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

PROTOCOL NO.: A3921215

PROTOCOL TITLE:

A Multicenter, Randomized, Double-Blind, Parallel-Group, Phase 3 Study to Demonstrate Non-Inferiority for the Efficacy of a Once Daily Dose of Tofacitinib Modified Release Tablet to a Twice Daily Dose of the Immediate Release Tablet in Adult Patients With Rheumatoid Arthritis on Background Methotrexate

Study Centers:

A total of 36 centers took part in the study and randomized patients in Japan.

Study Initiation and Final Completion Dates:

18 November 2014 and 15 March 2017

Phase of Development:

Phase 3

Study Objectives:

Primary Objective:

- To demonstrate the non-inferiority for efficacy of tofacitinib modified release (MR) 11 mg once daily (QD) to immediate release (IR) 5 mg twice daily (BID) for the treatment of signs and symptoms in patients with active rheumatoid arthritis (RA) on a stable background of methotrexate (MTX), as measured by Disease Activity Score (DAS) defined using 28 joint counts and C-reactive protein (DAS28-4[CRP]) change from baseline at Week 12.

Secondary Objectives:

- To evaluate the similarity in efficacy of tofacitinib MR 11 mg QD and IR 5 mg BID for the treatment of signs and symptoms of RA, as measured by DAS defined using 28 joint counts and erythrocyte sedimentation rate (DAS28-4[ESR]) change from Baseline, American College of Rheumatology (ACR) definition for calculating improvement in RA calculated as a ≥20%/50%/70% improvement in tender and swollen joint counts and ≥20%/50%/70% improvement in 3 of the 5 remaining ACR core set measures,

respectively (ACR20, ACR50, ACR70, respectively) responses, remission, and low disease activity (LDA), at Week 12.

- To evaluate the similarity in efficacy of tofacitinib MR 11 mg QD and IR 5 mg BID for physical function status as measured by Health Assessment Questionnaire-Disability Index (HAQ-DI) change from Baseline at Week 12.

- To evaluate the similarity in effects on patient's health outcome measures (change from Baseline in Short Form-36 [SF-36], Functional Assessment of Chronic Illness Therapy [FACIT] Fatigue and European Quality of Life-5 dimensions questionnaire [EQ-5D]) of tofacitinib MR 11 mg QD and IR 5 mg BID at Week 12.

- To evaluate the safety and tolerability of tofacitinib MR 11 mg QD in comparison with IR 5 mg BID in patients.

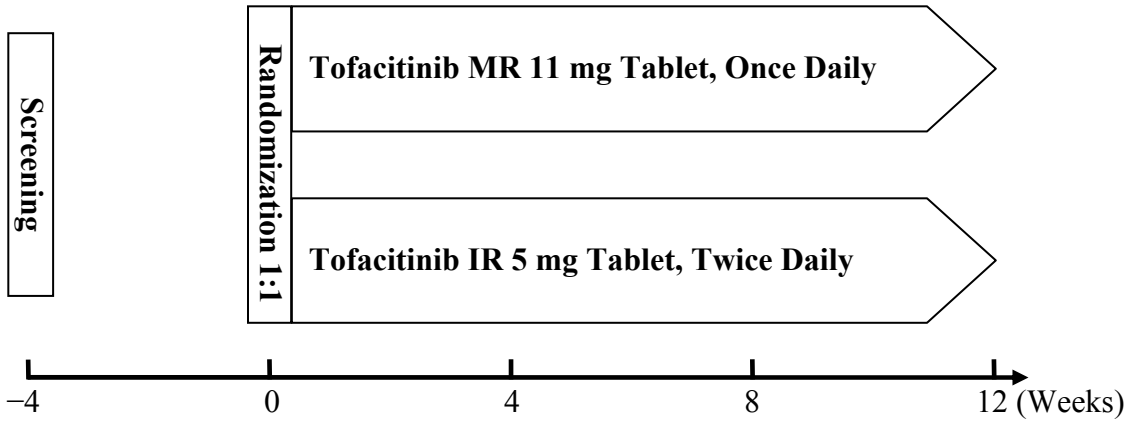
METHODS

Study Design:

This was a multicenter, randomized, double-blind, parallel group, Phase 3 study to evaluate the efficacy and safety of tofacitinib MR 11 mg tablet QD dose compared to IR 5 mg tablet BID dose at 12 weeks treatment in patients with moderate to severe active RA on a stable background MTX.

Patients were randomized in a 1:1 ratio into the tofacitinib MR 11 mg QD group and the tofacitinib IR 5 mg BID group. The study design schematic for the study is presented in Figure 1. The schedule of activities is presented in Table 1.

Figure 1. Study Design



Approximately 100 per arm, N=200.
Abbreviations: IR=Immediate release; MR=Modified release; N=Number of patients.

Table 1. Schedule of Activities

Visit Identifier	Visits				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	Baseline Day 1	Week 4	Week 8	Week 12 (EOS/ET)[a]
Study Day	**-27**	**1**	**29**	**57**	**85**
Visit Window (Days)	**+7 (-34 to 0)**	**0**	**±3**	**±3**	**±3**
Informed consent	X				
Medical history[b]	X				
Prior treatments/medications	X				
Concomitant treatments/ medications	X	→	→	→	X
Inclusion/exclusion criteria	X	X			
Complete physical examination[c]	X				
Targeted physical examination[c]		X	X		X
Vital signs, temperature[d]	X	X	X		X
Whole blood interferon-gamma release assay (Quantiferon-3G/QuantiFERON-TB Gold in-tube or T-SPOT)[e]	X				
12-lead electrocardiogram	X				
Chest X-ray (PA and lateral) or chest CT scan[f]	X				
Blood/urine					
Rheumatoid factor	X				
Hematology[g], chemistry panel[h]	X	X	X		X
Lipid profile (fasting)[i]	X	X	X		X
Serum pregnancy test (β-HCG)[j]	X				
Urine pregnancy test (β-HCG)[k]		X	X		X
Urinalysis[k]	X	X	X		X
Serum β-D-glucan and KL-6	X				
HIV serology	X				
HBsAg, HBcAb, HBsAb, HBV DNA testing (if necessary)[l]	X				
HCV Ab, HCV RNA PCR (if HCV Ab positive)	X				
Varicella-Zoster virus	X				
Lymphocyte subset markers[m]		X	X		X
Banked biospecimens (PGx sampling)		X			

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Study Day	**-27**	**1**	**29**	**57**	**85**
Visit Window (Days)	**+7 (-34 to 0)**	**0**	**±3**	**±3**	**±3**
ACR/DAS					
CRP	X	X	X		X
ESR	X	X	X		X
Joint assessment: tender/painful joint count: (68 joints), swollen joint count (66 joints)	X	X	X		X
Patient Assessment of Arthritis Pain (VAS)		X	X		X
Patient Global Assessment (VAS)		X	X		X
Physician Global Assessment (VAS)		X	X		X
HAQ-DI		X	X		X
SF-36 (Version 2, acute)		X	X		X
FACIT-fatigue scale		X			X
European Quality of Life Questionnaire		X			X
Randomization		X			
Study drug dispensing-new bottles supplied		X	X	X	
Dispense dosing diary		X	X	X	
Drug accountability			X	X	X
Review of patient dosing diary			X	X	X
Adverse events		X	→	→	X

Abbreviations: ACR=American College of Rheumatology; ALP=Alkaline phosphatase; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BCG=Bacille Calmette Guérin; β-HCG=Beta-human chorionic gonadotropin; CD=Cluster of differentiation; CK=Creatine kinase; CRP=C reactive protein; CT=Computed tomography; DAS=Disease Activity Score; DNA=Deoxyribonucleic acid; EOS=End of study; ESR=Erythrocyte sedimentation rate; ET=Early termination; FACIT=Functional Assessment of Chronic Illness Therapy; GGT=Gamma-glutamyl transferase; HAQ-DI=Health Assessment Questionnaire-Disability Index; HBcAb=Hepatitis B core antibody; HBsAb=Hepatitis B surface antibody; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; HCV=Hepatitis C virus; HCV Ab=Hepatitis C virus antibody; HEENT=Head, eyes, ears, nose and throat; HIV=Human immunodeficiency virus; IFN-γ=Interferon-gamma; IV=Intravenous; PA=Posteroanterior; PCR=Polymerase chain reaction; PGx=Pharmacogenomics; pH=Negative logarithm of the hydrogen ion concentration; PPD=Purified Protein Derivative; QFT-G=Quantiferon 3G/QuantiFERON-TB Gold In-tube; RA=Rheumatoid arthritis; RBC=Red blood cell; RNA=Ribonucleic acid; SF-36=Short Form-36; TB=Tuberculosis; VAS=Visual analog scale; WBC=White blood cell.

a. Study procedures were to be performed at the EOS or ET Visit.
b. Medical history included previous vaccination history, smoking status, average weekly alcohol consumption, family history of premature coronary heart disease, history of any prior episodes of herpes zoster and confirmation of RA diagnosis.
c. Complete physical exam included height, weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station,

Table 1. Schedule of Activities

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Study Day	-27	1	29	57	85
Visit Window (Days)	+7 (-34 to 0)	0	±3	±3	±3

gait, reflexes, motor and sensory function, coordination) and lymph nodes. Targeted physical examination included weight, examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes.

d. Temperature was collected as axillary temperature. The same method was used throughout the study.

e. Mantoux PPD tuberculin skin test was allowed, if there were 2 consecutive indeterminate results of QFT-G or T-SPOT test in patients who had not received BCG vaccination during screening period.

f. Chest X-ray (PA and lateral) or chest CT scan (with or without intravenous [IV] contrast) were obtained at screening or within 12 weeks prior to screening and read by a qualified radiologist or respiratologist. If necessary, a chest CT scan (with or without IV contrast) might have been performed during screening following initial performance of chest radiographs (PA and lateral) at the clinical discretion of the investigator. If pulmonary signs and symptoms were observed at and after baseline visit, unscheduled imaging test (eg, chest X-ray or chest CT scan) might have been performed based on the judgment by investigator as appropriate.

g. Hematology included hemoglobin, hematocrit, RBC count, WBC count with differential and platelet count.

h. Chemistry panel included blood urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP, GGT, albumin, CK.

i. Lipid profile included total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides under fasting condition.

j. Serum pregnancy test for women of childbearing potential only.

k. Dipstick in all cases; urinalysis included specific gravity, pH, protein, glucose, ketones, blood, nitrite, leukocyte esterase and urine sediment (microscopy). Urine culture was performed if clinically indicated. Urine pregnancy test (β-HCG) was required only for women who were of childbearing potential; could have been repeated more frequently if a menstrual cycle was missed, or if potential pregnancy was otherwise suspected.

l. HBV DNA assay might have been required for a subset of patients with specified serological test results.

m. Lymphocyte subset markers included CD3+, CD3−CD19+, CD3+CD4+CD8−, CD3+CD4−CD8+, CD3+CD16+CD56+, CD3−CD16+CD56+, CD3−CD16+CD56−, CD3−CD16−CD56+, CD3−CD16−CD56−, CD4/CD8.

Number of Subjects (Planned and Analyzed):

The following assumptions in treatment comparison for the primary endpoint were applied:

- One-sided type-I error (alpha) of 0.025;
- Patients assigned to tofacitinib MR 11 mg QD and IR 5 mg BID groups in a 1:1 ratio;
- Difference of treatment means is 0;
- A common standard deviation of 1.3 based on the previous tofacitinib studies.

Based on the forgoing assumptions, a total of at least 200 evaluable patients (100 in each treatment arm) were required to demonstrate non-inferiority with a power of 90% and a non-inferiority margin of 0.6, which was equal to the minimum improvement in disease activity by DAS consistent with a "moderate response" by the European League Against Rheumatism (EULAR) criteria. However, the minimal clinically important DAS28 change from baseline is 1.2.

It was anticipated that the sample size of 100 patients in each formulation group would provide 0.36 half-width of 2-sided 95% confidence interval (CI) for the difference on the change from baseline in DAS28-4(CRP) at Week 12 assuming a common standard deviation of 1.3.

A total of 333 patients were screened, of which 209 patients were randomized and treated. One hundred and four (104) patients were randomized to receive tofacitinib 11 mg QD and 105 patients were randomized to receive tofacitinib 5 mg BID.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Main Inclusion Criteria:

Patients having diagnosis of RA and those who were currently taking a stable dose of MTX; patients having no evidence of active or latent or inadequately treated tuberculosis were included in this study.

Main Exclusion Criteria:

Patients having evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic or allergic disease; patients having clinically significant infections within the past 6 months were excluded from this study.

Study Treatment:

Patients were provided with medication instructions relevant to their study treatment arm. Study drugs were taken according to the instructions provided to the patient.

Patients were instructed to take 1 tablet from each bottle in the morning and 1 tablet from bottle of IR in the evening, approximately 12 hours apart. Patients had to take 3 tablets per day and record drug compliance in the patient dosing diary.

If a tofacitinib dose was missed and the interval to the next scheduled dose was <6 hours, the missed dose of tofacitinib IR was not administered. Patients swallowed the whole study drug, and did not manipulate or chew the medication prior to swallowing.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- Change from Baseline in DAS28-4(CRP) at Week 12.

Secondary Efficacy Endpoints:

- Change from Baseline in DAS28-4(ESR) at Week 12;
- ACR20, ACR50 and ACR70 response at Week 12;
- Remission at Week 12, as assessed by: DAS28-4(CRP) <2.6 and DAS28-4(ESR) <2.6;
- LDA at Week 12, as assessed by: DAS28-4(CRP) ≤3.2 and DAS28-4(ESR) ≤3.2;
- Change from Baseline in HAQ-DI at Week 12;
- HAQ-DI response (decrease of at least 0.22) at Week 12;
- Change from Baseline in the SF-36 8 domain scores and 2 component scores at Week 12;
- Change from Baseline in the FACIT-Fatigue scale at Week 12;
- Change from Baseline in the EQ-5D at Week 12.

Safety Evaluations:

Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure [BP]), 12-lead electrocardiograms (ECGs), AEs including serious adverse events (SAEs) and safety laboratory tests.

Statistical Methods:

Analysis Sets: There were 3 analysis sets in this study:

Full Analysis Set: The full analysis set (FAS) included all patients who were randomized and received at least 1 dose of the randomized study drug.

Per Protocol Analysis Set: The per protocol analysis set (PPAS) included subset of the FAS dataset. The PPAS included all randomized patients who completed the 12 week study with no important protocol deviations that could impact the efficacy analysis. The list of

potentially important protocol deviations and the patients to be excluded from the PPAS were identified, reviewed, and finalized prior to the release of the database.

Safety Analysis Set: The safety analysis set included all patients who were randomized and received at least 1 dose of the randomized study drug. By definition, it is identical to the FAS defined above.

Analysis of Efficacy Parameters:

Analysis of Primary Efficacy Endpoints: The analysis was conducted using a linear mixed effect model with repeated measures (MMRM), which included treatment (tofacitinib MR 11 mg QD and IR 5 mg BID), visit, and treatment by visit interaction as fixed effects. Patients were a random effect and unstructured covariance was assumed for the within-patient errors. If there were convergence problems with this model, sequential structures were to be applied until the problems resolved; autoregressive 1 and compound symmetry.

If there was modeling of actual values, the explanatory variable of visit included baseline as one of the longitudinal values. When modeling the change from baseline values, the variable of visit started with the first post-baseline visit, and the actual baseline value was included as a covariate. At each visit, estimates of mean values, the mean differences between the treatment groups and the associated 2-sided 95% CI (Type I error [alpha] of 0.025 in each tail) was derived from the model. If the upper bound of the 2-sided 95% CI (Type I error of 0.025 in each tail) for the difference in change from baseline in DAS28-4(CRP) between the 2 treatment groups (MR 11 mg QD - IR 5 mg BID) was <0.6, then the treatment with 11 mg QD would be declared non-inferior to that of tofacitinib IR 5 mg BID.

The patient was required to have a baseline and at least 1 non-missing on-study assessment of DAS28-4(CRP) to be included in the analysis. Missing values were not imputed.

Sensitivity/Robustness Analyses: To support the interpretation of the primary analysis, robust sensitivity analyses were performed for the primary endpoint. However, the conclusions (non-inferiority) for comparison of the primary endpoint between tofacitinib MR 11 mg QD and IR 5 mg BID group was based on results of the primary analysis only.

Analysis of Secondary Endpoints: All analyses of secondary endpoints were based on the FAS.

The change from baseline in longitudinal continuous variables (ie, DAS28-4[ESR], HAQ-DI, other 6 components of the ACR criteria, the 8 domains and 2 component scores of SF-36) were analyzed using the MMRM model and the missing values were not imputed.

The change from baseline in non-longitudinal continuous variables (ie, EQ-5D utility score and FACIT fatigue scale) were analyzed using an analysis of covariance (ANCOVA) model and the missing values were not imputed.

Binary variables (ie, the ACR variables [ACR20, ACR50 and ACR70], DAS defined using 28 joint counts [DAS28] responses [DAS28 ≤3.2, DAS28 <2.6] which included DAS28-4[CRP] and DAS28-4[ESR], and decrease [at least 0.22] in HAQ-DI) were analyzed using the normal approximation to the difference in response rates.

Safety Parameters:

The AEs were listed and summarized within treatment group in accordance with the sponsor data standards. The AEs, SAEs and discontinuations due to AEs were also summarized by subsets.

Laboratory data were listed and summarized within treatment group in accordance with the sponsor data standards. Incidence of laboratory test abnormalities (including without regard to baseline abnormality) were summarized within each treatment group. For each planned time point, actual values and changes from baseline values were summarized within each treatment with descriptive statistics. The changes from baseline values were analyzed using the MMRM model. Instead of changes form baseline, percent changes from baseline were analyzed in lipid tests (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C] and triglyceride).

For each planned time point, actual values and change from baseline values in BP, weight and body mass index (BMI) were summarized within each treatment with descriptive statistics. The changes from baseline values in BP was analyzed using the MMRM model.

RESULTS

Subject Disposition and Demography:

Patient disposition is summarized in Table 2. A total of 333 patients were screened. One hundred and four (104) and 105 patients were randomized to receive tofacitinib 11 mg QD and tofacitinib 5 mg BID, respectively. A total of 14 patients (6.7%) were discontinued from the study. The reason for discontinuation were treatment related AEs (overall 11 patients [5.3%]: 3 patients [2.9%] in the tofacitinib 11 mg QD group and 8 patients [7.6%] in the tofacitinib 5 mg BID group), insufficient clinical response (no patient in the tofacitinib 11 mg QD group and 1 patient [1.0%] in the tofacitinib 5 mg BID group), medication error without associated AE (1 patient [1.0%] in the tofacitinib 11 mg QD group and no patient in the tofacitinib 5 mg BID group) and AE not related to study drug (1 patient [1.0%] in the tofacitinib 5 mg BID group and no patient in the tofacitinib 11 mg QD group).

Table 2. Patient Disposition

	Tofacitinib 11 mg QD	Tofacitinib 5 mg BID	Total
Screened: 333			
Assigned to study treatment	104	105	209
Treated	104 (100.0)	105 (100.0)	209 (100.0)
Completed	100 (96.2)	95 (90.5)	195 (93.3)
Discontinued	4 (3.8)	10 (9.5)	14 (6.7)
Relation to study drug not defined	1 (1.0)	1 (1.0)	2 (1.0)
Insufficient clinical response	0	1 (1.0)	1 (0.5)
Medication error without associated adverse event	1 (1.0)	0	1 (0.5)
Related to study drug	3 (2.9)	8 (7.6)	11 (5.3)
Adverse event	3 (2.9)	8 (7.6)	11 (5.3)
Not related to study drug	0	1 (1.0)	1 (0.5)
Adverse event	0	1 (1.0)	1 (0.5)
Analyzed for efficacy			
Full analysis set	104 (100.0)	105 (100.0)	209 (100.0)
Per protocol analysis set	99 (95.2)	94 (89.5)	193 (92.3)
Analyzed for safety			
Adverse events	104 (100.0)	105 (100.0)	209 (100.0)
Laboratory data	104 (100.0)	105 (100.0)	209 (100.0)

Discontinuations occurring outside the lag period had been attributed to the last study treatment received.
Abbreviations: BID=Twice daily; QD=Once daily.

The demographic characteristics of the 2 treatment groups were balanced between treatment groups (Table 3) with the following exceptions: the proportion of females and CRP and ESR levels was numerically higher in the tofacitinib 11 mg QD group. The majority of the treated patients were female (161/209 patients) and all the enrolled patients were Asian. The overall mean age of patients was 58.0 years (57.1 years in the tofacitinib 11 mg QD group and 58.9 years in the tofacitinib 5 mg BID group) (overall range: 27 years to 79 years). The overall mean weight was 56.7 kg (55.9 kg in the tofacitinib 11 mg QD group and 57.5 kg in the tofacitinib 5 mg BID group) (overall range: 35.4 kg to 100.8 kg).

Table 3. Demographic Characteristics

Number (%) of Patients	Tofacitinib 11 mg QD			Tofacitinib 5 mg BID			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
N	18	86	104	30	75	105	48	161	209
Age (years)									
18-44	6 (33.3)	12 (14.0)	18 (17.3)	4 (13.3)	7 (9.3)	11 (10.5)	10 (20.8)	19 (11.8)	29 (13.9)
45-64	8 (44.4)	49 (57.0)	57 (54.8)	17 (56.7)	41 (54.7)	58 (55.2)	25 (52.1)	90 (55.9)	115 (55.0)
≥65	4 (22.2)	25 (29.1)	29 (27.9)	9 (30.0)	27 (36.0)	36 (34.3)	13 (27.1)	52 (32.3)	65 (31.1)
Mean	54.7	57.6	57.1	58.0	59.3	58.9	56.8	58.4	58.0
SD	13.7	10.9	11.4	10.4	10.1	10.2	11.7	10.6	10.8
Range	30-79	27-79	27-79	34-79	33-79	33-79	30-79	27-79	27-79

Abbreviations: BID=Twice daily; N=Number of patients; QD=Once daily; SD=Standard deviation.

Efficacy Results:

Primary Efficacy Results:

Change From Baseline in DAS28-4(CRP) at Week 12: The statistical analysis of change from baseline in DAS28-4(CRP) (FAS, longitudinal model) at Week 12 is presented in Table 4. The least square (LS) mean change from baseline in DAS28-4(CRP) was -2.43 and -2.85 for MR 11 mg QD and IR 5 mg BID respectively. The point estimate of the difference (MR-IR) between the 2 groups was 0.43 with 95% CI (0.17-0.69). The non-inferiority criterion was not met for tofacitinib MR 11 mg QD as compared to tofacitinib 5 mg BID. Upper bound of the CI (0.69) was above the non-inferiority margin of 0.6. The difference in change from baseline between treatment arms in DAS28-4 CRP was statistically significant.

Table 4. Statistical Analysis of Change From Baseline in DAS28-4(CRP) at Week 12 (FAS, Longitudinal Model)

Treatment Group	N	LS Mean	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
			Difference	95% Confidence Interval	
				Lower	Upper
Tofacitinib 11 mg QD	100	-2.43	0.43	0.17	0.69
Tofacitinib 5 mg BID	95	-2.85			

The fixed effects of actual baseline values, treatment, visit, and treatment-by-visit interaction were included, unstructured covariance matrices was used.
Abbreviations: BID=Twice daily; DAS28-4(CRP)=Disease activity score defined using 28 joint counts and C-reactive protein; FAS=Full analysis set; LS=Least square; N=Number of patients; QD=Once daily.

Sensitivity analysis of change from baseline in DAS28-4(CRP) at Week 12 for the PPAS also supported the primary analysis (Table 5). The same finding was observed by sensitivity analysis with PPAS with an upper bound of 0.71, which was also greater than (outside) the non-inferiority boundary.

Table 5. Sensitivity Analysis: Statistical Analysis of Change From Baseline in DAS28-4(CRP) at Week 12 (PP, Longitudinal Model)

Treatment Group	N	LS Mean	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
			Difference	95% Confidence Interval	
				Lower	Upper
Tofacitinib 11 mg QD	99	-2.42	0.45	0.19	0.71
Tofacitinib 5 mg BID	94	-2.87			

The fixed effects of actual baseline values, treatment, visit, and treatment-by-visit interaction were included, unstructured covariance matrices was used.
Abbreviations: BID=Twice daily; DAS28-4(CRP)=Disease activity score defined using 28 joint counts and C-reactive protein; LS=Least square; N=Number of patients; PP=Per protocol; QD=Once daily.

In a subset analysis, the consistent finding was observed in difference between tofacitinib MR 11 mg QD and tofacitinib IR 5 mg BID in change from baseline of DAS28-4(CRP) at Week 12 in all subsets evaluated (sex [male, female], body weight [<55 kg, ≥55 kg],

age [<65 years old, ≥65 years old], rheumatoid factor at screening [negative, positive], disease duration [<5 years, ≥5 years], MTX dose at baseline [≤8 mg/week, >8 mg/week] and DAS28-4(CRP) at baseline [≤5.1, >5.1]).

Secondary Efficacy Results:

Change From Baseline in DAS28-4(ESR) at Week 12:

Statistical analysis of change from baseline in DAS28-4(ESR) per visit for FAS (longitudinal model) (at Week 12) is presented in Table 6.

Table 6. Statistical Analysis of Change From Baseline in DAS28-4(ESR) at Week 12 (FAS, Longitudinal Model)

Treatment Group	N	LS Mean	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
			Difference	95% Confidence Interval	
				Lower	Upper
Tofacitinib 11 mg QD	99	-2.50	0.37	0.11	0.63
Tofacitinib 5 mg BID	95	-2.86			

The fixed effects of actual baseline values, treatment, visit, and treatment-by-visit interaction were included, unstructured covariance matrices was used.
Abbreviations: BID=Twice daily; DAS28-4(ESR)=Disease activity score defined using 28 joint counts and erythrocyte sedimentation rate; FAS=Full analysis set; LS=Least square; N=Number of patients; QD=Once daily.

ACR20, ACR50 and ACR70 Response at Week 12:

Both treatments had clinically relevant ACR20 response rates that was maintained through to Week 12 (84.47% for tofacitinib 11 mg QD group and 79.81% for tofacitinib 5 mg BID group). The difference between the tofacitinib groups was not statistically significant at either time point.

Both treatments had clinically relevant response rates (FAS, NRI) through to Week 12 (67.96% for tofacitinib 11 mg QD group and 68.27% for tofacitinib 5 mg BID group). The difference (1.28 at Week 4 and -0.29 [last observation carried forward {LOCF}] at Week 12) between the tofacitinib groups was not statistically significant at either time point.

ACR70 response rates were significantly higher at Week 12 (31.07% for tofacitinib 11 mg QD group and 46.15% for tofacitinib 5 mg BID group) for patients in the tofacitinib 5 mg BID group ($p<0.05$).

The ACR20/50/70 response rates in MR 11 mg QD and IR 5 mg BID were 84.5/68.0/31.1 and 79.8/68.3/46.2, respectively which are higher than that typically seen in the historical global studies of tofacitinib (IR) 5 mg BID in RA, but consistent with previous results with IR tofacitinib in Japan. These categorical measures such as the ACR20 and ACR50 were nearly superimposable, while ACR70 seemed higher in the IR arm of this study. The overall magnitude of these responses was substantial. Due to lack of a placebo arm in the same

study, the placebo adjusted effect is unknown.Remission at Week 12, as Assessed by DAS28-4(CRP) <2.6 and DAS28-4(ESR) <2.6:

Table 7 shows the rates of patients achieving DAS28-4(CRP) <2.6 and DAS28-4(ESR) <2.6 at Week 12 (FAS, NRI, LOCF and no imputation).

There was a difference in the proportion of patients achieving remission. Remission response rate assessed by DAS28-4(CRP) <2.6 and DAS28-4(ESR) <2.6 at Week 12 was nominally significantly higher in the tofacitinib 5 mg BID group as compared with the 11 mg QD group (p<0.0051). More than 50% of patients in both the treatment groups achieved remission as assessed by DAS28-4(CRP) <2.6 at Week 12.

Table 7. Normal Approximation to Rate of Patients (%) Achieving DAS28-4(CRP) <2.6 and DAS28-4(ESR) <2.6 at Week 12 (FAS, NRI, LOCF and No Imputation)

Treatment Group	N	n	Response Rate	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
				Difference	95% Confidence Interval	
					Lower	Upper
DAS28-4(CRP) <2.6 rates (NRI)						
Tofacitinib 11 mg QD	103	52	50.49	-18.75	-31.86	-5.63
Tofacitinib 5 mg BID	104	72	69.23			
DAS28-4(CRP) <2.6 rates (LOCF)						
Tofacitinib 11 mg QD	103	53	51.46	-18.74	-31.79	-5.68
Tofacitinib 5 mg BID	104	73	70.19			
DAS28-4(CRP) <2.6 rates (no imputation)						
Tofacitinib 11 mg QD	100	52	52.00	-23.79	-36.83	-10.75
Tofacitinib 5 mg BID	95	72	75.79			
DAS28-4(ESR) <2.6 rates (NRI)						
Tofacitinib 11 mg QD	103	18	17.48	-17.14	-28.86	-5.42
Tofacitinib 5 mg BID	104	36	34.62			
DAS28-4(ESR) <2.6 rates (LOCF)						
Tofacitinib 11 mg QD	103	18	17.48	-17.14	-28.86	-5.42
Tofacitinib 5 mg BID	104	36	34.62			
DAS28-4(ESR) <2.6 rates (no imputation)						
Tofacitinib 11 mg QD	99	18	18.18	-19.71	-32.08	-7.35
Tofacitinib 5 mg BID	95	36	37.89			

Abbreviations: BID=Twice daily; DAS28-4(CRP)=Disease activity score defined using 28 joint counts and C-reactive protein; DAS28-4(ESR)=Disease activity score defined using 28 joint counts and erythrocyte sedimentation rate; LOCF=Last observation carried forward; N=Total number of patients; n=Number of patients; NRI=Non-responder imputation; QD=Once daily.

LDA at Week 12, as Assessed by DAS28-4(CRP) ≤3.2 and DAS28-4(ESR) ≤3.2:

Table 8 shows the rate of patients achieving DAS28-4(CRP) ≤3.2 and DAS28-4(ESR) ≤3.2 at Week 12 (FAS, NRI, LOCF and no imputation).

LDA response rate as assessed by DAS28-4(CRP) ≤3.2 and DAS28-4(ESR) ≤3.2 at Week 12 was higher in tofacitinib 5 mg BID group compared with the 11 mg QD group (p<0.3912).

More than 40% of patients in both treatment groups achieved LDA as assessed by DAS28-4(CRP) ≤3.2 and DAS28-4(ESR) ≤3.2 at Week 12.

Table 8. Normal Approximation to Rate of Patients (%) Achieving DAS28-4(CRP) ≤3.2 and DAS28-4(ESR) ≤3.2 at Week 12 (FAS, NRI, LOCF and No Imputation)

Treatment Group	N	n	Response Rate	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
				Difference	95% Confidence Interval	
					Lower	Upper
Normal approximation to DAS28-4(CRP) ≤3.2 rates per visit (FAS, NRI)						
Tofacitinib 11 mg QD	103	76	73.79	-5.06	-16.62	6.51
Tofacitinib 5 mg BID	104	82	78.85			
Normal approximation to DAS28-4(CRP) ≤3.2 rates per visit (FAS, LOCF)						
Tofacitinib 11 mg QD	103	78	75.73	-6.00	-17.13	5.12
Tofacitinib 5 mg BID	104	85	81.73			
Normal approximation to DAS28-4(CRP) ≤3.2 rates per visit (FAS, no imputation)						
Tofacitinib 11 mg QD	100	76	76.00	-10.32	-21.17	0.54
Tofacitinib 5 mg BID	95	82	86.32			
Normal approximation to DAS28-4(ESR) ≤3.2 rates per visit (FAS, NRI)						
Tofacitinib 11 mg QD	103	44	42.72	-17.86	-31.26	-4.46
Tofacitinib 5 mg BID	104	63	60.58			
Normal approximation to DAS28-4(ESR) ≤3.2 rates per visit (FAS, LOCF)						
Tofacitinib 11 mg QD	103	44	42.72	-19.78	-33.12	-6.45
Tofacitinib 5 mg BID	104	65	62.50			
Normal approximation to DAS28-4(ESR) ≤3.2 rates per visit (FAS, no imputation)						
Tofacitinib 11 mg QD	99	43	43.43	-22.88	-36.51	-9.26
Tofacitinib 5 mg BID	95	63	66.32			

Abbreviations: BID=Twice daily; DAS28-4(CRP)=Disease activity score defined using 28 joint counts and C-reactive protein; DAS28-4(ESR)=Disease activity score defined using 28 joint counts and erythrocyte sedimentation rate; LOCF=Last observation carried forward; N=Total number of patients; n=Number of patients; NRI=Non-responder imputation; QD=Once daily.

Change From Baseline in HAQ-DI at Week 12:

Table 9 represents the LS mean changes from baseline at Weeks 4 and 12 (FAS) in HAQ-DI for the treatment groups. The tofacitinib 5 mg BID and tofacitinib 11 mg QD patients demonstrated similar and clinically meaningful changes in HAQ-DI scores at Week 4 and Week 12 (p≥0.0612).

Table 9. Statistical Analysis of Change From Baseline in HAQ-DI per Visit (FAS, Longitudinal Model)

Visit	Treatment Group	N	LS Mean	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
				Difference	95% Confidence Interval	
					Lower	Upper
Week 4	Tofacitinib 11 mg QD	103	-0.26	0.09	0.00	0.19
	Tofacitinib 5 mg BID	104	-0.35			
Week 12	Tofacitinib 11 mg QD	99	-0.44	0.02	-0.09	0.13
	Tofacitinib 5 mg BID	95	-0.46			

The fixed effects of actual baseline values, treatment, visit, and treatment-by-visit interaction were included, unstructured covariance matrices was used.
Abbreviations: BID=Twice daily; HAQ-DI=Health assessment questionnaire-disability index; FAS=Full analysis set; LS=Least square; N=Number of patients; QD=Once daily.

HAQ-DI Response (Decrease of at Least 0.22) at Week 12:

Table 10 shows the normal approximation to rates of at least 0.22 improvement in HAQ-DI Week 12. A majority of patients in each treatment arm achieved this level of improvement. There was no statistically significant treatment difference observed in HAQ-DI response (decrease of at least 0.22). Both treatment arms achieved the minimal clinically important difference (0.22) for the HAQ-DI by Week 4, and responses were nearly identical between tofacitinib 11 mg QD and tofacitinib 5 mg BID at Week 12.

Table 10. Normal Approximation to Rates of Patients (%) With at Least 0.22 Improvement in HAQ-DI at Week 12 (FAS, NRI, LOCF and no Imputation)

Treatment Group	N	n	Response Rate	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
				Difference	95% Confidence Interval	
					Lower	Upper
NRI						
Tofacitinib 11 mg QD	103	65	63.11	5.41	-7.89	18.72
Tofacitinib 5 mg BID	104	60	57.69			
LOCF						
Tofacitinib 11 mg QD	103	67	65.05	2.55	-10.54	15.64
Tofacitinib 5 mg BID	104	65	62.50			
No imputation						
Tofacitinib 11 mg QD	99	64	64.65	1.49	-12.03	15.01
Tofacitinib 5 mg BID	95	60	63.16			

Abbreviations: BID=Twice daily; FAS=Full analysis set; HAQ-DI=Health assessment questionnaire-disability index; LOCF=Last observation carried forward; N=Number of patients; n=Number of patients with specified criteria; NRI=Non-responder imputation; QD=Once daily.

Change From Baseline in the SF-36 8 Domain Scores and 2 Component Scores at Week 12:

Table 11 shows the statistical analysis of change from baseline in SF-36 Mental Component at Week 12.

In general, improvements in SF-36 scores for patients who received tofacitinib 5 mg BID were numerically greater than for those who received tofacitinib 11 mg QD but this did not reach statistical significance.

Table 11. Statistical Analysis of Change From Baseline in SF-36 Mental Component Score per Visit (FAS, Longitudinal Model)

Visit	Treatment Group	N	LS Mean	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
				Difference	95% Confidence Interval	
					Lower	Upper
Week 4	Tofacitinib 11 mg QD	103	3.25	-0.78	-2.72	1.16
	Tofacitinib 5 mg BID	104	4.03			
Week 12	Tofacitinib 11 mg QD	99	5.29	0.21	-1.92	2.34
	Tofacitinib 5 mg BID	95	5.08			

The fixed effects of actual baseline values, treatment, visit, and treatment-by-visit interaction were included, unstructured covariance matrices was used.
Abbreviations: BID=Twice daily; FAS=Full analysis set; LS=Least square; N=Number of patients; QD=Once daily; SF-36=Short Form-36.

Change From Baseline in the FACIT-Fatigue Scale at Week 12:

Table 12 shows the statistical analysis of change from baseline in FACIT-fatigue scale at Week 12.

There were no statistically significant changes observed between the treatments for FACIT-fatigue scale at Week 12 (p=0.3753).

Table 12. Statistical Analysis of Change From Baseline in FACIT-Fatigue Scale per Visit (FAS, ANCOVA Model)

Visit	Treatment Group	N	LS Mean	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
				Difference	95% Confidence Interval	
					Lower	Upper
Week 12	Tofacitinib 11 mg QD	99	5.28	-0.84	-2.70	1.02
	Tofacitinib 5 mg BID	95	6.12			

The fixed effects of actual baseline values and treatment were included.
Abbreviations: ANCOVA=Analysis of covariance; BID=Twice daily; FACIT= Functional assessment of chronic illness therapy; FAS=Full analysis set; LS=Least square; N=Number of patients; QD=Once daily.

Change From Baseline in the EQ-5D at Week 12:

Table 13 shows the statistical analysis of change from baseline in EuroQol EQ-5D health state profile-utility score at Week 12.

Change in EuroQol EQ-5D health state profile-utility score was significantly greater for patients who received tofacitinib 5 mg BID compared with tofacitinib 11 mg QD (p=0.0483).

Table 13. Statistical Analysis of Change From Baseline in EuroQol EQ-5D Health State Profile-Utility Score per Visit (FAS, ANCOVA Model)

Visit	Treatment Group	N	LS Mean	Comparison Between 11 mg QD Versus 5 mg BID (11 mg QD – 5 mg BID)		
				Difference	95% Confidence Interval	
					Lower	Upper
Week 12	Tofacitinib 11 mg QD	99	0.20	-0.05	-0.10	0.00
	Tofacitinib 5 mg BID	95	0.25			

The fixed effects of actual baseline values and treatment were included.
Abbreviations: ANCOVA=Analysis of covariance; BID=Twice daily; EuroQol EQ-5D= European Quality of Life-5 dimensions questionnaire; FAS=Full analysis set; LS=Least square; N=Number of patients; QD=Once daily.

Safety Results:

Serious Adverse Events:

Overall, 5 patients in the tofacitinib 11 mg QD group and 4 patients in the tofacitinib 5 mg BID group experienced at least 1 SAE after dosing. The treatment-emergent SAEs by system organ class (SOC) and preferred term is presented in Table 14.

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 19.1) Preferred Term	Tofacitinib 11 mg QD	Tofacitinib 5 mg BID
Evaluable for Adverse Events	**104**	**105**
With Adverse Events	**5 (4.81)**	**4 (3.81)**
Blood and lymphatic system disorders	0	1 (0.95)
Anaemia	0	1 (0.95)
Infections and infestations	3 (2.88)	3 (2.86)
Pneumocystis jirovecii pneumonia	2 (1.92)	1 (0.95)
Pneumonia	1 (0.96)	1 (0.95)
Pneumonia bacterial	0	1 (0.95)
Injury, poisoning and procedural complications	1 (0.96)	0
Femoral neck fracture	1 (0.96)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.96)	0
Rectal cancer	1 (0.96)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.95)
Interstitial lung disease	0	1 (0.95)

Subjects were only counted once per treatment for each row.
Included data up to 999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (Version 19.1) coding dictionary applied.
Abbreviations: BID=Twice daily; incl=inclusive; MedDRA=Medical Dictionary for Regulatory Activities; QD=Once daily.

Adverse Events:

All-causality and treatment-related treatment-emergent AEs (TEAEs) are summarized in Table 15 and Table 16, respectively. The most frequently reported all-causalities and treatment-related AEs by preferred term were nasopharyngitis, blood creatine phosphokinase increased, and hepatic function abnormal (in both treatment groups).

Table 15. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 19.1) Preferred Term	Tofacitinib 11 mg QD	Tofacitinib 5 mg BID
Evaluable for Adverse Events	**104**	**105**
With Adverse Events	**54 (51.92)**	**52 (49.52)**
Blood and lymphatic system disorders	2 (1.92)	0
Iron deficiency anaemia	1 (0.96)	0
Leukopenia	1 (0.96)	0
Cardiac disorders	1 (0.96)	1 (0.95)
Cardiac failure	1 (0.96)	0
Palpitations	0	1 (0.95)
Ear and labyrinth disorders	1 (0.96)	2 (1.90)
Sudden hearing loss	0	1 (0.95)
Tinnitus	0	1 (0.95)
Vertigo	1 (0.96)	0
Eye disorders	2 (1.92)	1 (0.95)
Dry eye	1 (0.96)	0
Keratitis	0	1 (0.95)
Vision blurred	1 (0.96)	0
Gastrointestinal disorders	15 (14.42)	11 (10.48)
Abdominal discomfort	3 (2.88)	0
Abdominal pain upper	3 (2.88)	2 (1.90)
Constipation	1 (0.96)	2 (1.90)
Diarrhoea	3 (2.88)	1 (0.95)
Duodenal ulcer	1 (0.96)	0
Gastric polyps	1 (0.96)	0
Gastrooesophageal reflux disease	1 (0.96)	0
Large intestine polyp	0	2 (1.90)
Mouth ulceration	1 (0.96)	0
Nausea	1 (0.96)	1 (0.95)
Stomatitis	2 (1.92)	3 (2.86)
Tooth loss	0	1 (0.95)
Vomiting	1 (0.96)	1 (0.95)
General disorders and administration site conditions	2 (1.92)	3 (2.86)
Feeling hot	0	1 (0.95)
Malaise	1 (0.96)	1 (0.95)
Pyrexia	1 (0.96)	1 (0.95)
Hepatobiliary disorders	4 (3.85)	4 (3.81)
Hepatic function abnormal	3 (2.88)	4 (3.81)
Liver disorder	1 (0.96)	0
Immune system disorders	1 (0.96)	0
Seasonal allergy	1 (0.96)	0
Infections and infestations	18 (17.31)	25 (23.81)
Bronchitis	1 (0.96)	3 (2.86)
Bursitis infective	0	1 (0.95)
Cystitis	0	1 (0.95)
Enteritis infectious	1 (0.96)	0
Helicobacter infection	1 (0.96)	0
Herpes virus infection	0	1 (0.95)

Table 15. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 19.1) Preferred Term	Tofacitinib 11 mg QD	Tofacitinib 5 mg BID
Evaluable for Adverse Events	**104**	**105**
With Adverse Events	**54 (51.92)**	**52 (49.52)**
Herpes zoster	1 (0.96)	1 (0.95)
Infective tenosynovitis	0	1 (0.95)
Influenza	0	2 (1.90)
Nasopharyngitis	10 (9.62)	13 (12.38)
Oral herpes	1 (0.96)	2 (1.90)
Periodontitis	0	1 (0.95)
Pharyngitis	1 (0.96)	0
Sinusitis	0	1 (0.95)
Tinea pedis	0	2 (1.90)
Upper respiratory tract infection	1 (0.96)	0
Urinary tract infection	1 (0.96)	0
Injury, poisoning and procedural complications	2 (1.92)	3 (2.86)
Bone contusion	0	1 (0.95)
Contusion	0	1 (0.95)
Fall	1 (0.96)	2 (1.90)
Post-traumatic neck syndrome	0	1 (0.95)
Skin abrasion	0	1 (0.95)
Spinal compression fracture	1 (0.96)	1 (0.95)
Investigations	12 (11.54)	13 (12.38)
Alanine aminotransferase increased	0	2 (1.90)
Aspartate aminotransferase increased	0	3 (2.86)
Blood cholesterol increased	3 (2.88)	2 (1.90)
Blood creatine phosphokinase increased	4 (3.85)	2 (1.90)
Blood triglycerides increased	1 (0.96)	2 (1.90)
Blood urine present	0	1 (0.95)
Gamma-glutamyl transferase increased	1 (0.96)	2 (1.90)
Hepatic enzyme increased	1 (0.96)	1 (0.95)
Lipids abnormal	1 (0.96)	2 (1.90)
Low density lipoprotein increased	2 (1.92)	0
Lymphocyte count decreased	1 (0.96)	0
Weight increased	1 (0.96)	0
Metabolism and nutrition disorders	2 (1.92)	1 (0.95)
Dyslipidaemia	1 (0.96)	0
Hypercholesterolaemia	1 (0.96)	0
Hyperuricaemia	0	1 (0.95)
Musculoskeletal and connective tissue disorders	3 (2.88)	1 (0.95)
Back pain	1 (0.96)	0
Musculoskeletal stiffness	1 (0.96)	0
Pain in extremity	1 (0.96)	0
Rheumatoid arthritis	1 (0.96)	0
Spinal osteoarthritis	0	1 (0.95)
Nervous system disorders	8 (7.69)	3 (2.86)
Dizziness postural	1 (0.96)	0
Dysgeusia	1 (0.96)	0

Table 15. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 19.1) Preferred Term	Tofacitinib 11 mg QD	Tofacitinib 5 mg BID
Evaluable for Adverse Events	**104**	**105**
With Adverse Events	**54 (51.92)**	**52 (49.52)**
Head discomfort	2 (1.92)	0
Headache	1 (0.96)	2 (1.90)
Post herpetic neuralgia	1 (0.96)	1 (0.95)
Sciatica	1 (0.96)	0
Somnolence	1 (0.96)	0
Psychiatric disorders	1 (0.96)	0
Alcoholic hangover	1 (0.96)	0
Respiratory, thoracic and mediastinal disorders	3 (2.88)	6 (5.71)
Cough	0	1 (0.95)
Oropharyngeal pain	2 (1.92)	0
Rhinitis allergic	0	1 (0.95)
Upper respiratory tract inflammation	1 (0.96)	3 (2.86)
Vasomotor rhinitis	0	1 (0.95)
Skin and subcutaneous tissue disorders	4 (3.85)	4 (3.81)
Alopecia	0	1 (0.95)
Dermatitis contact	1 (0.96)	0
Drug eruption	1 (0.96)	1 (0.95)
Eczema	0	1 (0.95)
Ingrowing nail	0	1 (0.95)
Pruritus	0	1 (0.95)
Rash	2 (1.92)	0
Vascular disorders	0	1 (0.95)
Hot flush	0	1 (0.95)

Subjects were only counted once per treatment for each row.
Included data up to 999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (Version 19.1) coding dictionary applied.
Abbreviations: BID=Twice daily; MedDRA=Medical Dictionary for Regulatory Activities; QD=Once daily.

Table 16. Incidence of Treatment-Emergent Adverse Events – Treatment-Related

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 19.1) Preferred Term	Tofacitinib 11 mg QD	Tofacitinib 5 mg BID
Evaluable for Adverse Events	**104**	**105**
Blood and lymphatic system disorders	1 (1.0)	1 (1.0)
Anaemia	0	1 (1.0)
Iron deficiency anaemia	0	0
Leukopenia	1 (1.0)	0
Cardiac disorders	0	1 (1.0)
Cardiac failure	0	0
Palpitations	0	1 (1.0)
Ear and labyrinth disorders	1 (1.0)	0
Sudden hearing loss	0	0
Tinnitus	0	0
Vertigo	1 (1.0)	0
Eye disorders	0	1 (1.0)
Dry eye	0	0
Keratitis	0	1 (1.0)
Vision blurred	0	0
Gastrointestinal disorders	4 (3.8)	3 (2.9)
Abdominal discomfort	1 (1.0)	0
Abdominal pain upper	2 (1.9)	0
Constipation	0	2 (1.9)
Diarrhoea	0	0
Duodenal ulcer	0	0
Gastric polyps	0	0
Gastrooesophageal reflux disease	0	0
Large intestine polyp	0	0
Mouth ulceration	0	0
Nausea	1 (1.0)	1 (1.0)
Stomatitis	1 (1.0)	1 (1.0)
Tooth loss	0	0
Vomiting	1 (1.0)	0
General disorders and administration site conditions	2 (1.9)	2 (1.9)
Feeling hot	0	1 (1.0)
Malaise	1 (1.0)	1 (1.0)
Pyrexia	1 (1.0)	0
Hepatobiliary disorders	4 (3.8)	4 (3.8)
Hepatic function abnormal	3 (2.9)	4 (3.8)
Liver disorder	1 (1.0)	0
Immune system disorders	0	0
Seasonal allergy	0	0
Infections and infestations	14 (13.5)	19 (18.1)
Bronchitis	0	2 (1.9)
Bursitis infective	0	1 (1.0)
Cystitis	0	0
Enteritis infectious	1 (1.0)	0
Helicobacter infection	0	0
Herpes virus infection	0	1 (1.0)
Herpes zoster	1 (1.0)	1 (1.0)

Table 16. Incidence of Treatment-Emergent Adverse Events – Treatment-Related

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 19.1) Preferred Term	Tofacitinib 11 mg QD	Tofacitinib 5 mg BID
Evaluable for Adverse Events	**104**	**105**
Infective tenosynovitis	0	1 (1.0)
Influenza	0	2 (1.9)
Nasopharyngitis	6 (5.8)	7 (6.7)
Oral herpes	1 (1.0)	2 (1.9)
Periodontitis	0	1 (1.0)
Pharyngitis	1 (1.0)	0
Pneumocystis jirovecii pneumonia	2 (1.9)	1 (1.0)
Pneumonia	1 (1.0)	1 (1.0)
Pneumonia bacterial	0	1 (1.0)
Sinusitis	0	1 (1.0)
Tinea pedis	0	1 (1.0)
Upper respiratory tract infection	0	0
Urinary tract infection	1 (1.0)	0
Injury, poisoning and procedural complications	0	0
Bone contusion	0	0
Contusion	0	0
Fall	0	0
Femoral neck fracture	0	0
Post-traumatic neck syndrome	0	0
Skin abrasion	0	0
Spinal compression fracture	0	0
Investigations	9 (8.7)	13 (12.4)
Alanine aminotransferase increased	0	2 (1.9)
Aspartate aminotransferase increased	0	3 (2.9)
Blood cholesterol increased	3 (2.9)	2 (1.9)
Blood creatine phosphokinase increased	3 (2.9)	2 (1.9)
Blood triglycerides increased	1 (1.0)	2 (1.9)
Blood urine present	0	1 (1.0)
Gamma-glutamyltransferase increased	1 (1.0)	2 (1.9)
Hepatic enzyme increased	0	1 (1.0)
Lipids abnormal	1 (1.0)	2 (1.9)
Low-density lipoprotein increased	2 (1.9)	0
Lymphocyte count decreased	1 (1.0)	0
Weight increased	0	0
Metabolism and nutrition disorders	1 (1.0)	1 (1.0)
Dyslipidaemia	0	0
Hypercholesterolaemia	1 (1.0)	0
Hyperuricaemia	0	1 (1.0)
Musculoskeletal and connective tissue disorders	0	0
Back pain	0	0
Musculoskeletal stiffness	0	0
Pain in extremity	0	0
Rheumatoid arthritis	0	0
Spinal osteoarthritis	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	0

Table 16. Incidence of Treatment-Emergent Adverse Events – Treatment-Related

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 19.1) Preferred Term	Tofacitinib 11 mg QD	Tofacitinib 5 mg BID
Evaluable for Adverse Events	**104**	**105**
Rectal cancer	1 (1.0)	0
Nervous system disorders	3 (2.9)	2 (1.9)
Dizziness postural	0	0
Dysgeusia	0	0
Head discomfort	2 (1.9)	0
Headache	1 (1.0)	2 (1.9)
Post herpetic neuralgia	0	0
Sciatica	0	0
Somnolence	0	0
Psychiatric disorders	0	0
Alcoholic hangover	0	0
Respiratory, thoracic and mediastinal disorders	1 (1.0)	2 (1.9)
Cough	0	0
Interstitial lung disease	0	1 (1.0)
Oropharyngeal pain	1 (1.0)	0
Rhinitis allergic	0	0
Upper respiratory tract inflammation	0	1 (1.0)
Vasomotor rhinitis	0	0
Skin and subcutaneous tissue disorders	0	2 (1.9)
Alopecia	0	1 (1.0)
Dermatitis contact	0	0
Drug eruption	0	0
Eczema	0	1 (1.0)
Ingrowing nail	0	0
Pruritus	0	0
Rash	0	0
Vascular disorders	0	1 (1.0)
Hot flush	0	1 (1.0)
Total preferred term events	46	61

Patients were counted only once per treatment in each row.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (Version 19.1) coding dictionary applied.
Abbreviations: BID=Twice daily; incl=inclusive; MedDRA=Medical Dictionary for Regulatory Activities; QD=Once daily.

Permanent Discontinuations due to Adverse Events: The incidence of TEAEs leading to discontinuations is presented in Table 17. The most frequent AEs resulting in discontinuation overall were in the infections and infestations SOC (which occurred in 2 [1.9%] patients in the tofacitinib 11 mg QD group and 6 [5.7%] patients in the tofacitinib 5 mg BID group). The AEs leading to discontinuations were more frequent in the tofacitinib 5 mg BID group (13 TEAEs) as compared to the tofacitinib 11 mg QD group (3 TEAEs).

Table 17. Incidence of Treatment-Emergent Adverse Events Leading to Discontinuations

Number (%) of Patients With Adverse Events by: System Organ Class MedDRA Preferred Term	Tofacitinib 11 mg QD (N=104) n (%)	Tofacitinib 5 mg BID (N=105) n (%)
Blood and lymphatic system disorders	0	1 (1.0)
Anaemia	0	1 (1.0)
General disorders and administration site conditions	0	2 (1.9)
Feeling hot	0	1 (1.0)
Malaise	0	1 (1.0)
Infections and infestations	2 (1.9)	6 (5.7)
Bursitis infective	0	1 (1.0)
Cystitis	0	1 (1.0)
Infective tenosynovitis	0	1 (1.0)
Pneumocystis jirovecii pneumonia	1 (1.0)	1 (1.0)
Pneumonia	1 (1.0)	1 (1.0)
Pneumonia bacterial	0	1 (1.0)
Sinusitis	0	1 (1.0)
Investigations	1 (1.0)	0
Lymphocyte count decreased	1 (1.0)	0
Nervous system disorders	0	1 (1.0)
Headache	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders	0	1 (1.0)
Interstitial lung disease	0	1 (1.0)
Vascular disorders	0	1 (1.0)
Hot flush	0	1 (1.0)
Total preferred term events	3	13

Patients were counted only once per treatment in each row.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (Version 19.1) coding dictionary applied.
Abbreviations: BID=Twice daily; MedDRA=Medical dictionary for Regulatory Activities; N=Number of patients in the treatment group; n=Number of patients with specified criteria; QD=Once daily.

Dose Reductions or Temporary Discontinuations due to Adverse Events: The most frequent AE resulting in temporary discontinuations or dose reductions overall was nasopharyngitis (which occurred in 3 [2.9%] patients in the tofacitinib 11 mg QD group and 2 [1.9%] patients in the tofacitinib 5 mg BID group).

Deaths: There were no deaths among patients who participated in this study.

Clinical Laboratory Evaluation:

Creatine Kinase: The mean change from baseline in creatinine kinase levels at Week 12 was lower in the tofacitinib 11 mg QD group (42.91 U/L) as compared to the tofacitinib 5 mg BID group (52.23 U/L).

Hemoglobin: At Week 4, 2 (1.9%) patients in both tofacitinib groups had mild to moderately decreased hemoglobin. However, at Week 12, the proportion of patients with mild to moderately decreased hemoglobin was more than twice that in the tofacitinib 5 mg BID group (7 [7.4%] patients) as compared to the tofacitinib 11 mg QD group (3 [3.0%] patients).

Neutrophil Counts:

Overall, the proportion of patients with mild neutropenia was ≤4.9%. One (1) patient at Week 4 in the tofacitinib 11 mg QD group and 1 patient at Week 12 in the tofacitinib 5 mg BID group had moderate to severe neutropenia. No patient had potentially life-threatening neutropenia in either of the treatment groups.

Lymphocyte Counts:

Overall, the proportion of patients with mild and moderate lymphopenia was similar in both treatment groups. However, severe lymphopenia was reported more than twice as frequently in the tofacitinib 11 mg QD group as compared to the tofacitinib 5 mg BID group. No patient had potentially life-threatening lymphopenia in either of the treatment groups.

Platelets: A numerically greater mean decrease from baseline in platelets was observed in the tofacitinib 11 mg QD group as compared to the tofacitinib 5 mg BID group.

Increases in Transaminases and Bilirubin: Overall, the proportions of patients (without regard to baseline abnormality) who had AST and bilirubin values ≥1 × upper limit of normal (ULN) were greater in the tofacitinib 11 mg QD group (18.3% for AST and 14.4% for bilirubin) than in the tofacitinib 5 mg BID group (15.2% for AST and 4.8% for bilirubin), however the proportions of patients who had ALT increased was greater in the tofacitinib 5 mg BID group (12.4%) than in the tofacitinib 11 mg QD group (7.7%).

Mean AST, ALT and total bilirubin concentrations were similar in both treatment groups.

Serum Creatinine: A numerically greater mean increase from baseline in serum creatinine was observed in the tofacitinib 5 mg BID group as compared to the tofacitinib 11 mg QD group; the difference was not statistically significant.

Creatinine Clearance: A numerically greater mean decrease from baseline in creatinine clearance was observed in the tofacitinib 5 mg BID group as compared to the tofacitinib 11 mg QD group at Week 4.

Lipids:

Low-Density Lipoprotein Cholesterol: A numerically smaller mean increase from baseline in LDL-C was observed in the tofacitinib 11 mg QD group as compared to the tofacitinib 5 mg BID group, however, the difference was not statistically significant.

High-Density Lipoprotein Cholesterol: A numerically smaller mean increase from baseline in HDL-C was observed in the tofacitinib 11 mg QD group as compared to the tofacitinib 5 mg BID group, however, the difference was not statistically significant.

Low-Density Lipoprotein Cholesterol/High-Density Lipoprotein Cholesterol Ratio: A numerically larger mean decrease from baseline in LDL-C/HDL-C ratio was observed in the tofacitinib 11 mg QD group as compared to the tofacitinib 5 mg BID group at Week 4. By

Week 12, however, the ratio was approaching baseline values. There were no statistically significant differences between the treatment groups.

Triglycerides: A numerically greater mean increase from baseline in triglycerides was observed in the tofacitinib 5 mg BID group as compared to the tofacitinib 11 mg QD group, however, the difference was not statistically significant.

Total Cholesterol: A numerically smaller mean increase from baseline in total cholesterol was observed in the tofacitinib 5 mg BID group as compared to the tofacitinib 11 mg QD group, however, the difference was not statistically significant.

Patients With Hyperlipidemia: A greater shift towards higher LDL-C values was observed in both treatment groups between the baseline and maximum observed values on treatment.

Vital Signs:

Blood Pressure Measurements: A numerically greater mean increase from baseline in systolic BP (SBP) up to Week 4 was observed in the tofacitinib 11 mg QD group as compared to the tofacitinib 5 mg BID group, however, the difference was not statistically significant. From Week 4 until Week 12, SBP declined to baseline levels in both groups.

A numerically greater mean increase from baseline in diastolic BP up to Week 4 was observed in the tofacitinib 5 mg BID group as compared to the tofacitinib 11 mg QD group and declined until Week 12 in both groups, however, these differences were not statistically significant.

Electrocardiogram: No clinically significant abnormalities in ECG data were found in either of the treatment groups.

Physical Examination: No clinically significant abnormalities in physical examination were found in either of the treatment groups.

Weight: The mean increase from baseline in weight and BMI was numerically similar in both treatment groups.

CONCLUSIONS:

- Non-inferiority was not demonstrated for tofacitinib MR 11 mg QD + MTX compared to tofacitinib IR 5 mg BID + MTX as the upper bound of the 95% CI for the change from baseline DAS28-4(CRP) was 0.69 and was greater than the pre-specified non-inferiority margin of 0.6.

- Both formulations resulted in clinically meaningful responses across all primary/secondary endpoints. Results are robust using various sensitivity analyses.

- The LS mean changes from baseline in DAS28-4(ESR) at Week 4 (-1.76 and -2.03 for MR 11 mg QD and 5 mg BID, respectively) and Week 12 (-2.50 and -2.86 for

MR 11 mg QD and 5 mg BID, respectively) showed clinically meaningful decreases from baseline (improvements).

- The overall magnitude of ACR20/50/70 response rates (NRI) in MR 11 mg QD and IR 5 mg BID was substantial and nearly superimposable for ACR20 (Week 12: 84.47% for tofacitinib 11 mg QD group and 79.81% for tofacitinib 5 mg BID group) and ACR50 (Week 12: 67.96% for tofacitinib 11 mg QD group and 68.27% for tofacitinib 5 mg BID group) while ACR70 (31.07 for tofacitinib 11 mg QD group and 46.15 for tofacitinib 5 mg BID group) seemed higher in the IR arm of this study.

- Remission response rate (NRI) assessed by DAS28-4(CRP) <2.6 and DAS28-4(ESR) <2.6 at Week 12 for tofacitinib 11 mg QD versus (vs) 5 mg BID was 50.49% vs 69.23% for DAS28-4(CRP) <2.6 and 17.48% vs 34.62% for DAS28-4(ESR) <2.6.

- LDA response rate as assessed by DAS28-4(CRP) ≤3.2 and DAS28-4(ESR) ≤3.2 at Week 12 for tofacitinib 11 mg QD vs 5 mg BID was 73.79% vs 78.85% for DAS28-4(CRP) ≤3.2 and 42.72% vs 60.58% for DAS28-4(ESR) ≤3.2.

- Remission response rate assessed by DAS28-4(CRP) <2.6 and DAS28-4(ESR) <2.6 at Week 12 was nominally significantly higher in the tofacitinib 5 mg BID group as compared with the 11 mg QD group (p<0.0051). As had been reported previously, there was a difference in the proportion of patients achieving remission. The overall magnitude of the clinical responses was higher than typically seen in the historical global studies of tofacitinib in RA, but consistent with RA-BID studies previously conducted in Japan. Overrepresentation of profound responders in Japan, may have facilitated the detection of even minimal differences between the 2 formulations.

- LDA response rate as assessed by DAS28-4(CRP) ≤3.2 and DAS28-4(ESR) ≤3.2 at Week 12 was higher in tofacitinib 5 mg BID group compared with the 11 mg QD group (p<0.3912).

- There was no statistically significant treatment difference observed in HAQ-DI response (decrease of at least 0.22) and FACIT-fatigue scale at Week 12.

- There was nominal significant difference observed in Simplified Disease Activity Index, Clinical Disease Activity Index, and ACR/EULAR Boolean-based remission at Week 12.

- Numerically greater improvements in SF-36 scores was observed for patients who received tofacitinib 5 mg BID as compared to tofacitinib 11 mg QD but the difference was not statistically significant.

- Change in EuroQol EQ-5D health state profile-utility score was significantly greater for patients who received tofacitinib 5 mg BID compared with tofacitinib 11 mg QD (p=0.0483).

- Tofacitinib was well tolerated in this study. There were no new safety signals in this study. Safety profiles of the IR and MR formulations were similar.

- There were no deaths among patients who participated in this study.

- Overall, 5 patients in the tofacitinib 11 mg QD group and 4 patients in the tofacitinib 5 mg BID group experienced at least 1 SAE after dosing. The most frequently reported SAE by preferred term were pneumocystis jirovecii pneumonia (in tofacitinib 11 mg QD group) and pneumonia (in both treatment groups).