Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Tofacitinib versus Methotrexate in Rheumatoid Arthritis

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Section 2. Key Exclusion Criteria and Key Secondary Endpoints

Key exclusion criteria were: prior treatment with lymphocyte-depleting or alkylating agents; hemoglobin <9.0 g/dL or hematocrit <30%, white blood cell count $<3.0 \times 10^9$/L, absolute neutrophil count $<1.2 \times 10^9$/L, or platelet count $<100 \times 10^9$/L; estimated glomerular filtration rate <60 mL/min (abbreviated Modification of Diet in Renal Disease calculation); aspartate aminotransferase or alanine aminotransferase >1.5× the upper limit of normal; history of another autoimmune rheumatic disease except Sjögren's syndrome; history of serious infection, including hepatitis B/C or human immunodeficiency virus; evidence of active, latent or inadequately treated *Mycobacterium tuberculosis* infection; history of lymphoproliferative disorder; history of malignancy except adequately treated non-metastatic basal/squamous cell cancer of the skin or cervical carcinoma in situ.

Additional key secondary endpoints to those described in the article included (at all visits, unless stated otherwise): (i) the proportions of patients achieving ACR20/50/70 response (ACR70 response at Month 6 co-primary endpoint); (ii) change from baseline in physical function measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) (range 0–3: 0–1, mild to moderate physical difficulty; >1–2, moderate to severe disability; >2–3, severe to very severe disability);[1,2] (iii) the proportion of patients achieving Disease Activity Score (DAS) <2.6 (DAS28-remission) and ≤3.2 (low disease activity) in 28 joints based on DAS28-4(ESR) (range 0–9.4)[3] (a composite index of four weighted variables: 28 tender joint-count [range 0–28]; 28 swollen joint-count [range 0–28]; (iv) the level of disease activity is interpreted as low [DAS28≤3.2], moderate [3.2<DAS28≤5.1] or high [DAS28>5.1]; as per these criteria, DAS28<2.6 corresponds to being in remission;[4-6] (v) ESR [range 0–150]; Patient's Global Assessment of Disease Activity on a visual analog scale [range 0–100]; (vi) Patient's Assessment of Arthritis Pain on a visual analog scale [range 0–

100], and; (vii) the Functional Assessment of Chronic Illness Therapy-Fatigue (13-item questionnaire; range 0–52; higher scores represent less fatigue)[7] at Month 6.

Section 3. Statistical Analysis

The full analysis set for efficacy and safety included all randomized patients who received ≥1 dose of study medication and had a baseline and at least one post-baseline measurement.

To control the type I error rate in the primary analyses, co-primary efficacy endpoints were assessed sequentially using a step-down approach where statistical significance could be claimed:

- For tofacitinib 10 mg twice daily difference from methotrexate in progression in modified Total Sharp Score (mTSS), if P≤0.05.
- For tofacitinib 5 mg twice daily difference from methotrexate in progression in mTSS, if P≤0.05 and tofacitinib 10 mg difference from methotrexate in progression in mTSS also had P≤0.05.
- For tofacitinib 10 mg twice daily difference from methotrexate in rates of ACR70 response, if P≤0.05 and tofacitinib 10 mg difference from methotrexate in progression in mTSS also had P≤0.05.
- For tofacitinib 5 mg twice daily difference from methotrexate in rates of ACR70 response, if P≤0.05 and tofacitinib 10 mg difference from methotrexate in rates of ACR70 also had P≤0.05, and tofacitinib 5 mg difference from methotrexate in progression in mTSS if P ≤0.05 (Fig. S1)

No adjustment for multiple comparisons was applied to secondary endpoints; P≤0.05 was considered to indicate statistical significance.

The primary analysis for the change in mTSS from baseline to Month 6 was conducted by an analysis of covariance model that included baseline mTSS, duration of rheumatoid arthritis

and geographic region as covariates. For the primary analysis of mTSS and its components (erosion score and JSN score), missing values due to patient withdrawal were linearly extrapolated based on the baseline value and the post-baseline value prior to withdrawal. For the analysis of ACR70 response rates and other binary endpoints, the normal approximation for the difference in binomial proportions was used to test the superiority of each dose of tofacitinib to methotrexate. Missing values due to a patient dropping from the study for any reason were handled by setting the value to non-responsive (non-responder imputation; also applied to secondary endpoints with binary variables). HAQ-DI was expressed as least squares mean change from baseline and analyzed using a mixed-effect longitudinal model that included fixed effects of treatment, visit and treatment-by-visit interaction and covariates of baseline HAQ-DI, duration of rheumatoid arthritis and geographic region; patients were a random effect. Remaining continuous endpoints also followed this analysis. Safety data were summarized descriptively, and as least squares means for selected variables.

Section 4. Summary Narratives for Confirmed (n=6) and Unconfirmed Malignancies (n=1)

Confirmed

1. A 65-year-old man in the tofacitinib 10 mg twice daily treatment group discontinued the study due to high-grade B-cell Burkitt-like lymphoma on Day 149. The investigator considered the event to be related to study medication. His last dose of study medication was on Day 171. A fine-needle biopsy of the neck showed B-cell non-Hodgkin lymphoma. Staining for Epstein-Barr virus (EBV)-positive cells was equivocal. On Day 185, the patient was given chemotherapy and transferred to the local hospital for palliative care. As of the cut-off date for the 1-year analysis, no further information was available. The patient withdrew consent for further contact.

2. A 61-year-old woman in the tofacitinib 10 mg twice daily group experienced a serious adverse event of colon cancer. Relevant medical history included abdominal pain at the start of the study. The patient discontinued study medication on Day 351. On Day 378, the onset date of event was reported, which corresponded to the date of the first computed tomography scan diagnosing the mass itself. Records did not show any treatment given for the colon cancer. Approximately 5 months later, the patient developed a cerebrovascular accident, pneumonia, nervous system disorder, and disseminated intravascular coagulation considered medically significant. The patient died in her sleep. No autopsy was performed. Per the investigator, these events were considered to be not related to study drug.

3. A 65-year-old man in the tofacitinib 10 mg twice daily group had a prostate-specific antigen (PSA) level of 2.9 ng/mL several years prior to the study. The patient was randomized to treatment and PSA increased to 4.25 ng/mL after approximately 200 days of treatment. Following more than a year of study treatment, his PSA level was 5.99 ng/mL. A pathology report confirmed prostatic adenocarcinoma. Study drug was withdrawn shortly

thereafter. A month later, the patient was reported recovered from event after prostatic resection. The investigator considered the event to be not related to study drug, but likely to a pre-existing condition.

4. A 63-year-old man in the tofacitinib 5 mg twice daily group developed leukocytosis at approximately 3 months, and proliferation of lymphoid tissue at approximately 6 months, after the data cut-off date. Study medication was discontinued at this time. A specific diagnosis of T-lymphoproliferative T-cell chronic lymphocytic leukemia – non-Hodgkin lymphoma was made 3 months later (9 months after the data cut-off date). Staining for EBV-positive cells was reported as negative. Relevant medical history included splenectomy in 2003 due to suspected Felty's syndrome. The investigator considered the event to be unrelated to study drug.

5 A 71-year-old women in the tofacitinib 5 mg twice daily group died 765 days after the first dose of study medication. The cause of death was reported as diffuse non-Hodgkin lymphoma. The patient's previous medical history included cholelithiasis with cholecystectomy, ongoing cholestasis, ongoing varicose veins, ongoing osteochondrosis, urolithiasis and arterial hypertension. Concomitant medications included oral prednisolone, oral drotaverine hydrochloride, oral herbal (not otherwise specified) minerals and oral indapamide. Study medication was discontinued after Day 723. The patient died on Day 765, 12 days after being urgently hospitalized with a preliminary diagnosis of degenerative vertebral disease: paraparesis of lower extremities, hemorrhagic cystitis. The investigator reported the cause of death as diffuse non-Hodgkin lymphoma and considered there was a reasonable possibility that the event was related to study drug.

6. A 61-year-old woman in the methotrexate group reported diagnosis of cancer of stomach confirmed by gastroscopy at Day 412. The patient was receiving 20 mg

methotrexate/week at the time of the event. Study medication was discontinued after Day 357. Following subtotal resection of stomach and lymph nodes, the patient was considered to have recovered with sequelae. The investigator considered there was a reasonable possibility that the event was related to study drug.

Unconfirmed

1. An adrenal adenoma with cellular atypia, which the local pathologist was unable to confirm as malignant or benign, was also reported in a 38-year-old male receiving tofacitinib 5 mg twice daily. On Day 139, a computed tomography scan was performed, which was suggestive of suprarenal adenoma. The patient was admitted to hospital on Day 148 for adrenalectomy and cholecystectomy. A right adrenalectomy was performed on Day 150 to remove a right suprarenal adenoma; cholecystectomy was also performed on this date. The patient recovered from the event of adrenal adenoma on Day 150. The patient was withdrawn from the study on Day 174 in response to the events of osteonecrosis and adrenal adenoma. The last dose of tofacitinib tablets was administered on Day 126. The investigator considered there was not a reasonable possibility that the event was related to study drug.

Section 5. Summary Narratives for Deaths (n=4)

1. A 61-year-old woman in the tofacitinib 10 mg twice daily group had a serious adverse event of colon cancer. The patient discontinued study medication on Day 351. On Day 378, the onset date of event was reported, which corresponded to the date of the first computed tomography scan diagnosing the mass itself. Records did not show any treatment given for the colon cancer. Approximately 5 months later, the patient developed cerebrovascular accident, pneumonia, nervous system disorder, and disseminated intravascular coagulation considered medically significant. The patient died in her sleep approximately 530 days after the first dose of study medication. No autopsy was performed. These events were considered to be not related to study drug by the investigator.

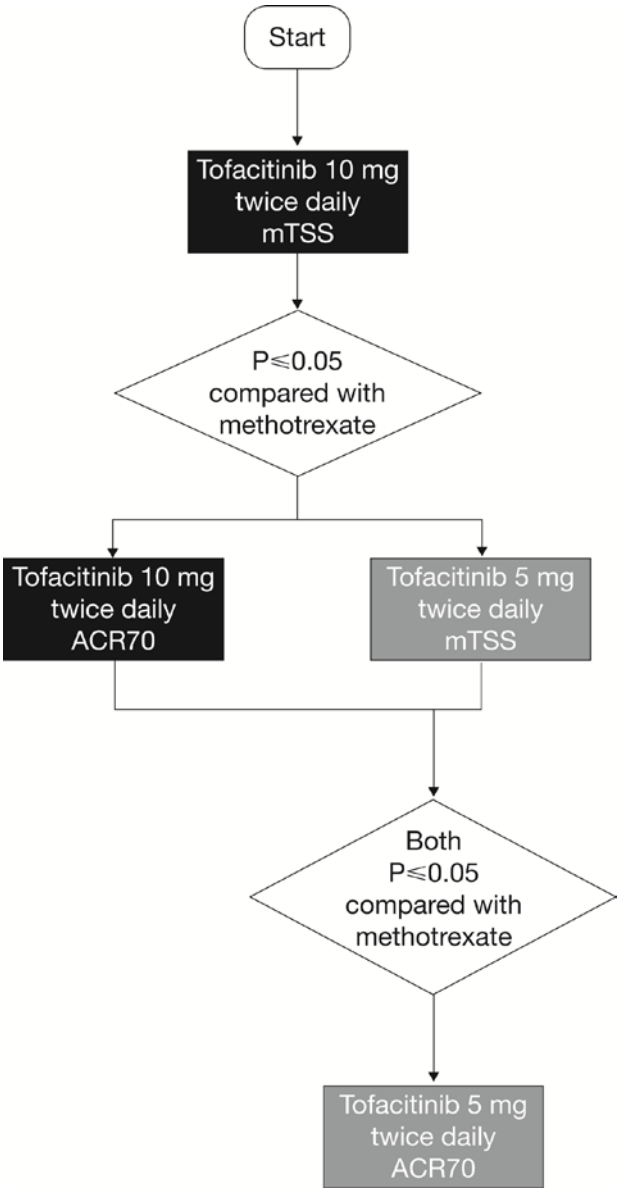
2. A 53-year-old woman in the tofacitinib 5 mg twice daily group was found dead at home 472 days after the first dose of study medication. The probable cause of the patient's death was myocardial infarction. The investigator reported the event term as "Death – unknown causes." No autopsy was performed. The patient had no prior medical history of any cardiovascular disease other than systemic arterial hypertension; after review of the information available, the external Cardiac Adjudication Review Committee determined this case as Sudden Cardiac Death. The patient's father died at age 45 and sister at age 36, both from myocardial infarction. The investigator considered there was a reasonable possibility that the event of death was related to study drug.

3. A 61-year-old-woman in the tofacitinib 5 mg twice daily group died 685 days after the first dose of study medication. Except for rheumatoid arthritis, the patient had not been treated for any other condition. Relevant medical history included that the patient was a heavy smoker and had undergone a lung X-ray examination at a rheumatology department that revealed a spheroidal shade at the top of right hilus, subsequently confirmed as

chondroma. The patient had no further lung problems. Relevant concomitant medications included oral ibuprofen and ongoing folic acid. The patient was reportedly without any difficulties on the date of death and autopsy findings included: atherosclerosis of coronary vessels and aorta grade II-III, chronic bronchitis, chronic pulmonary emphysema, post-partial resection of the right lung, chronic cor pulmonale, edema of the brain and edema of the lung. The investigator reported the cause of death as cardiac failure (Exacerbation of Chronic Heart Failure) considered to be not related to study drug.

4. A 71-year-old women in the tofacitinib 5 mg twice daily group died 765 days after the first dose of study medication. The cause of death was reported as diffuse non-Hodgkin lymphoma. The patient's previous medical history included cholelithiasis with cholecystectomy, ongoing cholestasis, ongoing varicose veins, ongoing osteochondrosis, urolithiasis and arterial hypertension. Concomitant medications included oral prednisolone, oral drotaverine hydrochloride, oral herbal (not otherwise specified) minerals and oral indapamide. Study medication was discontinued after Day 723. The patient died on Day 765, 12 days after being urgently hospitalized with a preliminary diagnosis of degenerative vertebral disease: paraparesis of lower extremities, hemorrhagic cystitis. The investigator reported the cause of death as diffuse non-Hodgkin lymphoma and considered there was a reasonable possibility that the event was related to study drug.

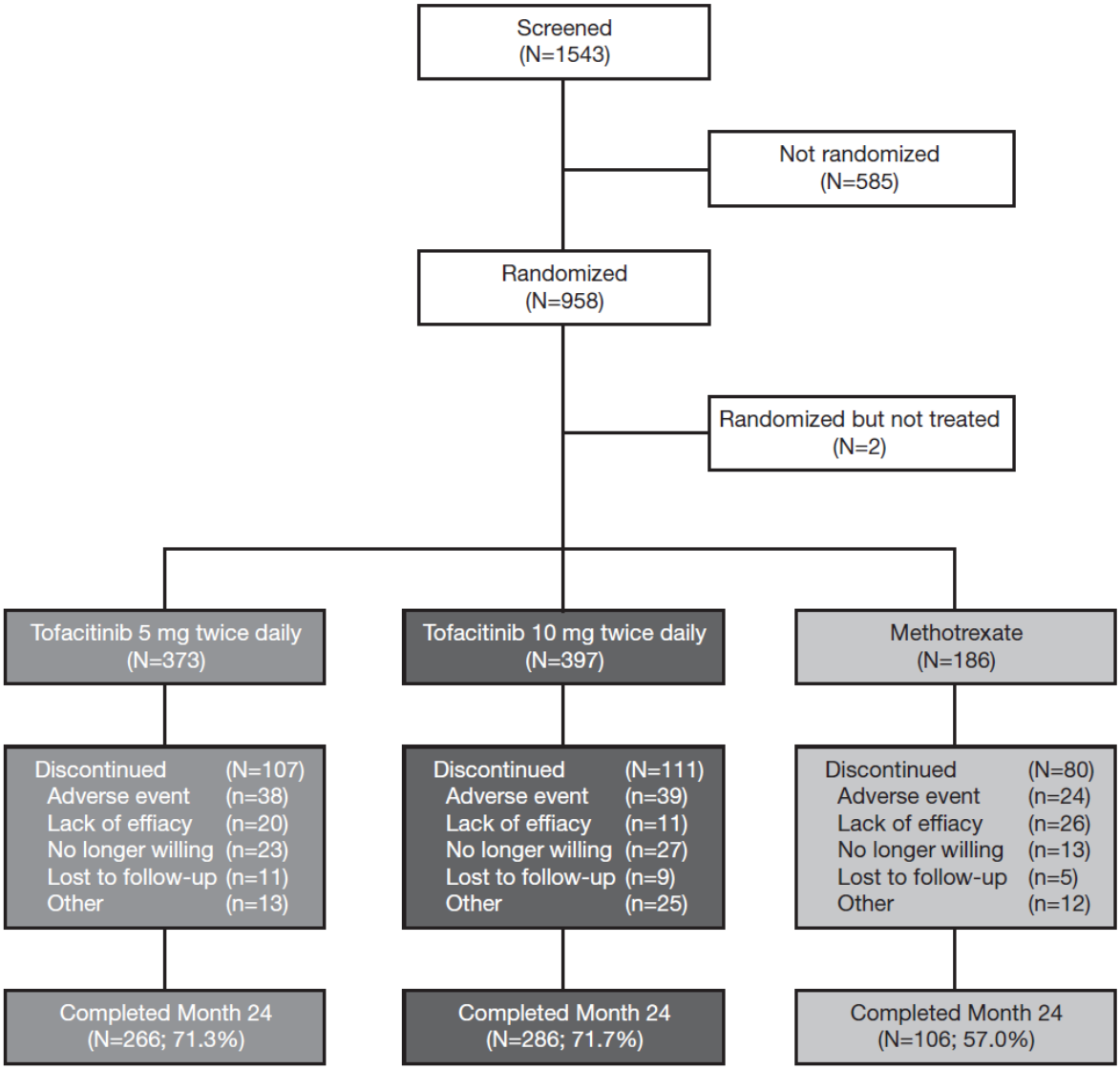
Figure S1. The Step-Down Approach to Assigning Statistical Significance for the Co-Primary Endpoints.



Testing continued along an arrow until a Diamond was false. All testing stopped when testing along all arrows stopped. Figure shows tested steps, but significance of a test (denoted by each Box) was determined when P≤0.05, provided the Box itself was reached while stepping through the figure.

ACR70, American College of Rheumatology (ACR)70 response: ≥70% improvement from baseline in both tender and swollen joint counts and ≥70% improvement in ≥3 of the five remaining ACR core set measures [pain, disability, CRP, patient and physician global assessments]), mTSS, modified total Sharp score

Figure S2. Patient Disposition.

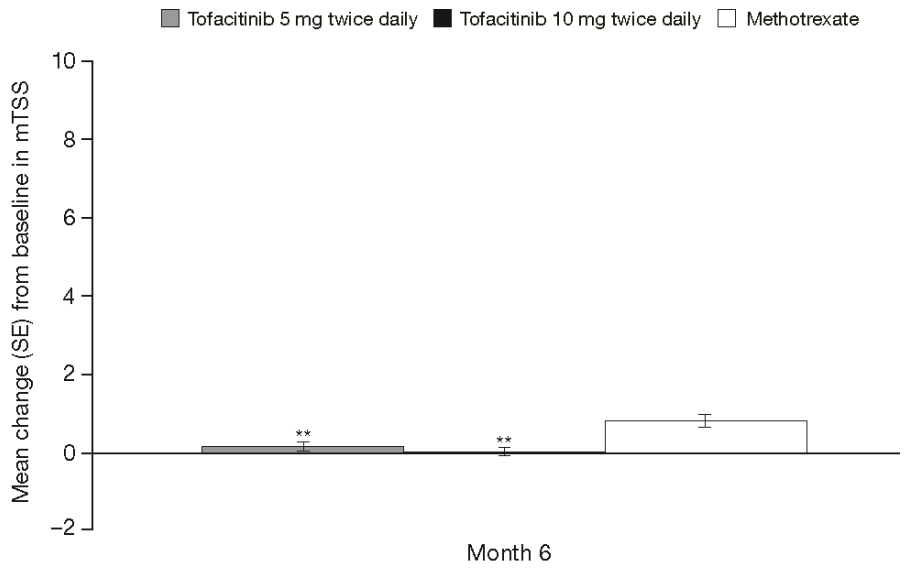


N, total number of patients; n, number of patients evaluable

The proportion of patients who discontinued due to adverse events is tabulated from the patient disposition or summary pages for discontinuations. The number of patients might not be the same as those in the safety summary, which uses the adverse event pages.

Figure S3. Preventive Effect on Radiographic Progression: (A) Mean Change From Baseline in mTSS at Month 6 (Co-Primary Endpoint[¥]), (B) Mean Change From Baseline in mTSS, (C) Erosion Score, and (D) Joint Space Narrowing Score Over Time (LEP).

A



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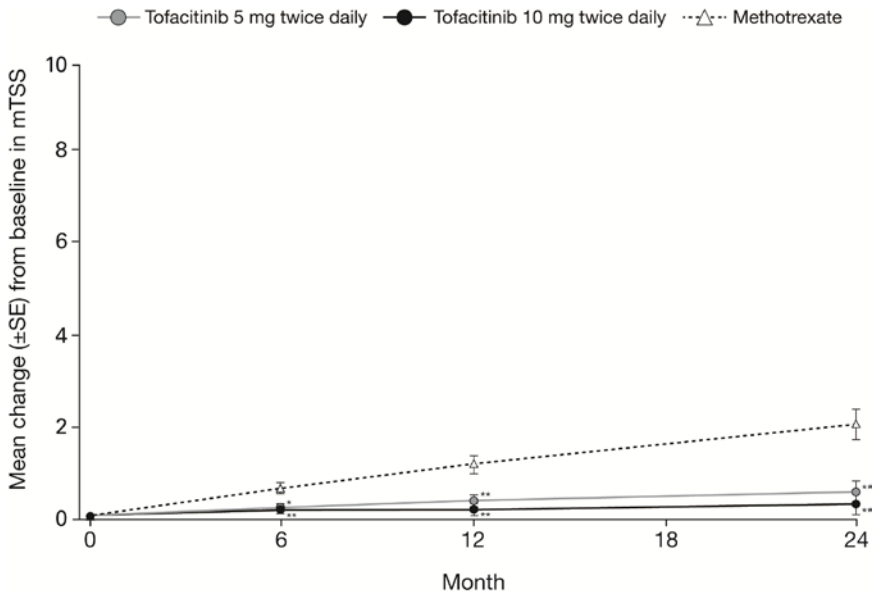

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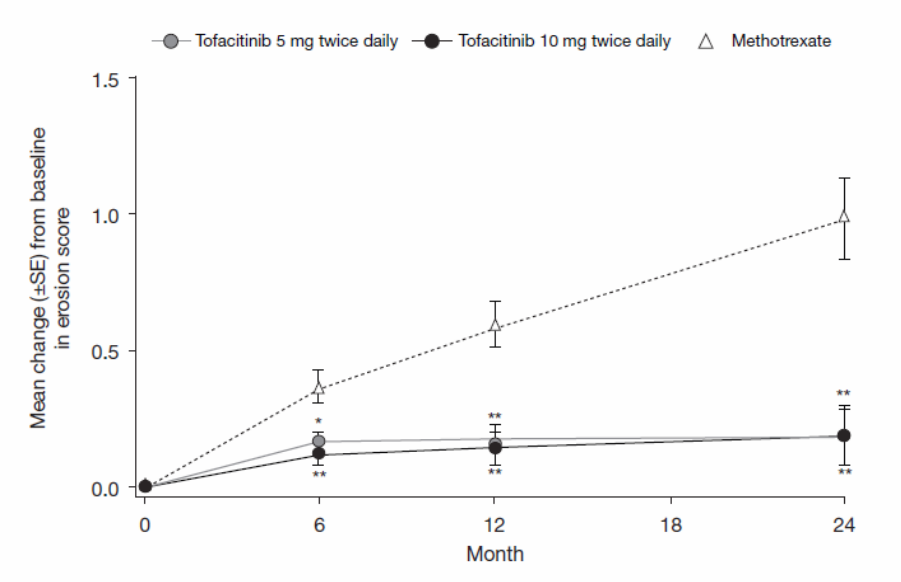

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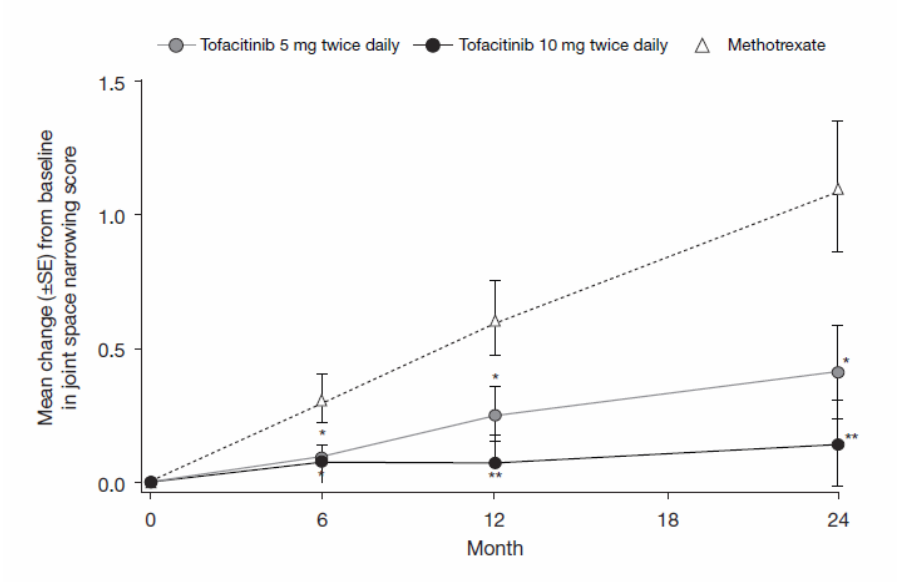


	Number of Patients at Visit/Baseline (n/N)		
	Month 6	**Month 12**	**Month 24**
Tofacitinib 5 mg twice daily	348/373	347/373	348/373
Tofacitinib 10 mg twice daily	372/396	373/396	373/396
Methotrexate	167/186	171/186	171/186

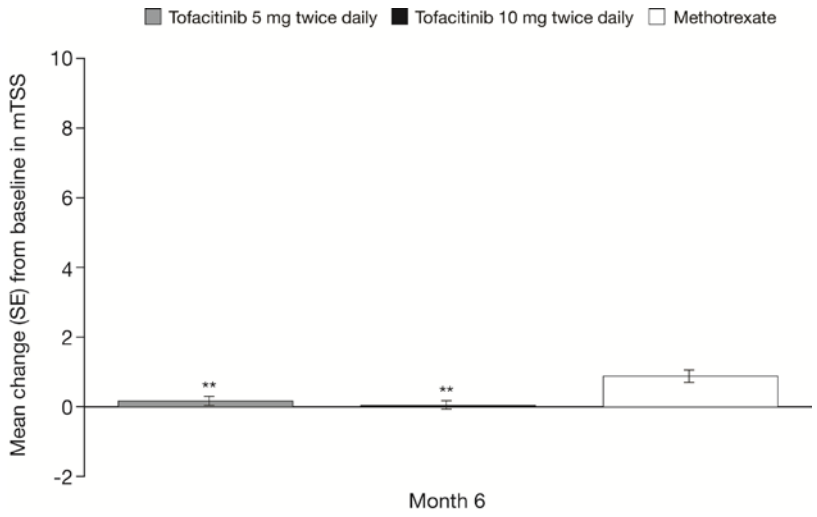
Patient numbers relate to Figure S3 B, C, and D

Values are least squares mean changes from baseline (baseline values are reported in Table 1)
LEP, imputation using linear extrapolation; mTSS, van der Heijde modified total Sharp score; SE, standard error
*P≤0.05; **P<0.001 versus methotrexate

Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week
[¥]Co-primary endpoint (mean change from baseline in mTSS) at Month 6 was derived from the pre-specified Year 1 interim dataset; mean changes from baseline in mTSS and component scores over time were derived from the final Year 2 dataset

Figure S4. Preventive Effect on Radiographic Progression using a Longitudinal Linear Model as Sensitivity Analysis with no Imputation for Missing Data: (A) Mean Change From Baseline in mTSS at Month 6 (Co-Primary Endpoint[¥]), (B) Mean Change From Baseline in mTSS, (C) Erosion Score, and (D) Joint Space Narrowing Score Over Time.

A



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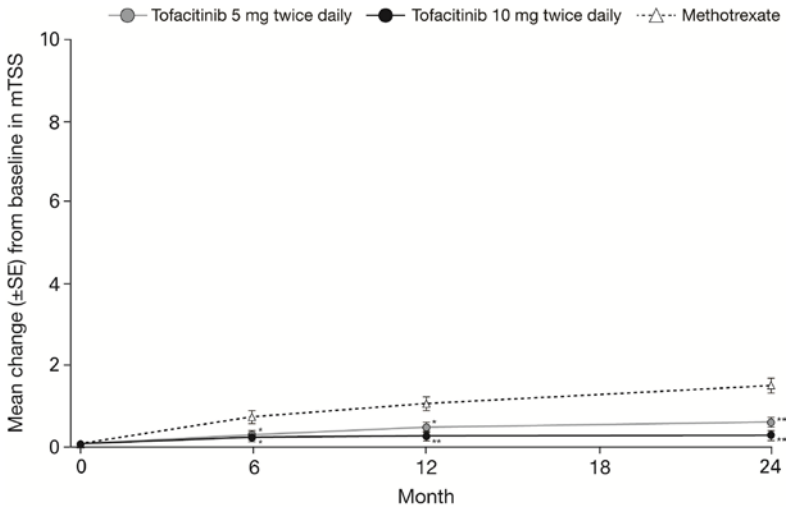

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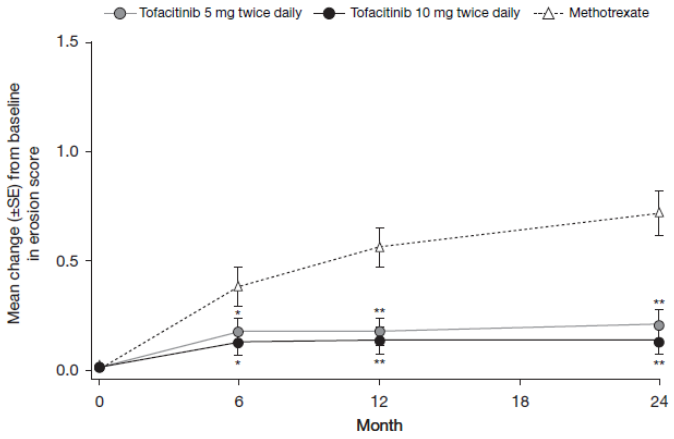

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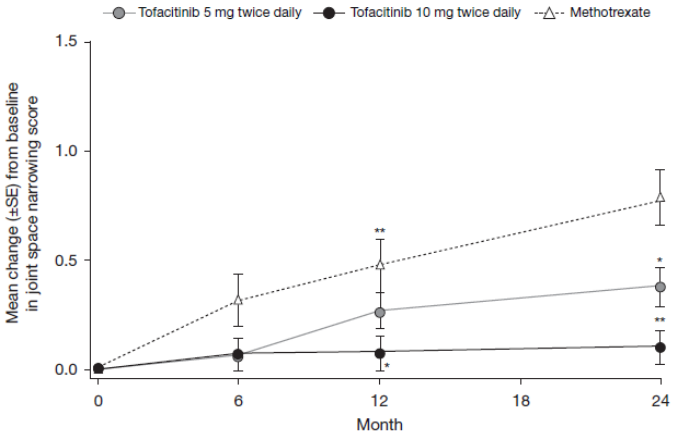


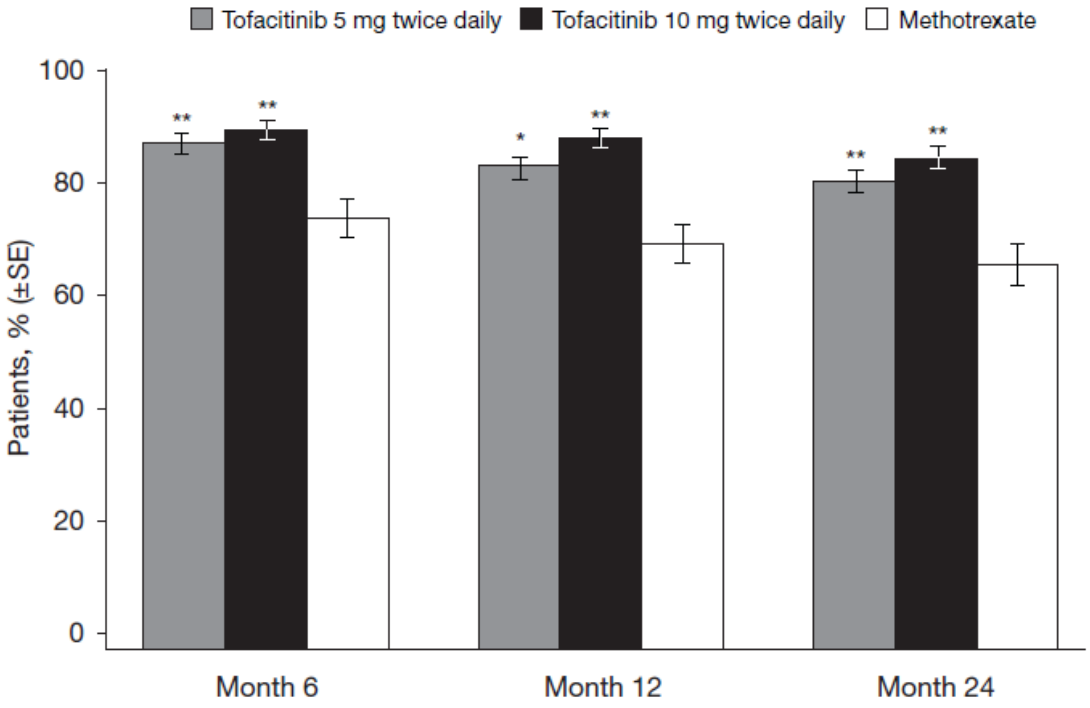
	Number of Patients at Visit/Baseline (n/N)		
	Month 6	**Month 12**	**Month 24**
Tofacitinib 5 mg twice daily	335/373	313/373	258/373
Tofacitinib 10 mg twice daily	364/396	330/396	282/396
Methotrexate	160/186	132/186	104/186

Patient numbers relate to Figure S4 B,C and D
The total number of patients contributing some data to the longitudinal model were 335 (tofacitinib 5 mg twice daily), 365 (tofacitinib 10 mg twice daily), and 164 (methotrexate).

Values are least squares mean changes from baseline
mTSS, van der Heijde modified total Sharp score; SE, standard error
*P≤0.05; **P<0.001 versus methotrexate

Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week
¥Co-primary endpoint (mean change from baseline in mTSS) at Month 6 was derived from the pre-specified Year 1 interim dataset; mean changes from baseline in mTSS and component scores over time were derived from the final Year 2 dataset

Figure S5. Proportion of Patients with no Structural Progression (≤0.5 Unit Increase From Baseline in mTSS) at Months 6, 12, and 24.

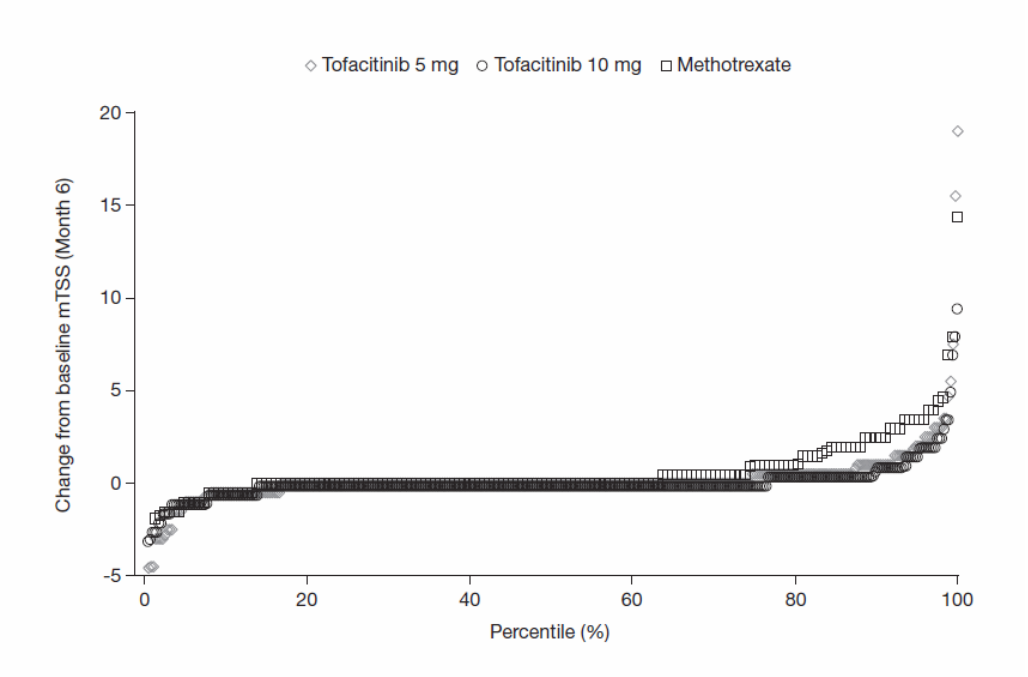


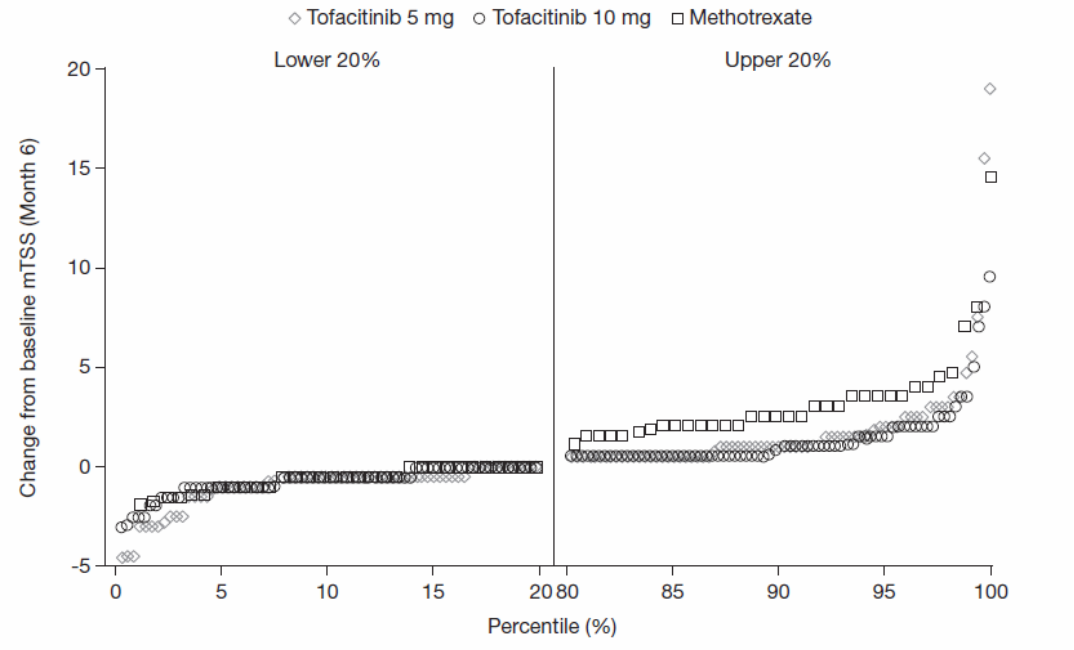
mTSS, van der Heijde modified total Sharp score; SE, standard error
Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

*P≤0.05; **P<0.001 versus methotrexate

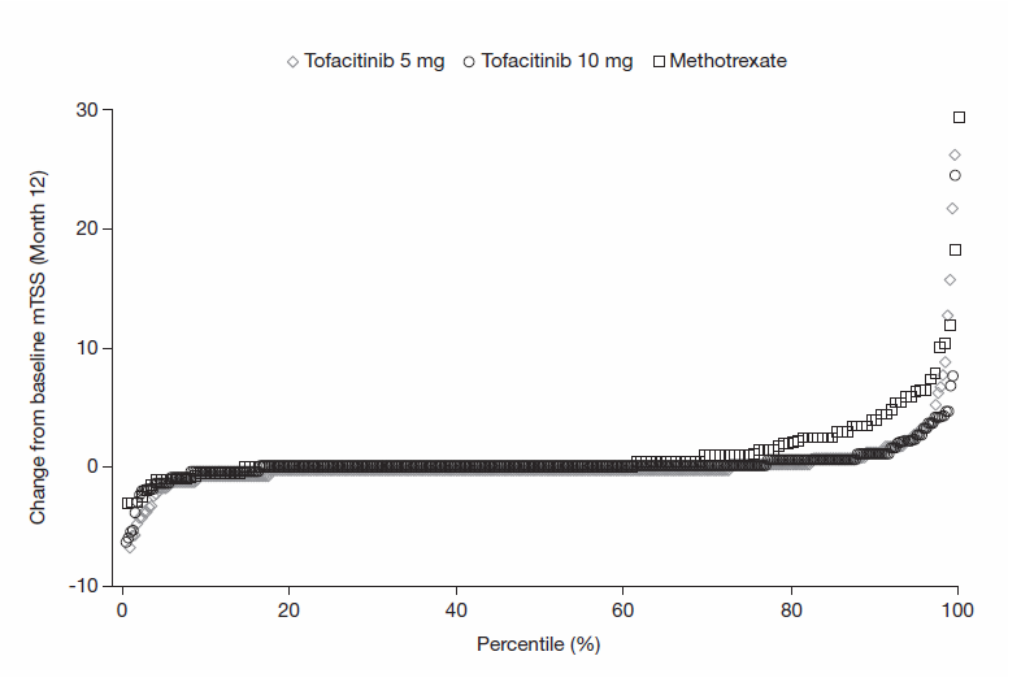
Figure S6. Cumulative Probability Plots for Change from Baseline in mTSS Showing the Full Percentile (0-100%), and the Lower (0-20%) and Upper (80-100%) Percentiles, at (A) Month 6, (B) Month 12, and (C) Month 24.

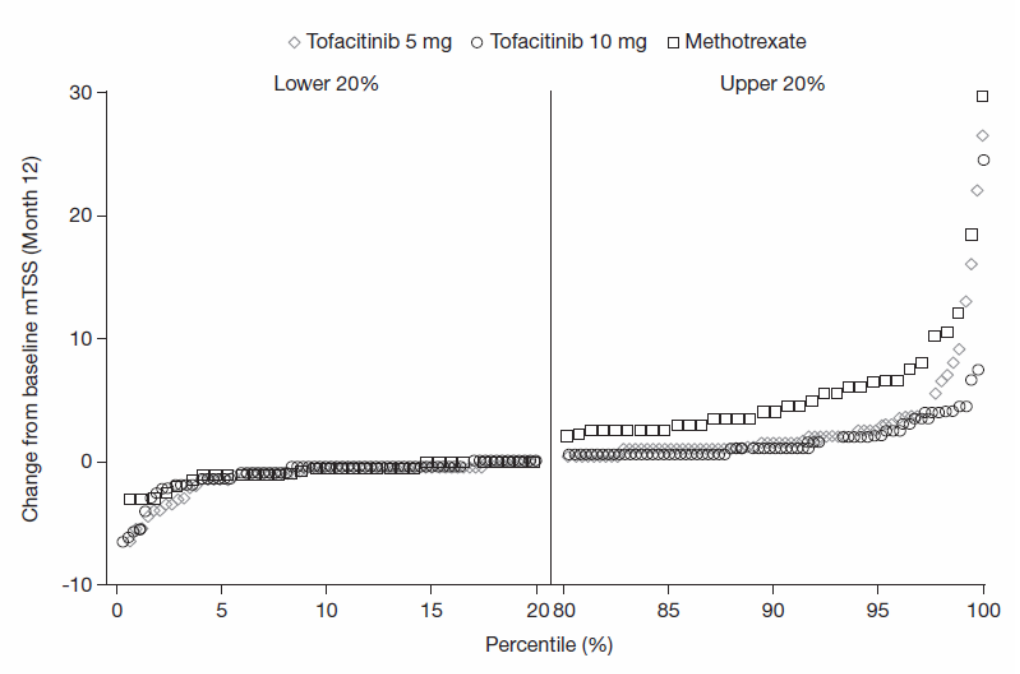
A



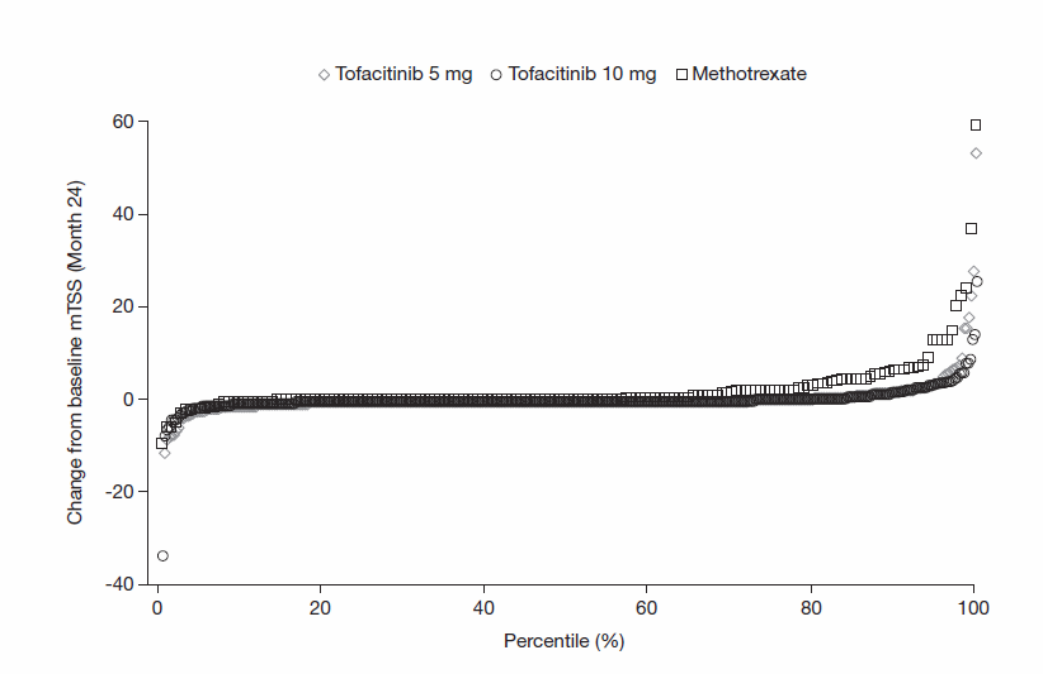


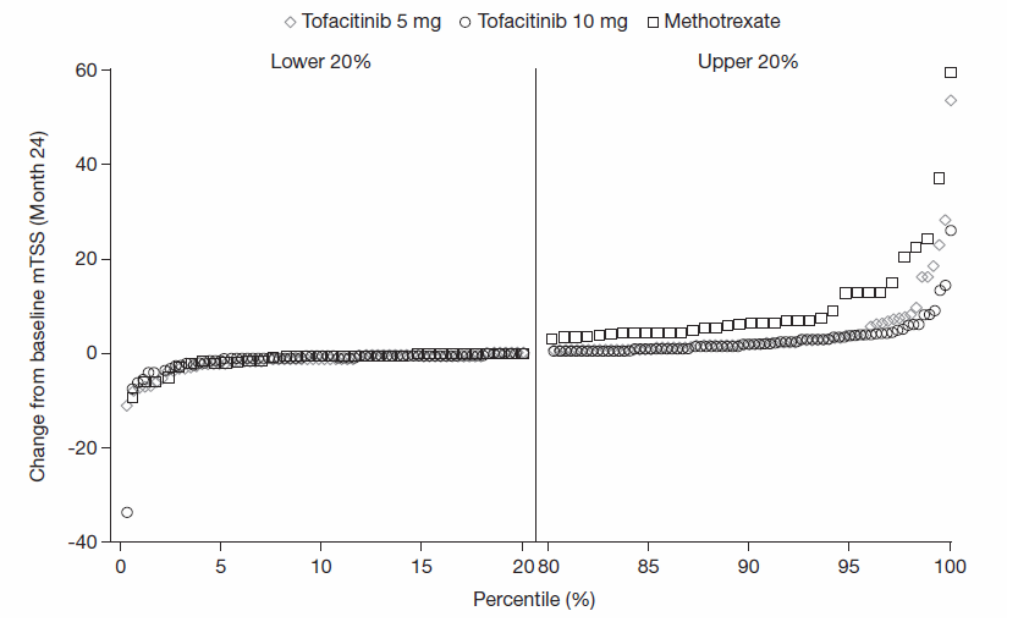
B


◇ Tofacitinib 5 mg ○ Tofacitinib 10 mg □ Methotrexate
Change from baseline mTSS (Month 12)
30
20
10
0
-10
0
20
40
60
80
100
Percentile (%)


◇ Tofacitinib 5 mg ○ Tofacitinib 10 mg □ Methotrexate
Lower 20%
Upper 20%
Change from baseline mTSS (Month 12)
30
20
10
0
-10
0
5
10
15
20
80
85
90
95
100
Percentile (%)

C

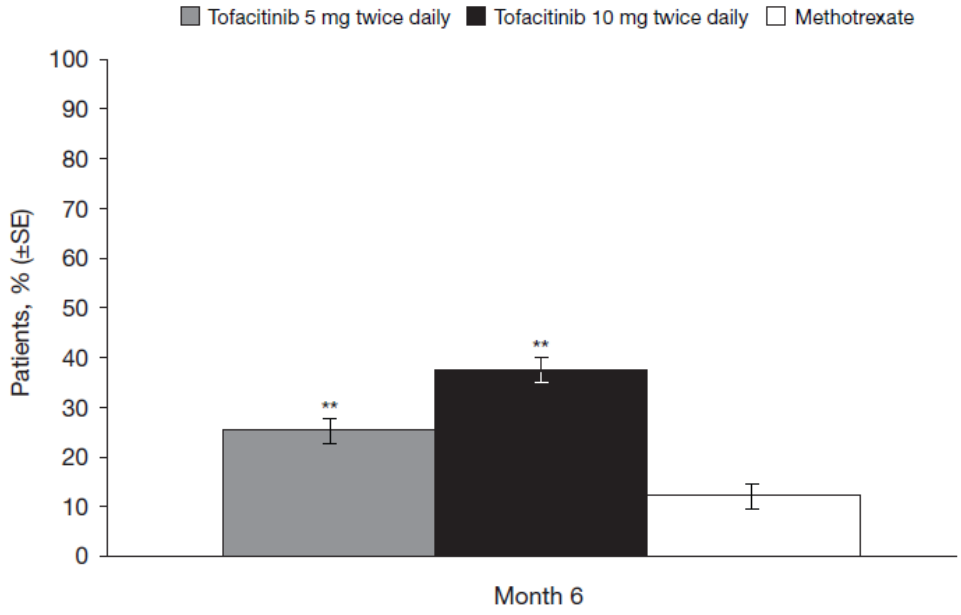




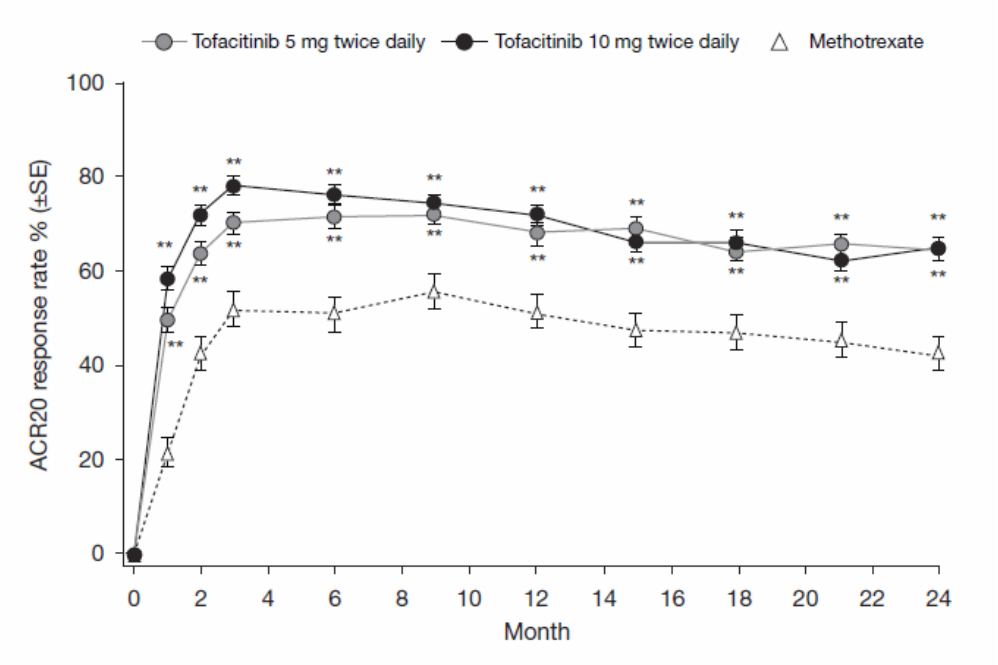
mTSS, van der Heijde modified total Sharp score
Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

Figure S7. (A) ACR70 at Month 6 (Co-Primary Endpoint[¥]), (B) ACR20, (C) ACR50, and (D) ACR70 Response Over Time (NRI, FAS).

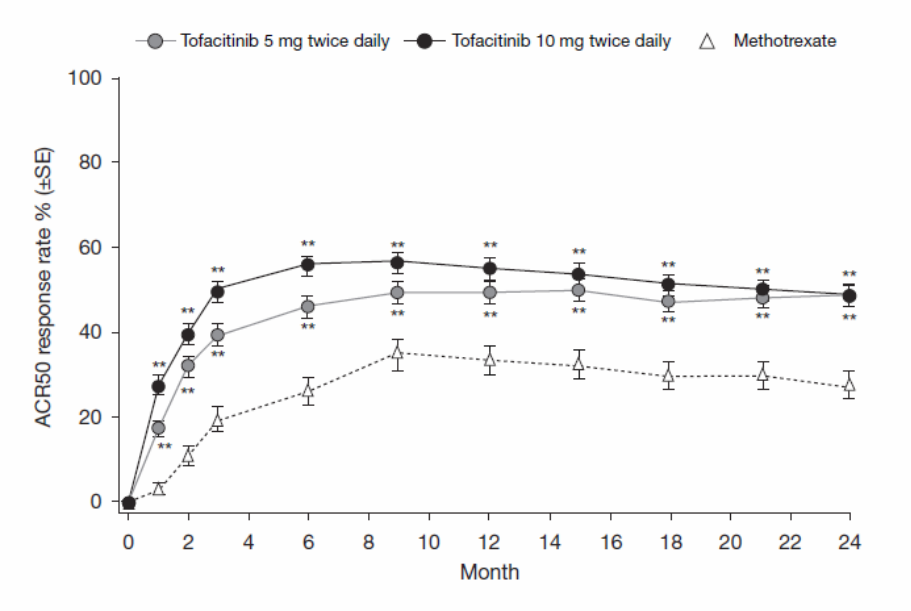
A



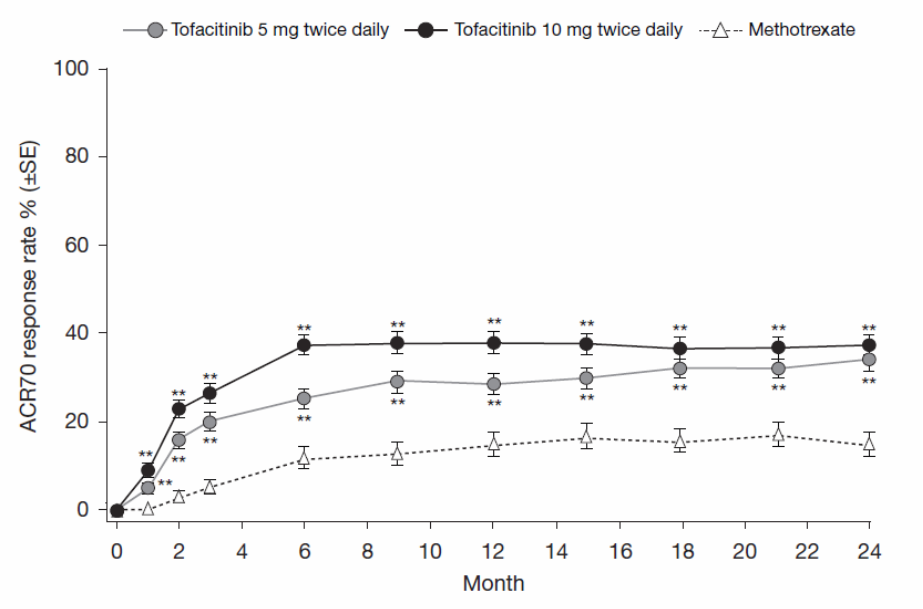
B



C



D)



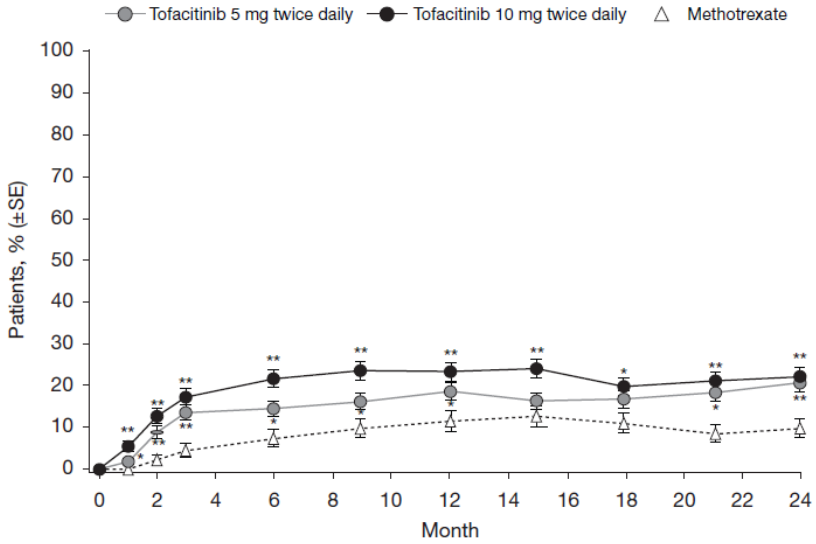
ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation; SE, standard error
*P≤0.05; **P<0.001 versus methotrexate

Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

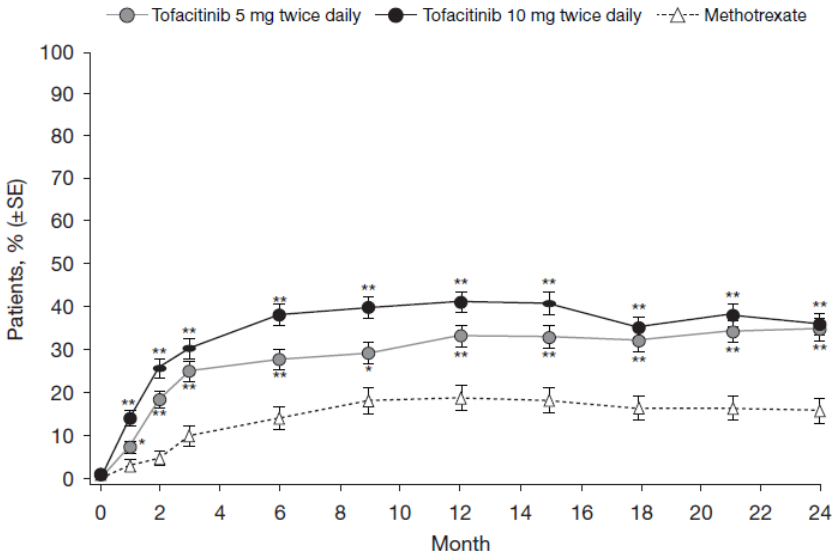
[¥]Co-primary endpoint (ACR70 at Month 6) was derived from the pre-specified Year 1 interim dataset; ACR70 responses over time were derived from the final Year 2 dataset.

Figure S8. Proportion of Patients Achieving DAS28-Defined (A) Remission (DAS28-4(ESR) <2.6), and (B) Low Disease Activity (DAS28-4(ESR) ≤3.2) (FAS, NRI) over 24 Months.

A



B



*P≤0.05; **P<0.001 versus methotrexate
Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; FAS, full analysis set; NRI, non-responder imputation; SE, standard error

Table S1. Further Details on Baseline Demographics and Disease Characteristics.[*]

	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
Female sex, no. (%)	286 (76.7)	327 (82.4)	145 (78.0)
White ethnic group, no. (%)	239 (64.1)	266 (67.0)	127 (68.3)
Age, mean years	50.3	49.3	48.8
Duration of rheumatoid arthritis			
Mean, years	2.9	3.4	2.7
Median, years	0.8	0.8	0.7
<2 years, %	67.0	63.7	66.1
<6 months, %	39.7	40.6	39.2
Tender joints, mean no.	25.7	25.1	25.4
Swollen joints, mean no.	16.3	15.6	16.8
HAQ-DI, mean[†]	1.54	1.50	1.52
mTSS, mean[‡]	19.1	17.9	16.1
mTSS, median[‡]	3.5	3.0	3.5
Erosion score, mean[¥]	9.1	9.1	8.4
Joint space narrowing score, mean[§]	10.0	8.8	7.7
DAS28-4(ESR), mean[¢]	6.62	6.54	6.60
DAS28-4(ESR) score of >5.1, %	94.4	93.7	93.0

	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
ESR, mm/h	55.6	53.4	56.0
CRP, mg/L	22.7	20.3	25.9
Positive for RF, %	82.3	81.6	84.4
Positive for anti-CCP antibodies, %	85.0	81.1	86.6
Prior treatment, nonbiologic disease modifying drug other than methotrexate, %	37.0	39.8	41.4
Leflunomide, n	22	25	13
Sulfasalazine, n	53	47	23
Anti-malarial drugs, n	89	116	57
Gold salt preparations, n	1	4	2

*There were no statistically significant differences between treatment group demographics and disease characteristics at baseline (subgroups under the 'Prior treatment, nonbiologic disease-modifying drug other than methotrexate' category were not statistically tested due to small patient numbers)

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire - Disability Index; mTSS, modified total Sharp Score; RF, rheumatoid factor

†Scores of 0 to 1 generally represent mild to moderate physical difficulty, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability; ‡Range 0–448, higher scores indicate greater structural damage;

[¥]Range 0–280, higher scores indicate greater erosive changes in the joints; [§]Range 0–168, higher scores indicate greater narrowing between joints; [¢]DAS28-4, range 0–9.4, higher scores indicate greater disease activity

Table S2. Further Details on Co-primary[¶] and Secondary Endpoints[§] at Months 6, 12, and 24.

	Month 6			Month 12			Month 24		
	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
ACR20[†], % (SE)	71.3**	76.1**	50.5	67.8**	71.6**	51.1	64.2**	64.2**	42.4
	(2.35)	(2.14)	(3.68)	(2.43)	(2.27)	(3.68)	(2.49)	(2.41)	(3.64)
ACR50[†], % (SE)	46.6**	56.4**	26.6	49.9**	55.6**	33.7	49.3**	49.2**	28.3
	(2.59)	(2.49)	(3.25)	(2.60)	(2.50)	(3.48)	(2.60)	(2.51)	(3.31)
ACR70[†¥], % (SE)	25.5**	37.7**	12.0	28.7**	38.1**	15.2	34.4**	37.6**	15.2
	(2.26)	(2.44)	(2.39)	(2.35)	(2.44)	(2.64)	(2.47)	(2.43)	(2.64)
DAS28-4(ESR) <2.6[†], % (SE)	14.6*	21.8**	7.60	18.7*	23.4**	11.70	20.8**	22.3**	9.94
	(1.91)	(2.13)	(2.02)	(2.10)	(2.19)	(2.45)	(2.19)	(2.15)	(2.28)
DAS28-4(ESR) ≤3.2[†], % (SE)	27.8**	38.2**	14.0	33.3**	41.1**	18.7	34.8**	36.0**	15.8
	(2.42)	(2.51)	(2.65)	(2.54)	(2.55)	(2.98)	(2.57)	(2.48)	(2.78)

	Month 6			Month 12			Month 24		
	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
Mean change (SE) from baseline in DAS28-4(ESR)[∫#]	-2.47** (0.07)	-2.88** (0.07)	-1.87 (0.10)	-2.78** (0.07)	-3.05** (0.07)	-2.20 (0.11)	-2.99** (0.08)	-3.16** (0.07)	-2.40 (0.12)
EULAR response (Good or Moderate)[†], % (SE)	79.0** (2.20)	84.1** (1.89)	60.82 (3.73)	76.6** (2.28)	79.6** (2.09)	59.7 (3.75)	68.7** (2.5)	69.6** (2.38)	49.12 (3.82)
Mean change (SE) from baseline in HAQ-DI[∫#]	-0.83** (0.03)	-0.94** (0.03)	-0.58 (0.04)	-0.87** (0.03)	-0.98** (0.03)	-0.68 (0.04)	-0.90** (0.03)	-1.01** (0.03)	-0.70 (0.05)
LS mean change (SE) from baseline in mTSS[‡¥#]	0.18* (0.12)	0.04** (0.11)	0.84 (0.16)	0.36** (0.14)	0.16** (0.14)	1.18 (0.20)	0.55** (0.25)	0.28** (0.24)	2.08 (0.34)
LS mean change (SE) from baseline in erosion score[‡]	0.14* (0.04)	0.10** (0.04)	0.35 (0.06)	0.13** (0.07)	0.12** (0.06)	0.58 (0.09)	0.16** (0.11)	0.16** (0.10)	0.98 (0.15)
LS mean change (SE) from baseline in joint space narrowing score[‡]	0.06* (0.06)	0.05* (0.06)	0.29 (0.09)	0.23* (0.10)	0.05* (0.10)	0.60 (0.14)	0.39* (0.18)	0.12** (0.17)	1.10 (0.25)

	Month 6			Month 12			Month 24		
	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
Patients with no radiographic progression (mTSS change from baseline ≤0.5)[‡], % (SE)	87.1** (1.79)	89.3** (1.60)	73.7 (3.40)	82.4* (2.04)	87.7** (1.70)	69.0 (3.53)	79.9** (2.14)	83.7** (1.91)	64.9 (3.64)

[†]Non-responder imputation; [‡]Linear extrapolation; [∫]Mixed-effect longitudinal model; [#]Least squares means from analysis of covariance or mixed-effect longitudinal model; [¶]Statistical significance at Month 6 (co-primary endpoint) was determined using the step-down approach; [¥]All data in this table were derived from the Year 2 dataset except the co-primary endpoints (ACR70 and mean change from baseline in mTSS) at Month 6 which were derived from the pre-specified Year 1 dataset; [§]No accounting for multiple comparisons; P≤0.05 was considered to indicate statistical significance

ACR, American College of Rheumatology; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire - Disability Index; LS, least squares; mTSS, modified total Sharp Score; SE, standard error

Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

*P≤0.05; **P<0.001 versus methotrexate

Table S3. ACR Core Components at Month 6.

	Tender / Painful Joint Count		Swollen Joint Count		Patient's Assessment of Pain		Patient's Global Assessment of Disease Activity		Physician's Global Assessment of Disease Activity		Health Assessment Questionnaire – Disability Index		C-Reactive Protein, mg/L	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Tofacitinib 5 mg twice daily														
Baseline	373	25.7 (0.7)	373	16.3 (0.5)	373	59.1 (1.2)	373	60.2 (1.3)	369	62.0 (0.9)	373	1.54 (0.03)	373	22.7 (1.4)
Month 6	340	8.7 (0.6)	340	4.7 (0.4)	340	27.1 (1.2)	340	28.4 (1.2)	339	22.2 (0.9)	340	0.69 (0.03)	339	5.2 (0.6)
Mean change from baseline at Month 6[#]	340	-16.0** (0.6)	340	-10.9* (0.4)	340	-31.9* (1.2)	340	-31.7* (1.2)	336	-39.0** (0.9)	340	-0.83** (0.03)	339	-17.0** (0.7)
Tofacitinib 10 mg twice daily														
Baseline	397	25.1 (0.7)	397	15.6 (0.4)	397	61.4 (1.2)	397	60.9 (1.1)	394	60.5 (0.9)	396	1.50 (0.03)	397	20.3 (1.2)

	Tender / Painful Joint Count		Swollen Joint Count		Patient's Assessment of Pain		Patient's Global Assessment of Disease Activity		Physician's Global Assessment of Disease Activity		Health Assessment Questionnaire – Disability Index		C-Reactive Protein, mg/L	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Month 6	367	6.6 (0.5)	367	3.7 (0.3)	366	24.2 (1.1)	366	24.8 (1.1)	366	18.3 (0.8)	366	0.57 (0.03)	366	3.1 (0.3)
Mean change from baseline at Month 6[#]	367	-18.1** (0.5)	367	-12.0** (0.4)	366	-35.4** (1.2)	366	-35.1** (1.2)	363	-42.5** (0.8)	365	-0.94** (0.03)	366	-18.8** (0.7)
Methotrexate														
Baseline	186	25.4 (1.1)	186	16.8 (0.8)	186	58.8 (1.7)	186	57.7 (1.8)	185	59.3 (1.3)	186	1.52 (0.05)	186	25.9 (2.3)
Month 6	158	12.0 (1.1)	158	6.3 (0.6)	158	30.9 (1.8)	158	32.1 (1.7)	158	27.3 (1.3)	158	0.92 (0.05)	158	12.2 (1.5)
Mean change from baseline at Month 6	158	-12.4 (0.8)	158	-9.4 (0.5)	158	-27.7 (1.7)	158	-27.0 (1.7)	157	-33.4 (1.3)	158	-0.58 (0.04)	158	-9.7 (1.0)

[#]Mean changes from baseline were estimated from a longitudinal model using least-squares means and comparisons versus methotrexate were tested. Values for baseline and Month 6 are simple means with no adjustment using any kind of model.

*P≤0.05; **P<0.001 versus methotrexate

ACR, American College of Rheumatology; SE, standard error

Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

Table S4. All-Causality Treatment-Emergent Adverse Events Occurring in ≥2% of Patients in Any Treatment Group over 24 Months.

Preferred Term	**Patients with Adverse Event, n (%)**		
	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
Adverse events	1097	1435	561
Anemia	15 (4.0)	12 (3.0)	7 (3.8)
Abdominal pain	8 (2.1)[†]	16 (4.0)[†]	2 (1.1)
Abdominal pain upper	12 (3.2)	13 (3.3)	5 (2.7)
Constipation	7 (1.9)	10 (2.5)	7 (3.8)[‡]
Diarrhea	15 (4.0)	24 (6.0)	15 (8.1)[‡]
Dyspepsia	13 (3.5)	18 (4.5)	9 (4.8)[‡]
Gastritis	13 (3.5)[†]	9 (2.3)	4 (2.2)
Gastroesophageal reflux disease	6 (1.6)	6 (1.5)	5 (2.7)
Nausea	27 (7.2)	30 (7.6)	40 (21.5)[‡]
Vomiting	11 (2.9)	13 (3.3)	11 (5.9)[‡]

Preferred Term	Patients with Adverse Event, n (%)		
	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
Asthenia	1 (0.3)	7 (1.8)	5 (2.7)
Fatigue	8 (2.1)	10 (2.5)	7 (3.8)‡
Edema peripheral	11 (2.9)	17 (4.3)†	5 (2.7)
Pyrexia	5 (1.3)	3 (0.8)	6 (3.2)
Bronchitis	20 (5.4)†	27 (6.8)†	4 (2.2)
Cystitis	8 (2.1)†	3 (0.8)	1 (0.5)
Gastroenteritis	11 (2.9)	15 (3.8)	7 (3.8)
Herpes zoster	13 (3.5)†	18 (4.5)†	2 (1.1)
Influenza	10 (2.7)†	11 (2.8)†	3 (1.6)
Nasopharyngitis	28 (7.5)	39 (9.8)†	13 (7.0)
Oral herpes	7 (1.9)	8 (2.0)	5 (2.7)
Pharyngitis	9 (2.4)	12 (3.0)	4 (2.2)

Preferred Term	Patients with Adverse Event, n (%)		
	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
Pneumonia	8 (2.1)†	4 (1.0)	1 (0.5)
Respiratory tract infection viral	12 (3.2)†	6 (1.5)	4 (2.2)
Sinusitis	9 (2.4)	9 (2.3)	5 (2.7)
Upper respiratory tract infection	30 (8.0)	39 (9.1)†	15 (8.1)
Urinary tract infection	17 (4.6)	26 (6.5)†	7 (3.8)
Alanine aminotransferase increased	8 (2.1)	15 (3.8)	11(5.9)‡
Aspartate aminotransferase increased	3 (0.8)	11 (2.8)	7 (3.8)‡
Blood creatine phosphokinase increased	16 (4.3)†	36 (9.1)†	2 (1.1)
Gamma-glutamyltransferase increased	8 (2.1)†	14 (3.5)†	2 (1.1)
Hemoglobin decreased	5 (1.3)	3 (0.8)	4 (2.2)
Weight increased	13 (3.5)†	17 (4.3)†	4 (2.2)
Dyslipidemia	8 (2.1)†	10 (2.5)†	1 (0.5)

Preferred Term	Patients with Adverse Event, n (%)		
	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
Hypercholesterolemia	9 (2.4)†	15 (3.8)†	1 (0.5)
Arthralgia	8 (2.1)	17 (4.3)	8 (4.3)‡
Arthritis	8 (2.1)	5 (1.3)	4 (2.2)
Back pain	19 (5.1)†	18 (4.5)†	4 (2.2)
Osteoarthritis	5 (1.3)	9 (2.3)†	2 (1.1)
Pain in extremity	9 (2.4)	7 (1.8)	3 (1.6)
Rheumatoid arthritis flare	10 (2.7)	7 (1.8)	5 (2.7)
Dizziness	7 (1.9)	9 (2.3)	4 (2.2)
Headache	26 (7.0)	34 (8.6)†	12 (6.5)
Cough	8 (2.1)	11 (2.8)	4 (2.2)
Acne	8 (2.1)†	2 (0.5)	0
Alopecia	10 (2.7)	8 (2.0)	5 (2.7)

Preferred Term	Patients with Adverse Event, n (%)		
	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
Rash	3 (0.8)	12 (3.0)†	3 (1.6)
Hypertension	26 (7.0)†	29 (7.3)†	7 (3.8)

†Event occurred more frequently in patients receiving tofacitinib 5 or 10 mg twice daily compared with methotrexate; ‡event occurred more frequently in patients receiving methotrexate compared with tofacitinib 5 or 10 mg twice daily; based on risk difference (percent of patients with an adverse event for tofacitinib minus that for methotrexate) of >1 or <-1; not adjusted for multiplicity and is for estimation purposes only.

Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

Table S5. Serious Adverse Events Over 24 Months (1 Patient per Term Unless Indicated Otherwise).

MedDRA System Organ Class	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
Blood and lymphatic system disorders		Disseminated intravascular coagulation	
Cardiac disorders	Angina pectoris (2 patients), unstable angina, myocardial ischemia, cardiac failure	Cardiac failure congestive, myocardial ischemia	Atrial flutter, atrial fibrillation, atrioventricular block first degree
Eye disorders	Cataract (2 patients), scleritis		
Gastrointestinal disorders	Abdominal hernia, abdominal wall hematoma, gastric ulcer, esophageal ulcer, enterocolitis, gastroenteritis, gastric ulcer perforation	Abdominal pain, colonic stenosis, diarrhea, gastritis, constipation, pancreatitis, salivary gland calculus	Hemorrhoids, salivary gland calculus, pancreatitis, inguinal hernia
General disorders and administration site conditions	Chest pain, lumbar hernia, pyrexia	Noncardiac chest pain, chest pain	

MedDRA System Organ Class	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
Hepatobiliary disorders		Cholecystitis acute, biliary colic hepatomegaly	Cholelithiasis
Immune system disorders	Hypersensitivity		
Infections and infestations	Pneumonia (2 patients), herpes zoster, dengue fever, gastrointestinal infection, pleural infection, subcutaneous abscess, tonsillitis bacterial, sepsis, erysipelas	Pneumonia, herpes zoster, herpes zoster disseminated, gastroenteritis (2 patients), bone tuberculosis, pyelonephritis chronic, diverticulitis, lower respiratory tract infection	Nasopharyngitis, gastroenteritis, sialoadenitis, chronic hepatitis C, varicella
Injury, poisoning and procedural complications	Humerus fracture, fracture, tendon rupture, patella fracture	Joint dislocation, wrist fracture, upper limb fracture, compression fracture, humerus fracture, ankle fracture, gunshot wound	Ankle fracture, femoral neck fracture, fall, humerus fracture
Musculoskeletal and connective tissue disorders	Muscle hemorrhage, osteonecrosis, rheumatoid arthritis	Arthralgia, osteoarthritis (3 patients), pathological fracture, spinal column stenosis	Intervertebral disc protrusion, musculoskeletal chest pain, rheumatoid arthritis, arthralgia

MedDRA System Organ Class	Tofacitinib 5 mg Twice Daily (N=373)	Tofacitinib 10 mg Twice Daily (N=397)	Methotrexate (N=186)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-Hodgkin lymphoma, T-cell cytolytic leukemia	Burkitt-like lymphoma, prostate cancer, colon cancer	Gastric cancer
Nervous system disorders	Carotid artery stenosis, cerebrovascular accident	Cerebrovascular accident (2 patients), demyelinating polyneuropathy, nervous system disorder	
Psychiatric disorders		Psychotic disorder	Psychotic disorder
Renal and urinary disorders	Calculus urinary	Hydronephrosis, ureteric stenosis	Urinary tract disorder
Reproductive system and breast disorders	Ovarian cyst	Uterine polyp, endometrial hyperplasia (2 patients)	Metrorrhagia
Respiratory, thoracic and mediastinal disorders		Bronchitis chronic, chronic obstructive pulmonary disease (2 patients)	
Skin and subcutaneous tissue disorders	Erythema annulare		Erythema multiforme
Vascular disorders	Deep vein thrombosis	Rheumatoid vasculitis	Deep vein thrombosis (2 patients)

MedDRA, Medical Dictionary for Regulatory Activities

Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

Table S6. Further Details on Laboratory Data at Months 6, 12, and 24.

	Month 6			Month 12			Month 24		
	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
Mean change from baseline[#]									
Absolute neutrophil count, $10^3/mm^3$ (SE)	-1.18* (0.09)	-1.42** (0.09)	-0.83 (0.13)	-1.17 (0.09)	-1.50** (0.09)	-0.97 (0.14)	-1.26 (0.10)	-1.61 (0.09)	-1.03 (0.15)
Absolute lymphocyte count, $10^3/mm^3$ (95% CI)	0.03** (-0.03, 0.09)	0.04** (-0.02, 0.10)	-0.15 (-0.24, -0.06)	-0.11 (-0.17, -0.04)	-0.18 (-0.24, -0.12)	-0.13 (-0.22, -0.03)	-0.35* (-0.41, -0.28)	-0.44** (-0.51, -0.38)	-0.22 (-0.32, -0.11)
Hemoglobin, g/dL (SD)[‡]	0.49 (1.11)	0.32 (1.07)	0.16 (1.02)	0.47 (1.19)	0.31 (1.05)	0.26 (1.11)	0.57 (1.26)	0.24 (1.12)	0.30 (1.15)
LDL-c, mg/dL, % change (SE)	14.47** (1.54)	19.51** (1.48)	2.12 (2.18)	16.77** (1.58)	22.05** (1.52)	2.24 (2.29)	18.57** (1.65)	21.63** (1.59)	3.91 (2.47)

	Month 6			Month 12			Month 24		
	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
HDL-c, mg/dL, % change	20.70**	20.76**	6.89	18.68**	19.15**	2.96	16.79**	17.38**	6.98
(SE)	(1.41)	(1.35)	(2.00)	(1.43)	(1.38)	(2.08)	(1.49)	(1.43)	(2.21)
Serum creatinine, mg/dL	0.08**	0.09**	0.03	0.09**	0.09**	0.04	0.10**	0.10**	0.04
(SE)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)
Incidence, n (%)									
Neutropenia (SE)									
ANC ≥1.5 to <2 × $10^3/\mu L$	6 (1.8)	10 (2.7)	4 (2.5)	6 (1.9)	16 (4.9)	1 (<1.0)	9 (3.5)	12 (4.3)	1 (<1.0)
ANC ≥0.5 to <1.5 × $10^3/\mu L$	3 (<1.0)	4 (1.1)	0	3 (<1.0)	1 (<1.0)	0	1 (<1.0)	5 (1.8)	0

	Month 6			Month 12			Month 24		
	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
ANC <0.5 × 10^3/μL	0	0	0	0	0	0	0	0	0
Lymphopenia									
1.5 - ≤2.0 × 10^9/L lymphocytes	116 (34.2)	112 (30.9)	62 (39.2)	109 (35.2)	101 (30.8)	47 (36.2)	82 (32.0)	71 (25.5)	36 (35.3)
0.5 - <1.5 × 10^9/L lymphocytes	85 (25.1)	93 (25.6)	51 (32.3)	100 (32.3)	127 (38.7)	43 (33.1)	116 (45.3)	158 (56.8)	36 (35.3)
<0.5 × 10^9/L lymphocytes	0	2 (<1.0)	0	0	0	0	1 (<1.0)	1 (<1.0)	0
Decreased hemoglobin									

	Month 6			Month 12			Month 24		
	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
Decrease of ≥1 g/dL to ≤2 g/dL versus baseline	23 (6.8)	25 (6.8)	18 (11.4)	26 (8.4)	31 (9.8)	16 (12.2)	18 (7.0)	27 (9.7)	5 (4.9)
Decrease of >2 g/dL to <3 g/dL versus baseline or an actual hemoglobin value of >7 g/dL, but <8 g/dL	2 (<1.0)	4 (1.1)	1 (<1.0)	3 (<1.0)	0	2 (1.5)	2 (<1.0)	3 (1.1)	3 (2.9)
Decrease of ≥3 g/dL versus baseline or an actual hemoglobin value of ≤7 g/dL	0	0	1 (<1.0)	1 (<1.0)	0	0	0	0	1 (<1.0)

	Month 6			Month 12			Month 24		
	Tofacitinib 5 mg Twice Daily (N=373)	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**	**Tofacitinib 5 mg Twice Daily (N=373)**	**Tofacitinib 10 mg Twice Daily (N=397)**	**Methotrexate (N=186)**
LDL-c <100 mg/dL at baseline and ≥130 mg/dL over Months 0–24							41 (11.0)	47 (11.8)	5 (2.7)

[‡]No comparison of tofacitinib versus methotrexate available; [#]Least squares means from analysis of covariance or mixed-effect longitudinal model;

ANC, absolute neutrophil count; CI, confidence interval; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SD, standard deviation; SE, standard error

Mean methotrexate dose at end of titration (Month 3) = 18.5 mg/week

*P≤0.05; **P<0.001 versus methotrexate

Table S7. Hepatic Aminotransferases and Increase in Serum Creatinine Data from Months 0 to 24.[†]

	Tofacitinib 5 mg Twice Daily	**Tofacitinib 10 mg Twice Daily**	**Methotrexate**
	(N=373)	**(N=397)**	**(N=186)**
AST ≥1 × ULN	121 (32.9)	143 (36.1)	56 (30.4)
AST ≥3 × ULN	6 (1.6)	6 (1.5)	6 (3.3)
ALT ≥1 × ULN	132 (35.9)	150 (37.9)	79 (42.9)
ALT ≥3 × ULN	11 (3.0)	12 (3.0)	13 (7.1)
Serum creatinine ≥33% increase	37 (9.9)	38 (9.6)	5 (2.7)
Serum creatinine >50% increase	6 (1.6)	11 (2.8)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

[†]Confirmed (by two consecutive tests)

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