0
Erysipelas	1 (0.3)	1	1	0	0	0	0	0	0
Gastroenteritis	1 (0.3)	1	0	2 (0.5)	2	1	1 (0.5)	1	0
Gastrointestinal infection	1 (0.3)	1	0	0	0	0	0	0	0
Herpes zoster	1 (0.3)	1	1	1 (0.3)	1	0	0	0	0
Herpes zoster disseminated	0	0	0	1 (0.3)	1	1	0	0	0
Lower respiratory tract infection	0	0	0	1 (0.3)	1	1	0	0	0
Nasopharyngitis	0	0	0	0	0	0	1 (0.5)	1	1
Pleural infection	1 (0.3)	1	1	0	0	0	0	0	0
Pneumonia	2 (0.5)	2	2	1 (0.3)	1	0	0	0	0
Pyelonephritis chronic	0	0	0	1 (0.3)	1	0	0	0	0
Sepsis	1 (0.3)	1	0	0	0	0	0	0	0
Sialoadenitis	0	0	0	0	0	0	1 (0.5)	1	0
Subcutaneous abscess	1 (0.3)	1	1	0	0	0	0	0	0
Tonsillitis bacterial	1 (0.3)	1	1	0	0	0	0	0	0
Tuberculosis	0	0	0	1 (0.3)	1	1	0	0	0
Varicella	0	0	0	0	0	0	1 (0.5)	1	1
Injury, poisoning and procedural complications	5 (1.3)	5	1	6 (1.5)	8	0	3 (1.6)	4	0
Anastomotic stenosis	0	0	0	1 (0.3)	1	0	0	0	0
Ankle fracture	0	0	0	1 (0.3)	1	0	1 (0.5)	1	0
Fall	0	0	0	0	0	0	1 (0.5)	1	0
Femoral neck fracture	0	0	0	0	0	0	1 (0.5)	1	0
Foetal exposure during pregnancy	1 (0.3)	1	0	0	0	0	0	0	0
Gun shot wound	0	0	0	1 (0.3)	1	0	0	0	0
Humerus fracture	1 (0.3)	1	0	1 (0.3)	1	0	1 (0.5)	1	0
Joint dislocation	0	0	0	1 (0.3)	1	0	0	0	0
Lower limb fracture	1 (0.3)	1	0	0	0	0	0	0	0
Patella fracture	1 (0.3)	1	1	0	0	0	0	0	0
Spinal compression fracture	0	0	0	1 (0.3)	1	0	0	0	0
Tendon rupture	1 (0.3)	1	0	0	0	0	0	0	0
Upper limb fracture	0	0	0	1 (0.3)	1	0	0	0	0
Wrist fracture	0	0	0	1 (0.3)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	4 (1.1)	4	0	6 (1.5)	8	0	4 (2.2)	4	0
Arthralgia	0	0	0	1 (0.3)	1	0	1 (0.5)	1	0
Arthropathy	0	0	0	1 (0.3)	1	0	0	0	0
Intervertebral disc protrusion	1 (0.3)	1	0	0	0	0	1 (0.5)	1	0
Muscle haemorrhage	1 (0.3)	1	0	0	0	0	0	0	0
Musculoskeletal chest pain	0	0	0	0	0	0	1 (0.5)	1	0
Osteoarthritis	0	0	0	3 (0.8)	3	0	0	0	0
Osteonecrosis	1 (0.3)	1	0	0	0	0	0	0	0
Pathological fracture	0	0	0	1 (0.3)	1	0	0	0	0
Rheumatoid arthritis	1 (0.3)	1	0	0	0	0	1 (0.5)	1	0
Spinal column stenosis	0	0	0	1 (0.3)	2	0	0	0	0

Table 64. Treatment-Emergent Serious Adverse Events (Treatment Related) by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v16.0) Preferred Term	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Methotrexate		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.1)	4	1	3 (0.8)	3	1	1 (0.5)	1	1
Adrenal adenoma	1 (0.3)	1	0	0	0	0	0	0	0
Colon cancer stage IV	0	0	0	1 (0.3)	1	0	0	0	0
Gastric cancer	0	0	0	0	0	0	1 (0.5)	1	1
High grade B-cell lymphoma Burkitt-like lymphoma	0	0	0	1 (0.3)	1	1	0	0	0
Lymphoproliferative disorder	1 (0.3)	1	0	0	0	0	0	0	0
Non-Hodgkin's lymphoma	1 (0.3)	1	1	0	0	0	0	0	0
Prostate cancer	0	0	0	1 (0.3)	1	0	0	0	0
Uterine leiomyoma	1 (0.3)	1	0	0	0	0	0	0	0
Nervous system disorders	2 (0.5)	2	0	3 (0.8)	4	1	0	0	0
Carotid artery stenosis	1 (0.3)	1	0	0	0	0	0	0	0
Cerebrovascular accident	1 (0.3)	1	0	2 (0.5)	2	1	0	0	0
Demyelinating polyneuropathy	0	0	0	1 (0.3)	1	0	0	0	0
Nervous system disorder	0	0	0	1 (0.3)	1	0	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	0	2 (0.5)	2	0	0	0	0
Pregnancy	0	0	0	2 (0.5)	2	0	0	0	0
Psychiatric disorders	0	0	0	1 (0.3)	1	0	1 (0.5)	1	0
Psychotic disorder	0	0	0	1 (0.3)	1	0	1 (0.5)	1	0
Renal and urinary disorders	1 (0.3)	1	0	1 (0.3)	1	0	1 (0.5)	1	0
Calculus urinary	1 (0.3)	1	0	0	0	0	0	0	0
Hydronephrosis	0	0	0	1 (0.3)	1	0	0	0	0
Urinary tract disorder	0	0	0	0	0	0	1 (0.5)	1	0
Reproductive system and breast disorders	1 (0.3)	1	0	3 (0.8)	3	1	0	0	0
Endometrial hyperplasia	0	0	0	2 (0.5)	2	1	0	0	0
Ovarian cyst	1 (0.3)	1	0	0	0	0	0	0	0
Uterine polyp	0	0	0	1 (0.3)	1	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.3)	2	0	0	0	0
Chronic obstructive pulmonary disease	0	0	0	1 (0.3)	2	0	0	0	0
Skin and subcutaneous tissue disorders	1 (0.3)	1	1	0	0	0	1 (0.5)	1	1
Erythema annulare	1 (0.3)	1	1	0	0	0	0	0	0
Erythema multiforme	0	0	0	0	0	0	1 (0.5)	1	1
Vascular disorders	1 (0.3)	1	0	1 (0.3)	1	0	2 (1.1)	2	1
Deep vein thrombosis	1 (0.3)	1	0	0	0	0	1 (0.5)	1	0
Peripheral artery thrombosis	0	0	0	0	0	0	1 (0.5)	1	1
Rheumatoid vasculitis	0	0	0	1 (0.3)	1	0	0	0	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v16.0) coding dictionary applied.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment emergent all causalities adverse events.
n2: The number of occurrences of treatment emergent causally related to treatment adverse events.
BID = twice a day; incl = including, MedDRA = Medical Dictionary for Regulatory Activities; v = version.

A higher proportion of subjects discontinued the study from the MTX group than the 2 tofacitinib groups at all timepoints (Table 65). The main difference between the MTX and tofacitinib groups was observed in related discontinuations due to lack of efficacy, for which a greater proportion of discontinuations were reported in the MTX group and this increased at each timepoint.

Table 65. Summary of Adverse Events Resulting in Discontinuation (All Causalities) by Preferred Term (2 Year Analysis)

Number (%) of Subjects	Tofacitinib 5 mg BID (N=373)	Tofacitinib 10 mg BID (N=397)	Methotrexate (N=186)
Month 3			
Discontinuations related to study drug	10 (2.7)	7 (1.8)	10 (5.4)
Adverse event	5 (1.3)	4 (1.0)	3 (1.6)
Lack of efficacy	5 (1.3)	3 (0.8)	7 (3.8)
Discontinuations not related to study drug	13 (3.5)	10 (2.5)	7 (3.8)
Adverse event	1 (0.3)	2 (0.5)	1 (0.5)
Lost to follow-up	3 (0.8)	0	1 (0.5)
Other	3 (0.8)	5 (1.3)	2 (1.1)
Withdrawal of consent	6 (1.6)	3 (0.8)	3 (1.6)
Total	23 (6.2)	17 (4.3)	17 (9.1)
Month 6			
Discontinuations related to study drug	18 (4.8)	12 (3.0)	21 (11.3)
Adverse event	9 (2.4)	8 (2.0)	8 (4.3)
Lack of efficacy	9 (2.4)	4 (1.0)	13 (7.0)
Discontinuations not related to study drug	22 (5.9)	24 (6.0)	14 (7.5)
Adverse event	2 (0.5)	7 (1.8)	2 (1.1)
Lost to follow-up	5 (1.3)	3 (0.8)	1 (0.5)
Other	4 (1.1)	8 (2.0)	5 (2.7)
Withdrawal of consent	11 (2.9)	6 (1.5)	6 (3.2)
Total	40 (10.7)	36 (9.1)	35 (18.8)
Month 12			
Discontinuations related to study drug	27 (7.2)	23 (5.8)	30 (16.1)
Adverse event	13 (3.5)	16 (4.0)	12 (6.5)
Lack of efficacy	14 (3.8)	7 (1.8)	18 (9.7)
Discontinuations not related to study drug	39 (10.5)	44 (11.1)	23 (12.4)
Adverse event	9 (2.4)	8 (2.0)	4 (2.2)
Lost to follow-up	8 (2.1)	4 (1.0)	3 (1.6)
Other	7 (1.9)	13 (3.3)	7 (3.8)
Withdrawal of consent	15 (4.0)	19 (4.8)	9 (4.8)
Total	66 (17.7)	67 (16.9)	53 (28.5)
Month 24			
Subject died	2 (0.5)	0	0
Discontinuations related to study drug	43 (11.5)	36 (9.1)	44 (23.7)
Adverse event	23 (6.2)	25 (6.3)	18 (9.7)
Lack of efficacy	20 (5.4)	11 (2.8)	26 (14.0)
Discontinuations not related to study drug	62 (16.6)	75 (18.9)	36 (19.4)
Adverse event	15 (4.0)	14 (3.5)	6 (3.2)
Lost to follow-up	11 (2.9)	9 (2.3)	5 (2.7)
Other	13 (3.5)	25 (6.3)	12 (6.5)
Withdrawal of consent	23 (6.2)	27 (6.8)	13 (7.0)
Total	107 (28.7)	111 (28.0)	80 (43.0)

There were 2 fatalities which occurred post-therapy.
BID = twice daily, N = number of subjects.

Death: A total of 5 subject deaths were reported during the study (Table 66). One subject died prior to randomization and the subject did not receive study drug. Two of the subject deaths occurred during the study after Month 12 and 2 occurred post therapy. Three subject deaths occurred in the tofacitinib 5 mg BID group (non-Hodgkin's lymphoma, cardiac failure

and unknown death [possible sudden cardiac death]) and 1 subject's death occurred in the tofacitinib 10 mg BID group (colon cancer stage IV). The events of non-Hodgkin's lymphoma and death were reported as treatment-related.

Table 66. Death Summary

Number of Subjects Evaluable for Adverse Events	Pre-Randomization (N=1543)		Tofacitinib 5 mg BID (N=373)		Tofacitinib 10 mg BID (N=397)	
	n	n1	n	n1	n	n1
System Organ Class Preferred Term						
Cardiac disorders	0	0	1	1	0	0
Acute myocardial infarction	0	0	1	1	0	0
General disorders and administration site conditions	1	0	0	0	0	0
Death	1	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1	1	1	0
Colon cancer stage IV	0	0	0	0	1	0
Non-Hodgkin's lymphoma	0	0	1	1	0	0
Respiratory, thoracic and mediastinal disorders	0	0	1	0	0	0
Bronchitis chronic	0	0	1	0	0	0
Total number of fatalties from adverse events[a]	1		3		1	
Total number of deaths all causes[b]	1		3		1	

A subjec'st death could be associated with more than one treatment if the first onset date of the case falls within multiple treatment group periods.
n: The number of adverse events associated with a fatality.
n1: The number of adverse events associated with a fatality and thought to be associated or related to treatment.
Source of actual treatment group is OC (Oracle Clinical) or PIMS (Phase I Management System). Source of SAE is SDW (Safety Data Warehouse)
MedDRA v.17.0 coding dictionary applied.
A fatality could be associated with multiple events.
a. Total number of deaths in this reporting group thought to be causally related to adverse events.
b. Total number of deaths (all causes) in this reporting group. This included deaths not related to the trial.

A greater decrease from Baseline in neutrophils was observed in the tofacitinib 10 mg group compared to the tofacitinib 5 mg BID group. A statistically significantly greater increase from Baseline in HDL-cholesterol was observed in the tofacitinib groups (5 mg and 10 mg BID) compared to the MTX group ($p \leq 0.0002$). The most notable difference between treatment groups was observed in subjects with aspartate transaminase or alanine transaminase of >3×upper limit of normal (ULN) in the MTX group compared to tofacitinib groups; hemoglobin values of <8.0 g/dL or that dropped ≥2 g/dL below Baseline were observed in all 3 treatment groups; elevations in serum creatinine ≥33% above the average of Screening and Baseline values were seen in the tofacitinib groups (5 mg and 10 mg BID). Changes from Baseline in systolic and diastolic blood pressure were small in the tofacitinib groups.

CONCLUSIONS:

- Treatment with tofacitinib (5 mg or 10 mg BID) was efficacious in structure preservation as measured by mTSS at Month 6, and demonstrated a statistically significant difference in change from Baseline compared to MTX.

- Tofacitinib (both 5 mg and 10 mg BID) was efficacious at Months 12 and 24 in structure preservation. Both tofacitinib treatment groups demonstrated a statistically significant ($p \leq 0.0004$) difference in change in mTSS from Baseline compared to MTX at these timepoints.

- Treatment with tofacitinib (5 mg or 10 mg BID) was efficacious in reducing the signs and symptoms of RA in subjects with RA as measured by the ACR70 response rate at Month 6 (co-primary endpoint) and demonstrated statistically significant differences from MTX as early as Month 1 ($p < 0.001$) and all other timepoints measured.

- The proportion of subjects showing no radiographic progression (change from Baseline in mTSS ≤0.5 units) in the tofacitinib groups (5 mg BID and 10 mg BID) was statistically significantly ($p \leq 0.001$) superior to the proportions in the MTX group at Months 6, 12 and 24.

- Evaluation of subsets of subjects with poor prognostic factors for radiographic progression (as measured at Baseline) indicated a consistent pattern of benefit of both the tofacitinib 5 mg and 10 mg BID doses compared with MTX in structure preservation.

- The cumulative distribution plots of changes from Baseline in mTSS, erosion scores, and JSN scores for the tofacitinib 5 mg BID and 10 mg BID groups were similar to one another and similarly different from the plots for the MTX group.

- Treatment with tofacitinib (5 mg or 10 mg BID) was efficacious in improving the physical function status of subjects with RA as measured by HAQ-DI response rate at Months 1 through 24, and demonstrated statistically significant differences from MTX as early as Month 1.

- Statistically significant improvement from Baseline in HAQ-DI, DAS28-4 (ESR), DAS28-3 (CRP) and CRP were demonstrated in both tofacitinib 5 mg BID and 10 mg BID groups compared with the MTX treatment group at Months 1 through 24.

- A greater proportion of subjects had consecutive responses of DAS28-3 (CRP) and DAS28-4 (ESR) <2.6 in the tofacitinib 5 mg BID and 10 mg BID groups compared with the MTX for the majority of responses.

- For all efficacy endpoints efficacy with tofacitinib was sustained through to Month 24 and a durability of response was observed.

- Patient and Physician Global Assessment of arthritis and Patient Assessment of Arthritis Pain demonstrated significant improvement from Baseline in both tofacitinib 5 mg BID and 10 mg BID groups compared with the MTX treatment group at Month 1 through 24.

- Improvements in subjects treated with tofacitinib were consistently greater in the 10 mg BID group compared to the 5 mg BID group for mTSS analysis, all components of ACR assessments (Joint Counts, Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, Physician Global Assessment of arthritis, CRP, and HAQ-DI scores) and the DAS28 scores.

- For the outcomes measurements of SF-36, EQ-5D, and FACIT-Fatigue scales improvements were observed in the tofacitinib groups when compared to the MTX group. The results from the MOS-SS, RA-HCRU, and WLQ did not show consistent differences between the tofacitinib groups and the MTX group.

- There were no new safety signals in this study.

- There were a total of 5 fatal cases reported during the study. One fatal case occurred prior to randomization and the subject did not receive study drug. Two fatal events in the tofacitinib 5 mg BID group were reported as treatment-related.

- Overall, the incidence of AEs was similar among the treatment groups. The most frequently reported AEs were those coded to the MedDRA SOCs of infections and infestations, gastrointestinal disorders and investigations. With the exception of nausea, the incidence of subjects with all individual TEAEs were similar in the tofacitinib groups with that in the MTX group.

- There were slightly less discontinuations due to AEs in the tofacitinib 5 mg and 10 mg BID groups compared to the MTX group.

- The proportions of subjects with treatment-related TEAEs were similar across the 3 treatments. The frequencies of SAEs (all causality) were similar across the treatment groups in this study.

- A greater proportion of AEs were observed in the tofacitinib groups (5 mg and 10 mg BID) compared to the MTX group in the SMQs for hypertension and dyslipidemia.

- Changes in laboratory parameters observed for tofacitinib 5 mg BID and 10 mg BID relative to MTX were consistent with data from previous clinical trials, including dose-dependent decreases in neutrophil counts and increases in HDL, LDL, and total cholesterol levels.

- There were also increases in serum creatinine in all 3 treatment groups; these were greater in the tofacitinib groups than the MTX group. The mean changes in the tofacitinib groups were not dose-dependent.

- Through Month 24, the frequency of subjects with creatine kinase elevations was higher in the tofacitinib groups than for the MTX group.

- Changes in systolic blood pressure were small and variable across treatment groups, although there was an observed decrease in diastolic blood pressure in the MTX group compared to the tofacitinib groups. There was no clear dose-response relationship in the tofacitinib groups.

- The proportions of subjects meeting the JNC7 criteria for Stage 1 or 2 hypertension remained relatively stable throughout the 12 months of therapy with no consistent change across dose groups.

- The proportion of subjects with stage 1 and 2 hypertension was similar in all 3 treatment groups. The proportion of subjects with hypertension remained similar to Baseline levels for the majority of timepoints.

- The mean increase from Baseline in BMI was greater in the tofacitinib groups (5 mg and 10 mg BID) than in the MTX group at all timepoints although the overall changes were small in all 3 treatment groups (<1.5 kg/m^2 at all timepoints).

- The safety profiles of tofacitinib 5 mg BID and 10 mg BID were similar to those seen in previous studies of tofacitinib in subjects with active RA.

- Overall, the efficacy and safety results from this Year-2 analysis are consistent with the Year-1 analysis.