Tofacitinib (CP-690,550) in Patients With Rheumatoid Arthritis Receiving Methotrexate

Twelve-Month Data From a Twenty-Four–Month Phase III Randomized Radiographic Study

Désirée van der Heijde,[1] Yoshiya Tanaka,[2] Roy Fleischmann,[3] Edward Keystone,[4] Joel Kremer,[5] Cristiano Zerbini,[6] Mario H. Cardiel,[7] Stanley Cohen,[3] Peter Nash,[8] Yeong-Wook Song,[9] Dana Tegzová,[10] Bradley T. Wyman,[11] David Gruben,[11] Birgitta Benda,[12] Gene Wallenstein,[11] Sriram Krishnaswami,[11] Samuel H. Zwillich,[11] John D. Bradley,[11] Carol A. Connell,[11] and the ORAL Scan Investigators

Objective. **The purpose of this 24-month phase III study was to examine structural preservation with tofacitinib in patients with rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX). Data from a planned 12-month interim analysis are reported.**

Methods. **In this double-blind, parallel-group, placebo-controlled study, patients receiving background MTX were randomized 4:4:1:1 to tofacitinib at 5 mg twice daily, tofacitinib at 10 mg twice daily, placebo to tofacitinib at 5 mg twice daily, and placebo to tofacitinib at 10 mg twice daily. At month 3, nonresponder placebo-treated patients were advanced in a blinded manner to receive tofacitinib as indicated above; remaining placebo-treated patients were advanced at 6 months. Four primary efficacy end points were all analyzed in a step-down procedure.**

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[1]Désirée van der Heijde, MD, PhD: Leiden University Medical Center, Leiden, The Netherlands; [2]Yoshiya Tanaka, MD, PhD: University of Occupational and Environmental Health, Kitakyushu, Japan; [3]Roy Fleischmann, MD, Stanley Cohen, MD: Metroplex Clinical Research Center, Dallas, Texas; [4]Edward Keystone, MD, FRCPC: University of Toronto, Toronto, Ontario, Canada; [5]Joel Kremer, MD: Albany Medical College, Albany, New York; [6]Cristiano Zerbini, MD, PhD: Centro Paulista de Investigação Clinica, São Paulo, Brazil; [7]Mario H. Cardiel, MD, MSc: Centro de Investigacion Clinica de Morelia, Morelia, Mexico; [8]Peter Nash, MBBS (Hons), FRACP: Nambour Hospital, Sunshine Coast Nambour, Queensland, Australia, and University of Queensland, St. Lucia, Queensland, Australia; [9]Yeong-Wook Song, MD, PhD: Seoul National University Hospital, Seoul, Korea; [10]Dana Tegzová, MD: Institute of Rheumatology, Prague, Czech Republic; [11]Bradley T. Wyman, PhD, David Gruben, PhD, Gene Wallenstein, PhD, Sriram Krishnaswami, PhD, Samuel H. Zwillich, MD, John D. Bradley, MD, Carol A. Connell, RN, PhD: Pfizer Inc, Groton, Connecticut; [12]Birgitta Benda, MD, PhD: Pfizer Inc, Collegeville, Pennsylvania.

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Address correspondence to Désirée van der Heijde, MD, PhD, Department of Rheumatology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. E-mail: mail@dvanderheijde.nl.

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Results. **At month 6, response rates according to the American College of Rheumatology 20% improvement criteria for tofacitinib at 5 mg and 10 mg twice daily were higher than those for placebo (51.5% and 61.8%, respectively, versus 25.3%; both $P < 0.0001$). At month 6, least squares mean (LSM) changes in total modified Sharp/van der Heijde score for tofacitinib at 5 mg and 10 mg twice daily were 0.12 and 0.06, respectively, versus 0.47 for placebo ($P = 0.0792$ and $P \leq 0.05$, respectively). At month 3, LSM changes in the Health Assessment Questionnaire disability index score for tofacitinib at 5 mg and 10 mg twice daily were −0.40 (significance not declared due to step-down procedure) and −0.54 ($P < 0.0001$), respectively, versus −0.15 for placebo. At month 6, rates of remission (defined as a value <2.6 for the 4-variable Disease Activity Score in 28 joints using the erythrocyte sedimentation rate) for tofacitinib at 5 mg and 10 mg twice daily were 7.2% (significance not declared due to step-down procedure) and 16.0% ($P < 0.0001$), respectively, versus 1.6% for placebo. The safety profile was consistent with findings in previous studies.**

Conclusion. **Data from this 12-month interim analysis demonstrate that tofacitinib inhibits progression of structural damage and improves disease activity in patients with RA who are receiving MTX.**

Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease characterized by inflammation and destruction of the joints, substantial disability, and a significant impact on health status and quality of life. This results in a substantial economic burden to patients and society (1).

Tofacitinib (CP-690,550) is a novel JAK inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy in RA (2,3). In kinase assays, tofacitinib inhibits JAK-1, JAK-2, and JAK-3, and to a lesser extent tyrosine kinase 2; in cellular settings, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK-3 and/or JAK-1 with functional selectivity over JAK-2–paired receptors. Inhibition of JAK-1 and JAK-3 by tofacitinib blocks signaling through the common γ-chain–containing receptors for several cytokines, including interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 (3,4), which are integral to lymphocyte function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response.

In phase IIb dose-ranging studies that evaluated a dose range of 1–15 mg twice daily, tofacitinib demonstrated sustained efficacy and manageable safety over 24 weeks in patients with active RA when used as monotherapy (5) or in combination with background methotrexate (MTX) (6). Tofacitinib doses of 5 and 10 mg twice daily were selected as optimal for evaluation in phase III, which includes a broad range of therapeutic scenarios investigating tofacitinib as monotherapy (7) or in combination with MTX (8–10) and non-MTX nonbiologic disease-modifying antirheumatic drugs (DMARDs) (11).

The purpose of this phase III study was to examine structural preservation, improvements in signs and symptoms of RA, and physical function, and to evaluate safety and tolerability with tofacitinib at 5 and 10 mg twice daily over 24 months in adult patients with active RA with an inadequate response to MTX. Data from a planned 12-month interim analysis of this study are reported here.

PATIENTS AND METHODS

Patients. Eligible patients were age ≥18 years with a diagnosis of active RA based on the American College of Rheumatology (ACR) 1987 revised criteria (12). Active disease was defined by ≥6 tender/painful joints (68-joint count) and ≥6 swollen joints (66-joint count) and by an erythrocyte sedimentation rate (ESR) (Westergren method) of >28 mm/hour or a C-reactive protein level of >7 mg/liter (reference range 0–10 mg/liter). Patients were also required to have evidence of ≥3 distinct joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs as determined by the investigator, or, if radiographic evidence of joint erosions was unavailable, IgM rheumatoid factor (RF) positivity or antibodies to cyclic citrullinated peptide (anti-CCP). Stable doses of MTX were required (15–25 mg weekly for ≥6 weeks; stable doses <15 mg were allowed only if there were safety issues at higher doses). Stable doses of low-dose corticosteroids (≤10 mg/day prednisone or equivalent) and nonsteroidal antiinflammatory drugs (NSAIDs) were allowed. Prior use of biologic or nonbiologic DMARDs was permitted.

Key exclusion criteria were hemoglobin <9.0 gm/dl, hematocrit <30%, white blood cell count $<3.0 \times 10^9$/liter, absolute neutrophil count $<1.2 \times 10^9$/liter, or platelet count $<100 \times 10^9$/liter; estimated glomerular filtration rate ≤40 ml/minute (Cockcroft-Gault calculation); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >1.5× the upper limit of normal (ULN); recent, current, or chronic infection, including hepatitis B or C or human immunodeficiency virus; evidence of active, latent, or inadequately treated *Mycobacterium tuberculosis* infection; or history of lymphoproliferative disorder or malignancy except for adequately treated nonmetastatic basal/squamous cell cancer of the skin or cervical carcinoma in situ.

Study design and treatment. This was a phase III, randomized, double-blind, parallel-group, placebo-controlled study (Pfizer protocol A3921044) in 111 centers in North America, South America, Europe, Asia, and Australia with the first visit of the first patient on March 31, 2009; this analysis

includes all patients' 12-month data with the last visit of the last patient on April 1, 2011. A list of the ORAL Scan trial (Oral Rheumatoid Arthritis triaL A3921044) study investigators is provided in Appendix A. The study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice in the European Community, and local country regulations. The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Boards and the Independent Ethics Committees of the investigational centers. All patients provided written, informed consent.

Using an interactive voice recognition system, patients were randomized 4:4:1:1 to 1 of 4 sequences: tofacitinib at 5 mg twice daily, tofacitinib at 10 mg twice daily, placebo to tofacitinib at 5 mg twice daily, and placebo to tofacitinib at 10 mg twice daily, all in combination with MTX. For ethical reasons, patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months (defined as nonresponders) were advanced in a blinded manner to their predetermined dose of tofacitinib as indicated above. All patients continuing to receive placebo were advanced in a blinded manner to tofacitinib after 6 months. A nonresponder patient randomized to tofacitinib was also advanced in a blinded manner but continued to receive the same treatment and dose for the duration of the study. Increases in NSAIDs and systemic corticosteroids were not permitted; decreases were allowed only if required to protect patient safety.

Efficacy assessments. Coprimary efficacy end points evaluated tofacitinib at 5 or 10 mg twice daily versus placebo with respect to the response rates according to the ACR 20% improvement criteria (ACR20 response rates) (13) (at month 6), the mean change from baseline in total modified Sharp/van der Heijde score (SHS) (14) (at month 6), the mean change from baseline in the Health Assessment Questionnaire disability index (HAQ DI) score (15) (at month 3), and rates of remission, defined as a 4-variable Disease Activity Score in 28 joints using the ESR (DAS28-ESR) <2.6 (16) (at month 6). Key secondary end points included ACR20, ACR50, and ACR70 response rates and DAS28-ESR assessments (at all visits) and changes from baseline in the ACR core set of disease activity measures (17) (at month 6). Key secondary end points for structural preservation included rates of nonprogressors (≤0.5 unit change from baseline in total SHS or erosion score) (18) (at months 6, 12, and 24), changes from baseline in total SHS (at months 12 and 24), and changes from baseline in erosion score and joint space narrowing (JSN) score (at months 6, 12, and 24). Patient-reported outcomes were assessed throughout and included, in addition to the HAQ DI score, the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) (19) and the patient's assessment of arthritis pain (on a visual analog scale) (15).

Radiographic methods. Radiographs for each patient were scored by 2 independent readers (who were blinded to patient randomization sequence and visit) according to the total SHS (14). The 2 readers' scores for each patient were averaged and used for the final score.

Safety assessments. Safety end points included incidence and severity of clinical laboratory abnormalities and vital signs and of all adverse events (AEs). A Cardiovascular Safety Endpoint Adjudication Committee (all external independent consultants), blinded to treatment group assignment, reviewed all potential cardiovascular events and deaths.

Statistical analysis. Sample size was determined based on structural progression (total SHS) (see Supplementary Appendix 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract). The full analysis set was the primary analysis population for efficacy and safety. This included all randomized patients who received ≥1 dose of study drug and had ≥1 postbaseline measurement (including safety data). If the end point was a change from baseline, a baseline measurement was needed. The normal approximation for difference in binomial proportions was used to test superiority of each tofacitinib dose against placebo with respect to ACR20 response rate and rates of DAS28-ESR <2.6; nonresponder imputation (NRI; setting the ACR20 response rate or the rate of DAS28-ESR <2.6 to nonresponsive) addressed missing data. NRI was applied to patients who discontinued for any reason and to patients who, at month 3, had not achieved a 20% improvement in tender and swollen joint counts regardless of treatment assignment; this analysis therefore assumed that nonresponder patients at month 3 were those for whom treatment had failed for the remainder of the study, even if they subsequently fulfilled the ACR20 criteria.

Thus, the primary analysis used NRI at month 6; as a secondary analysis and to account for tofacitinib-treated patients who "advanced" at month 3 (because of lack of meeting the response criteria) to the same dose of tofacitinib, an NRI "without an advancement penalty" was employed. This allowed assessment of clinical changes in these patients at month 6 who were receiving a stable dose of tofacitinib since day 1. The primary analysis was more conservative than it has been historically applied (NRI alone), since in order to be counted as having achieved an ACR20 response at month 6 in the primary analysis, patients are first required to have a 20% improvement in both tender and swollen joint counts at month 3. For further details of the NRI analysis, see Supplementary Appendix 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract.

For total SHS, the primary analysis was an analysis of variance model for change from baseline to month 6, and included baseline total SHS as a covariate. A patient must have had ≥1 postbaseline radiograph to be included in the linearly extrapolated analysis. Patients who advanced before month 6 (nonresponders) had their month 6 measurements imputed using a linear extrapolation from month 3 radiographs even when month 6 radiographs were available, regardless of treatment assignment. Since all placebo-treated patients advanced by or at month 6, placebo data for month 12 were imputed using linear extrapolation from month 3 or month 6 radiographic scores, whichever was the last month at which placebo was dosed before advancement to tofacitinib. The approach of using month 3 radiographs for linear extrapolation for all treatment groups for advanced patients is similar to applying the NRI advancement penalty to all treatment groups, and is used to treat tofacitinib- and placebo-treated groups the same way in the analysis and not introduce bias in favor of tofacitinib. All total SHS–related variables were imputed using this method. Associated binary variables (e.g., rates of patients

Table 1. Demographic and baseline clinical characteristics of the patients*

	Tofacitinib 5 mg twice daily (n = 321)	Tofacitinib 10 mg twice daily (n = 316)	Placebo to tofacitinib 5 mg twice daily (n = 81)	Placebo to tofacitinib 10 mg twice daily (n = 79)
Female, no. (%)	269 (83.8)	273 (86.4)	65 (80.2)	72 (91.1)
White, no. (%)	152 (47.4)	144 (45.6)	36 (44.4)	36 (45.6)
Age, mean ± SD years	53.7 ± 11.6	52.0 ± 11.4	53.2 ± 11.5	52.1 ± 11.8
Disease duration, mean (range) years	8.9 (0.3–43.0)	9.0 (0.3–42.0)	8.8 (0.6–30.8)	9.5 (0.4–43.5)
Tender joints (0–68), mean	24.1	23.0	23.3	22.6
Swollen joints (0–66), mean	14.1	14.4	14.0	14.5
Total SHS (0–448)				
Mean	31.1	37.3	35.0	30.1
Median	13.0	13.0	16.0	14.0
Average annual radiographic progression rate, units per year	5	5.5	—†	—†
Erosion score (0–280), mean	13.8	17.7	14.5	14.3
Patients with erosion score ≥3, %	60.1	65.4	—‡	—‡
JSN score (0–168), mean	17.3	19.6	20.5	15.8
HAQ DI score (0–3), mean	1.41	1.39	1.40	1.23
Four-variable DAS28-ESR (0–9.4), mean	6.34	6.25	6.25	6.29
Three-variable DAS28-CRP (0–9.4), mean	5.22	5.20	5.14	5.18
ESR, mean mm/hour	50.1	50.5	47.8	54.4
CRP, mean mg/liter	15.5	17.0	12.2	15.3
RF positive, %	75.2	77.6	79.7	75.3
Anti-CCP positive, %	85.9	84.4	84.0	82.3
Prior MTX, %	100	99.7§	100	100
Prior DMARDs other than MTX, %	60.1	60.8	76.5	58.2
Prior TNF inhibitors, %	19.3	15.8	9.9	8.9
Prior non–TNF inhibitor biologic agents, %	5.3	4.7	3.7	2.5

* In some cases the number of patients sampled was less than the total number of patients in each group. SHS = modified Sharp/van der Heijde score; JSN = joint space narrowing; HAQ DI = Health Assessment Questionnaire disability index; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; DAS28-CRP = DAS28 using the C-reactive protein level; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor.
† The mean value in the 2 placebo-treated groups combined was 4.8 units per year.
‡ The mean value in the 2 placebo-treated groups combined was 68.3%.
§ One patient was randomized but died before receiving medication.

with no progression) were analyzed using normal approximation to the binomial.

The HAQ DI score was expressed as change from baseline. The analysis was performed using a mixed-effects repeated-measures model that included the fixed effects of treatment, visit, treatment-by-visit interaction, and baseline; patients were a random effect. Secondary end points that were binary variables were analyzed by NRI; last observation carried forward analysis was performed to support robustness of results. Continuous end points followed the analysis described for HAQ DI score; values were set to "missing" for months 3–6 for patients who advanced at month 3. Supplementary efficacy analyses were performed to verify the robustness of the primary results (see Supplementary Appendix 3, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract). Safety data were summarized.

To control the Type I error rate in the primary analyses, coprimary efficacy end points were assessed sequentially using a step-down approach in the following order: ACR20 response rates, mean change in total SHS, mean change in HAQ DI score, and rates of DAS28-ESR <2.6. For each end point, and for each dose group, the comparison with placebo was conducted using a significance (alpha) level set at 0.05 (2 sided) or equivalently 0.025 (1 sided); *P* values were significant based on the step-down procedure (see Supplementary Figure 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract). For key secondary end points, *P* values are presented with no adjustment for multiple comparisons, with their nominal values. For all analyses up to and including month 6, placebo sequences are pooled as 1 group, while for any analysis post–month 6, each placebo sequence is presented separately.

RESULTS

Patient disposition and demographics. Overall, 797 patients were randomized and treated (tofacitinib at 5 mg twice daily, n = 321; tofacitinib at 10 mg twice daily, n = 316; placebo to tofacitinib at 5 mg twice daily, n = 81; placebo to tofacitinib at 10 mg twice daily, n = 79). At month 3, 42 (51.9% of the placebo to 5 mg tofacitinib group) and 37 (46.8% of the placebo to 10 mg

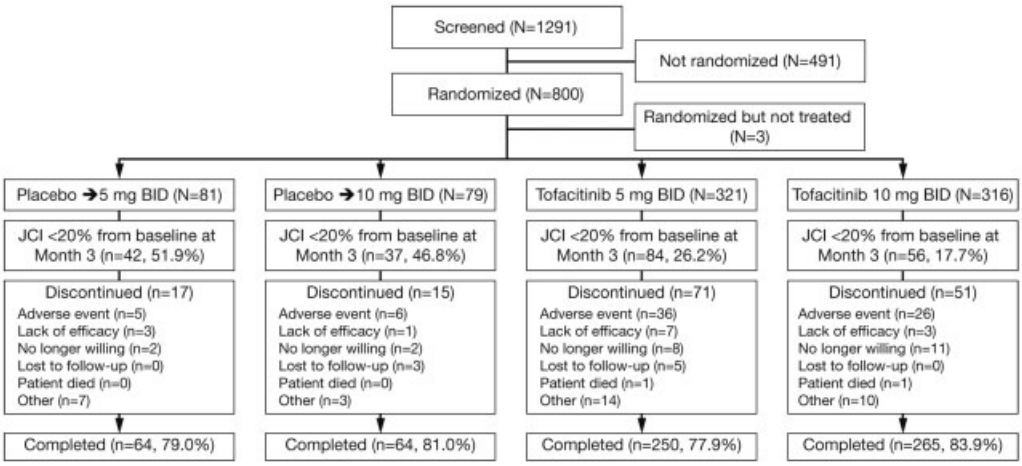

Figure 1. Disposition of the study patients. Patients in the treatment arms were randomized to receive tofacitinib starting at month 0 at either 5 mg twice daily (BID) or 10 mg twice daily. Placebo-treated patients were randomized to receive placebo during months 0–6 and then tofacitinib at either 5 mg twice daily or 10 mg twice daily during months 6–12. All placebo-treated patients who had not achieved 20% improvement in swollen and tender joint counts after 3 months were advanced in a blinded manner to receive tofacitinib at 5 or 10 mg twice daily. Completed patients were those still receiving study treatment at the date of cutoff (April 1, 2011). JCI = (swollen and tender) joint count improvement.

tofacitinib group) nonresponder placebo-treated patients advanced to tofacitinib; 84 patients (26.2%) and 56 patients (17.7%) randomized to tofacitinib 5 mg and 10 mg twice daily, respectively, were also nonresponders at month 3. Baseline demographics (Table 1) and rates of discontinuation of study treatment (Figure 1) were similar across groups. The mean age of the patients was 53 years, the mean duration of RA was 9.0 years, 53.8% of the patients were nonwhite, and 85.2% were female. At baseline, the mean total SHS ranged from 30.1 to 37.3, and average annual radiographic progression rates were similar across groups (Table 1). The proportions of patients with an erosion score ≥3 at baseline were 68.3%, 60.1%, and 65.4% in the placebo-treated, 5 mg tofacitinib–treated, and 10 mg tofacitinib–treated groups, respectively.

Efficacy. *Coprimary efficacy end points.* The ACR20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, versus 25.3% for patients receiving placebo ($P < 0.0001$ for both comparisons). The least squares mean (LSM) changes in total SHS at month 6 were 0.12 and 0.06 for patients receiving tofacitinib 5 mg and 10 mg twice daily, respectively, versus 0.47 for patients receiving placebo ($P = 0.0792$ [not significant] and $P \leq 0.05$, respectively). Since tofacitinib at 5 mg twice daily failed to be statistically significant for radiographic progression, and due to the step-down procedure applied to primary efficacy end points, significance was not declared for the HAQ DI score or DAS28-ESR <2.6 for tofacitinib at 5 mg twice daily. LSM changes in the HAQ DI score at month 3 for tofacitinib at 5 mg and 10 mg twice daily were –0.40 and –0.54, respectively, versus –0.15 for placebo (5 mg twice daily, significance not declared for this coprimary end point; 10 mg twice daily, $P < 0.0001$). Rates of remission as defined by DAS28-ESR <2.6 at month 6 were 7.2% and 16.0% for tofacitinib at 5 mg and 10 mg twice daily, respectively, versus 1.6% for placebo (5 mg twice daily, significance not declared for this coprimary end point; 10 mg twice daily, $P < 0.0001$).

Signs and symptoms. Statistically significant improvements with tofacitinib were seen in ACR50 (32.4% for 5 mg twice daily, 43.7% for 10 mg twice daily, 8.4% for placebo [$P < 0.0001$ for both]) and ACR70 (14.6% for 5 mg twice daily, 22.3% for 10 mg twice daily, 1.3% for placebo [$P < 0.0001$ for both]) responses versus placebo at month 6. At month 12, ACR20, ACR50, and ACR70 response rates were 48.5%, 32.7%, and 18.8%, respectively, for tofacitinib at 5 mg twice daily and 57.0%, 41.1%, and 27.5%, respectively, for tofacitinib at 10 mg twice daily. A significant improvement in ACR20/50/70 responses for each tofacitinib dose versus placebo was seen by month 1 (first visit postbaseline). ACR response data are presented in Figures 2A and B. Changes from baseline in the ACR core set of disease activity measures (at month 6) are presented in Supplementary Table 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract. Significant effects on the rate

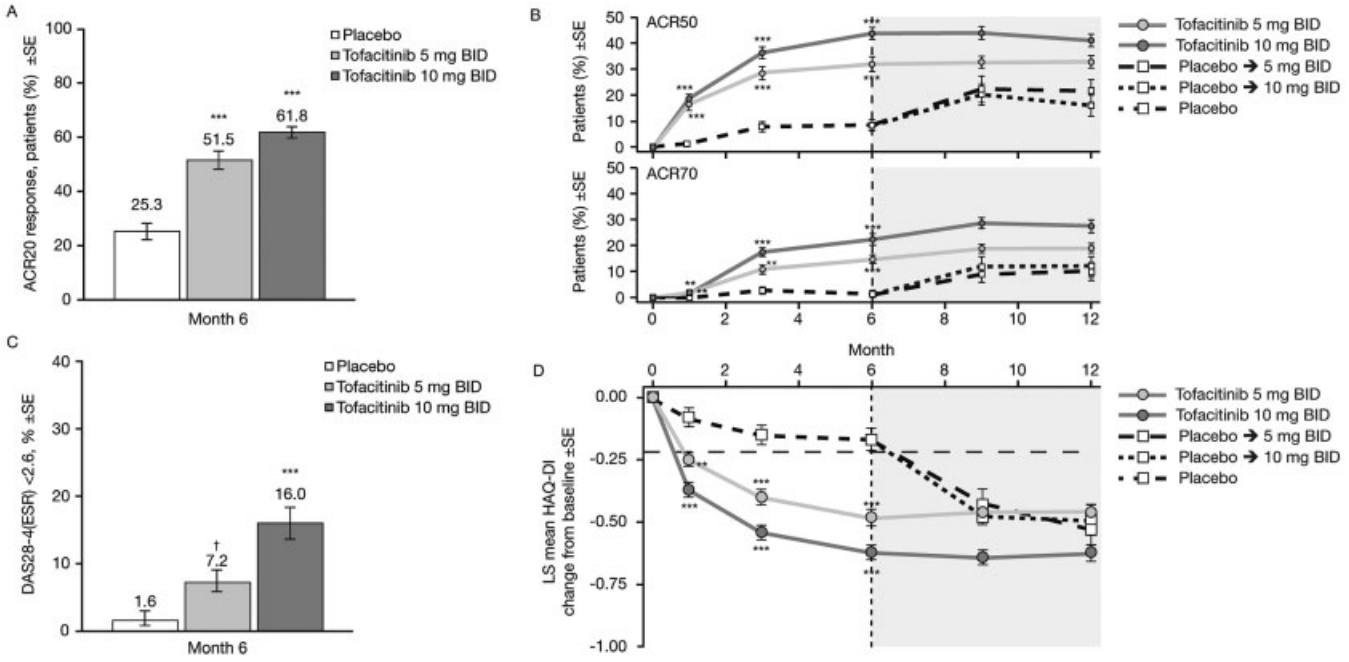

Figure 2. A, Response rates according to the American College of Rheumatology 20% improvement criteria (ACR20 response rates) at month 6. **B,** ACR50 and ACR70 response rates over time. **C,** Percentages of patients scoring <2.6 at month 6 on the 4-variable Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR). **D,** Least squares (LS) mean changes over time in Health Assessment Questionnaire disability index (HAQ DI) scores. The dashed horizontal line represents the minimal clinically important difference of –0.22 for the HAQ DI score. Values are the mean ± SEM. *P* values are presented for analyses up to and including month 6 (the time at which all the patients in the placebo group were switched to tofacitinib), where placebo sequences are pooled as 1 group. *P* values over time are from secondary analyses where there is no adjustment for multiple comparisons; at month 3, *P* values shown are not subject to the step-down approach for the coprimary efficacy end points. ** = $P < 0.01$; *** = $P < 0.001$ versus placebo. † = significance not declared. BID = twice daily. See Figure 1 for description of groups.

of ACR20 response with tofacitinib as compared with placebo were seen in all geographic regions at month 6 ($P = 0.024$ and $P = 0.0002$ for the comparison of 5 mg and 10 mg twice daily versus placebo, respectively, in the US; $P = 0.0145$ and $P = 0.0113$, respectively, in South America; $P = 0.0045$ and $P = 0.0021$, respectively, in Europe; $P = 0.0005$ and $P < 0.0001$, respectively, in the rest of the world).

Rates of DAS28-ESR <2.6 reached 10.6% and 15.2% in the groups receiving tofacitinib at 5 mg and 10 mg twice daily, respectively, by month 12. By month 6, low disease activity (DAS28-ESR ≤3.2) was achieved by 14.3% and 28.4% of patients receiving tofacitinib at 5 mg and 10 mg twice daily, respectively, versus 3.1% of patients receiving placebo ($P < 0.0001$ for both comparisons). At month 12, the rates of DAS28-ESR ≤3.2 for patients receiving tofacitinib at 5 mg and 10 mg twice daily increased to 23.4% and 30.7%, respectively. At month 6, LSM changes from baseline in DAS28-ESR were significant for tofacitinib at both 5 mg twice daily (–2.1) and 10 mg twice daily (–2.5) versus placebo (–1.3) ($P < 0.0001$ for both comparisons); at month 12, these values were –2.3 and –2.5 for tofacitinib at 5 mg and 10 mg twice daily, respectively. Data for selected DAS28-ESR measurements are presented in Figure 2C and in Supplementary Figure 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract.

Physical function and other patient-reported outcomes. Changes from baseline in HAQ DI scores over time are presented in Figure 2D. At month 6, the LSM changes from baseline in FACIT-F for tofacitinib at 5 mg and 10 mg twice daily were 5.6 and 6.9, respectively, versus 2.1 for placebo ($P < 0.001$ and $P < 0.0001$, respectively). Significant improvements in patient's assessment of arthritis pain were also reported for tofacitinib versus placebo at month 6 (see Supplementary Table 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract).

Structural preservation. At baseline, radiographs were available for 98.7% of patients across treatment

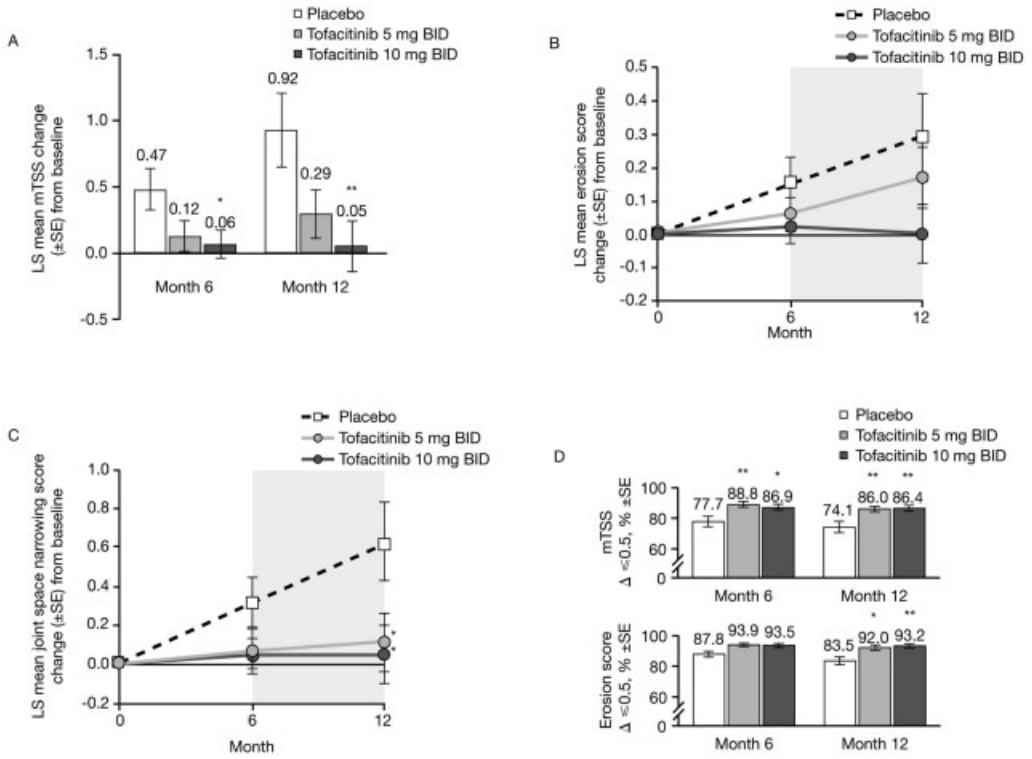

Figure 3. A–C, Least squares (LS) mean changes in total modified Sharp/van der Heijde score (total SHS; mTSS) at months 6 and 12 (**A**) and in erosion score (**B**) and joint space narrowing score (**C**) over time. **D,** Proportions of nonprogressors (those with changes from baseline of ≤0.5 in total SHS or erosion score) at months 6 and 12. Values are the mean ± SEM. ∗ = $P \leq 0.05$; ∗∗ = $P < 0.01$ versus placebo. BID = twice daily.

sequences. The difference from placebo in mean changes from baseline in total SHS at month 12 was statistically significant for tofacitinib at 10 mg twice daily ($P < 0.01$) but not at 5 mg twice daily ($P = 0.0558$). Treatment with both tofacitinib doses resulted in less progression from baseline in both components of the total SHS (erosion score and JSN score) versus placebo at months 6 and 12; changes in these scores were statistically significant at month 12 for JSN, but not for erosion, for both tofacitinib-treated groups versus the placebo-treated group ($P \leq 0.05$). Mean changes from baseline in total SHS, erosion score, and JSN score are presented in Figures 3A–C.

The proportion of patients with no radiographic progression (≤0.5 unit increase from baseline in total SHS) at months 6 and 12 was similar in both tofacitinib-treated groups and significantly greater than in the placebo-treated group (both $P \leq 0.05$). At month 6, the proportion of patients with no progression in erosion score (≤0.5 unit increase from baseline) was numerically greater, but not statistically significantly different, in the tofacitinib-treated groups versus the placebo-treated group ($P > 0.05$) (Figure 3D). The proportion of patients with no progression in erosion score at month 12 was significantly greater in both tofacitinib-treated groups versus the placebo-treated group ($P \leq 0.05$) (Figure 3D).

Changes from baseline in total SHS, JSN score, and erosion score were computed for each patient, and individual values were arranged in cumulative probability plots to show the distribution of changes for the population as a whole. The plots of changes from baseline in total SHS, JSN score, and erosion score at months 6 and 12 for both tofacitinib-treated groups were very similar and were different from the plot for the placebo-treated group. Cumulative probability plots for total SHS at months 6 and 12 are presented in Figure 4.

In post hoc analyses of subsets of patients with prognostic factors predictive of greater progression of joint damage (20,21) (anti-CCP positivity, 4-variable DAS28-ESR >5.1, anti-CCP positivity and/or RF positivity with erosion score ≥3, and baseline total SHS greater than baseline median total SHS), more pronounced effects were observed for tofacitinib at 5 mg

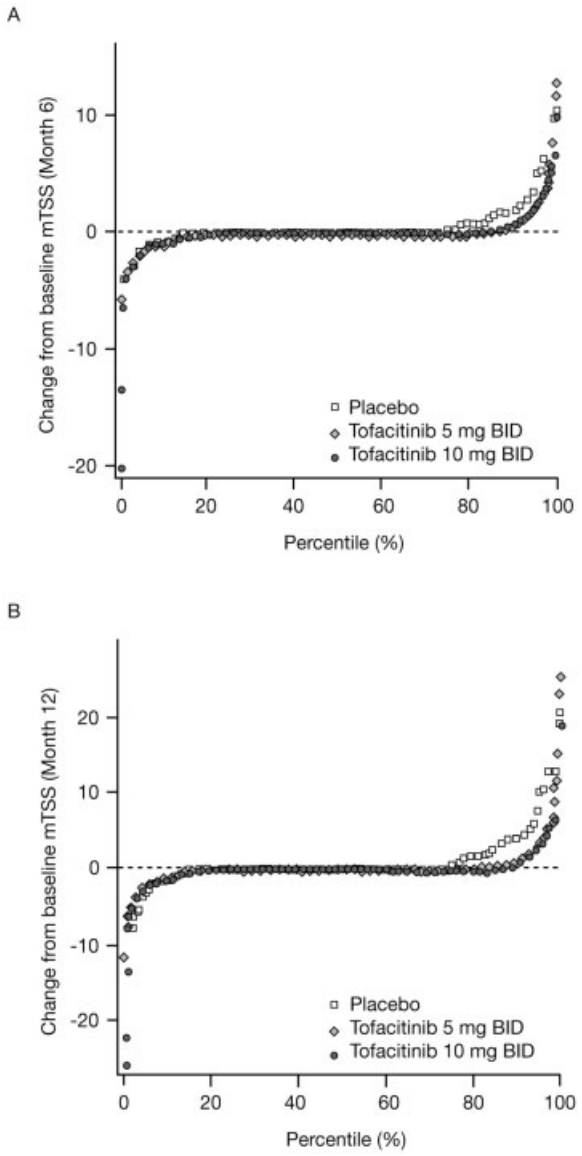

Figure 4. Cumulative probability plots showing change from baseline in total modified Sharp/van der Heijde score (total SHS; mTSS) at months 6 (**A**) and 12 (**B**). BID = twice daily.

and 10 mg twice daily, with greater differences from placebo (see Supplementary Figure 3, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract).

Supplementary analyses. Sensitivity analyses, including multiple imputation/generalized estimating equation analyses for ACR and 4-variable DAS28-ESR <2.6 response rates and a random coefficients model for total SHS, confirmed the primary analyses (see Supplementary Appendix 4, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract).

Safety and tolerability. Treatment-emergent AEs during months 0–3 were reported with similar frequency in patients treated with tofacitinib at 5 mg twice daily (157 of 321 [48.9%]), tofacitinib at 10 mg twice daily (171 of 316 [54.1%]), and placebo (73 of 160 [45.6%]). During months 3–6, treatment-emergent AEs were reported for 145 patients (45.2%) and 111 patients (35.1%) randomized to tofacitinib at 5 mg and 10 mg twice daily, respectively. In months 6–12 (when all patients randomized to placebo had advanced to active treatment), the incidence of treatment-emergent AEs was similar for tofacitinib sequences (51.7% receiving tofacitinib at 5 mg twice daily [n = 166], 55.1% receiving tofacitinib at 10 mg twice daily [n = 174]) and placebo sequences (42.0% advancing from placebo to tofacitinib at 5 mg twice daily [n = 34], 44.3% advancing from placebo to tofacitinib at 10 mg twice daily [n = 35]) (see Supplementary Table 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract).

The most frequently reported treatment-emergent AEs from months 0–12, by system organ class, were infections and infestations, gastrointestinal disorders, and abnormalities in laboratory measurements leading to investigations. Treatment-emergent AEs occurring in >2% of patients in any treatment group are summarized by Medical Dictionary for Regulatory Activities preferred terms in Supplementary Table 3, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract.

The incidence of serious AEs and discontinuations due to AEs across treatment groups was similar in each of months 0–3, 3–6, and 6–12 (see Supplementary Table 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract). Incidence rates of serious infections per 100 patient-years (95% confidence intervals [95% CIs]) through month 12 for placebo, tofacitinib at 5 mg twice daily, and tofacitinib at 10 mg twice daily were 3.68 (95% CI 0.92–14.71), 4.17 (95% CI 2.55–6.80), and 2.32 (95% CI 1.21–4.46), respectively. There were 7 opportunistic infections; doses reported were at event onset. Three were classified as serious as per the protocol (*Pneumocystis jiroveci pneumonia* [tofacitinib at 5 mg twice daily], cytomegalovirus sialadenitis [tofacitinib at 10 mg twice daily], and cytomegalovirus viremia [tofacitinib at 10 mg twice daily]) and 4 as nonserious (lymph node tuberculosis [tofacitinib at 10 mg twice daily] and esophageal candidiasis [tofacitinib at 5 mg twice daily, n = 2; tofacitinib at 10 mg twice daily, n = 1]) (see Supplemen-

tary Table 4, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract).

There were 6 deaths. Three patients receiving tofacitinib at 5 mg twice daily withdrew from the study due to AEs (acute respiratory distress syndrome and viral pneumonia, n = 1; metastatic lung cancer, n = 1; and *P jiroveci pneumonia*, n = 1) and subsequently died. One patient in the placebo-treated group withdrew due to acute renal failure before advancement to tofacitinib and then died (due to cardiac arrest and several AEs). Two patients died prior to withdrawing from the study, 1 from pneumonia (in the group receiving tofacitinib at 5 mg twice daily) and 1 from aspiration (in the group receiving tofacitinib at 10 mg twice daily). All deaths were attributed to the study treatment (including the placebo-treated patient who died) by the investigator, except for the patient who died following aspiration of a glycerine swab. Details surrounding these events are described in Supplementary Table 4, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract.

Six patients treated with tofacitinib experienced 6 nonfatal cardiovascular events that met adjudication event criteria. Three events were adjudicated as being cardiovascular: angina pectoris (in the group receiving tofacitinib at 5 mg twice daily), coronary artery disease (in the group receiving tofacitinib at 5 mg twice daily), and carotid artery stenosis (in the group receiving tofacitinib at 10 mg twice daily). Three were adjudicated as being cerebrovascular: cerebral infarction (1 in the group receiving tofacitinib at 10 mg twice daily) and lacunar infarction (2 in the group receiving tofacitinib at 10 mg twice daily [1 event occurred postrandomization but before treatment]). No patient had congestive heart failure.

Nine patients were diagnosed as having carcinomas: basal cell carcinoma (3 in the 5 mg tofacitinib–treated group, 1 in the 10 mg tofacitinib–treated group), stomach adenocarcinoma (1 in the 5 mg tofacitinib–treated group, 1 in the 10 mg tofacitinib–treated group), bone squamous cell carcinoma (1 in the 5 mg tofacitinib–treated group), breast mucinous adenocarcinoma (1 in the 10 mg tofacitinib–treated group), and non-Hodgkin's lymphoma (1 in the 10 mg tofacitinib–treated group). One patient in the 10 mg tofacitinib–treated group was diagnosed as having squamous cell carcinoma of the cervix; a biopsy sample was not available for central laboratory adjudication.

Changes in laboratory parameters observed for tofacitinib versus placebo included decreases in mean neutrophil counts, increases in mean low-density lipoprotein (LDL) cholesterol, and small increases in mean serum creatinine (Figure 5). No patient had a confirmed

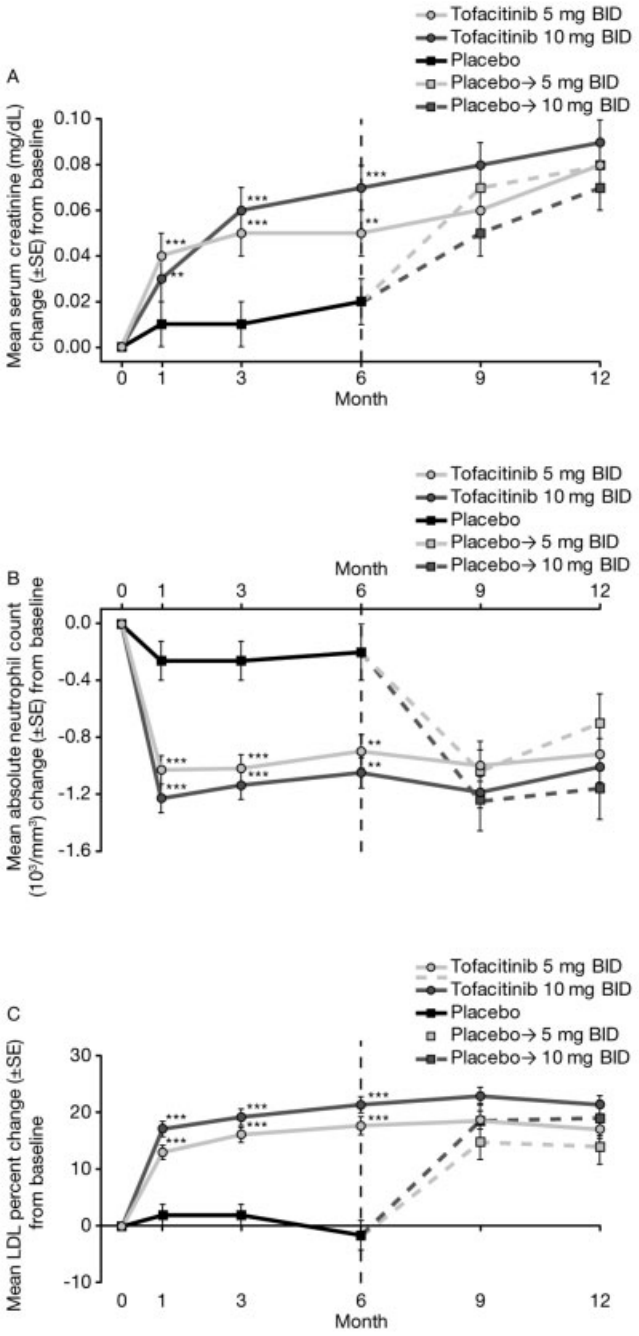

Figure 5. Mean changes from baseline in serum creatinine levels (**A**), absolute neutrophil counts (**B**), and low-density lipoprotein (LDL) cholesterol levels (**C**) over time. Values are the mean ± SEM. *P* values are presented for analyses up to and including month 6 (the time at which all the patients in the placebo group were switched to tofacitinib), where placebo sequences are pooled as 1 group. ** = $P < 0.01$; *** = $P < 0.001$ versus placebo. BID = twice daily. See Figure 1 for description of groups.

absolute neutrophil count $<0.5 \times 10^3/mm^3$ (see Supplementary Table 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract), and no patient withdrew due to leukopenia. Over the 12-month period, increases in serum creatinine >50% from baseline were observed in 5 patients: 1 in the 5 mg tofacitinib–treated group (<1.0%), 3 in the 10 mg tofacitinib–treated group (<1.0%), and 1 in the placebo to 5 mg tofacitinib–treated group after advancement to tofacitinib (1.2%); elevations were attributable to variability over time. None of these patients experienced renal failure. The patient in the placebo to 5 mg tofacitinib–treated group discontinued due to confirmed (occurring at 2 consecutive visits) elevations >50% in serum creatinine; values stabilized following discontinuation.

All mean safety laboratory values stabilized after month 3. Incidences of increases in AST and ALT ≥1× ULN at month 6 were more frequent in active treatment groups. Elevations ≥3× ULN for AST and ALT were infrequent, and were generally single occurrences that spontaneously returned to normal limits without relation to time in the study; these elevations occurred across treatment sequences (see Supplementary Table 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract), and none were accompanied by bilirubin increases ≥2× ULN.

DISCUSSION

Tofacitinib has proven efficacious clinically in recent trials for the treatment of signs and symptoms of RA and improving physical function when given as monotherapy or in combination with MTX (6,7,22) and could provide a therapeutic alternative to augment the current therapy paradigm. The purpose of this study was to examine whether tofacitinib at 5 and 10 mg twice daily has an effect on structural progression in adult patients with active RA with an inadequate response to MTX. In addition, the study was designed to provide pivotal efficacy data concerning the reduction in signs and symptoms of RA and improvement in physical function, and to provide safety data for tofacitinib at 5 and 10 mg twice daily over 24 months.

Twelve-month data from this 24-month study provide evidence of the efficacy of inhibition of structural damage with tofacitinib. Based on published literature, the placebo was estimated to have a mean increase (deterioration) from baseline of ≥1.4 units, and the observed difference between tofacitinib and placebo would be ≥0.8 units in total SHS at month 6, whereas the observed change from baseline in mean total SHS for the placebo group at month 6 was, in fact, only 0.47 units, with both tofacitinib arms showing negligible increases (0.06 and 0.12 units) from baseline. This was approximately one-fifth of that predicted from the estimated mean annual radiographic progression at baseline of 4.8 units/year, and was significantly less than the progression of radiographic joint damage expected in DMARD-inadequate responder populations based on historical data (23–25).

These findings are also consistent with the reported trend toward decreased disease progression in RA patients over time, attributable to improved treatment (26–28), which, combined with the need to minimize duration of patient exposure to placebo treatment, makes the demonstration of a structural benefit more challenging (as seen here with the nonsignificant results with tofacitinib at 5 mg twice daily). Importantly, a substantial proportion of patients in this study also had prior treatment with tumor necrosis factor inhibitors or other biologic therapies. Despite randomization, the proportion of placebo-treated patients with prior biologic treatment was lower, which potentially disfavors the observed effect of tofacitinib as patients with prior biologic treatment usually represent a population with more severe disease.

Despite the limited degree of joint damage progression observed in the entire study population, more pronounced effects were observed for tofacitinib at 5 and 10 mg twice daily in post hoc analyses of the subset of patients with poor prognostic factors. Interestingly, these subgroups at risk for greater progression of joint damage showed maintained or increased differentiation between both doses of tofacitinib and placebo treatments.

Consistent with findings in other studies (6,7), tofacitinib at 5 and 10 mg twice daily demonstrated benefits in reducing the signs and symptoms of RA and improving physical function. Patients receiving tofacitinib also demonstrated clinically meaningful improvements in levels of fatigue and pain. Improvements were significant regardless of geographic region, consistent with previous studies (7,29). Across end points, there was no consistent pattern favoring any particular region.

Frequencies of AEs, serious AEs, and serious infections were similar across sequences. There were 6 deaths and 7 opportunistic infections (of which 3 were serious AEs) occurring during the 12-month period. Treatment with tofacitinib resulted in dose-dependent mean increases in LDL cholesterol and decreases in

mean neutrophil counts versus placebo. Elevations in serum creatinine >50% from baseline were infrequent. Potentially important increases (>3× ULN) in liver enzymes were uncommon, despite background treatment with MTX. Longer-term monitoring of patients receiving tofacitinib is ongoing in long-term extension programs from randomized studies.

Overall, the results of this 12-month analysis from a 24-month phase III study confirm findings seen previously in phase II and phase III studies in patients with active RA treated with tofacitinib and, for the first time, provide evidence of the potential to inhibit progression of structural damage.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. van der Heijde had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Van der Heijde, Tanaka, Fleischmann, Keystone, Zerbini, Cardiel, Tegzová, Wyman, Gruben, Wallenstein, Krishnaswami, Zwillich, Connell.

Acquisition of data. Van der Heijde, Tanaka, Fleischmann, Keystone, Kremer, Zerbini, Cardiel, Nash, Song, Tegzová, Wallenstein, Krishnaswami, Bradley.

Analysis and interpretation of data. Van der Heijde, Fleischmann, Keystone, Kremer, Zerbini, Cardiel, Cohen, Nash, Tegzová, Wyman, Gruben, Benda, Wallenstein, Krishnaswami, Zwillich, Bradley, Connell.

ROLE OF THE STUDY SPONSOR

The authors employed by Pfizer Inc had roles in study design, data analysis, data interpretation, writing of the manuscript, and agreement to submit the manuscript for publication. All authors, including authors employed by Pfizer Inc, approved the content of the submitted manuscript. Pfizer Inc paid a contractor for statistical analysis of the data and funded editorial support provided by a contractor.

REFERENCES

1. Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. Am J Manag Care 2007;13 Suppl 9:S237–51.
2. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. Immunol Rev 2009;228:273–87.
3. Ghoreschi K, Jesson MI, Li X, Lee JL, Ghosh S, Alsup JW, et al. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). J Immunol 2011;186:4234–43.
4. Meyer DM, Jesson MI, Li X, Elrick MM, Funckes-Shippy CL, Warner JD, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond) 2010;7:41.
5. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012;64:617–29.
6. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum 2012;64:970–81.
7. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367:495–507.
8. Burmester GR, Blanco R, Charles-Schoemann C, Wollenhaupt J, Zerbini CA, Benda B, et al, and the ORAL Step Investigators. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, in combination with methotrexate, in patients with active rheumatoid arthritis with an inadequate response to tumor necrosis factor-inhibitors: a 6-month phase 3 study [abstract]. Arthritis Rheum 2011;63 Suppl:S279.
9. Van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19.
10. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al, on behalf of the ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013. Epub ahead of print.
11. Kremer JM, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, in combination with traditional DMARDS: a phase 3 efficacy and safety study in patients with active rheumatoid arthritis with an inadequate response to DMARDs [abstract]. Ann Rheum Dis 2011;70 Suppl 3:170.
12. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
13. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
14. Van der Heijde DM. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261–3.
15. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol 1982;9:789–93.
16. Radboud University Nijmegen Medical Centre. DAS28. URL: http://www.das-score.nl.
17. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729–40.

18. Van der Heijde D, Simon L, Smolen J, Strand V, Sharp J, Boers M, et al. How to report radiographic data in randomized clinical trials in rheumatoid arthritis: guidelines from a roundtable discussion. Arthritis Rheum 2002;47:215–8.
19. Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer 2002;94:528–38.
20. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625–39.
21. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69: 964–75.
22. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH, and the Tofacitinib Study Investigators. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken) 2011;63:1150–8.
23. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al for the Anti–Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594–602.
24. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al, TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) Study Investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004; 363:675–81.
25. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400–11.
26. Finckh A, Choi HK, Wolfe F. Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. Ann Rheum Dis 2006;65:1192–7.
27. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: a meta-analysis. Arthritis Rheum 2006;55: 864–72.
28. Rahman MU, Buchanan J, Doyle MK, Hsia EC, Gathany T, Parasuraman S, et al. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis 2011;70:1631–40.
29. Kremer JM, Zerbini C, Lee EB, Gruben D, Krishnaswami S, Zwillich SH, et al. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor: analysis of efficacy endpoints by subgroups in a pooled phase 2 and 3 rheumatoid arthritis study population [abstract]. Ann Rheum Dis 2012;71 Suppl 3:203.

APPENDIX A: THE ORAL SCAN (A3921044) STUDY INVESTIGATORS

The following investigators participated in the study.

Asia. Dr. Prabha Adhikari (India), Dr. Kouichi Amano (Japan), Dr. Sang-Cheol Bae (Korea), Dr. Srikantiah Chandrashekara (India), Dr. Arvind K Chopra (India), Dr. Ping-Ning Hsu (Taiwan), Dr. Mitsuhiro Iwahashi (Japan), Dr. Jugal Kishore Kadel (India), Dr. Yojiro Kawabe (Japan), Dr. Eun-Mi Koh (Korea), Dr. Joung-liang Lan (Taiwan), Dr. Soo-Kon Lee (Korea), Dr. Hsiao-Yi Lin (Taiwan), Dr. Lieh-bang Liou (Taiwan), Dr. Ming-Fei Liu (Taiwan), Dr. Kiyoshi Migita (Japan), Dr. Toshiaki Miyamoto (Japan), Dr. Nobuyuki Miyasaka (Japan), Dr. Shunsuke Mori (Japan), Dr. Yasuhiko Munakata (Japan), Dr. Shuji Ohta (Japan), Dr. Sung-Hwan Park (Korea), Dr. Won Park (Japan), Dr. Uppuluri Ramakrishna Rao (India), Dr. Seung Cheol Shim (Korea), Dr. Vineeta Shobha (India), Dr. Yeong-Wook Song (Korea), Dr. Yoshinari Takasaki (Japan), Dr. Tsutomu Takeuchi (Japan), Dr. Yoshiya Tanaka (Japan), Dr. Shigeto Tohma (Japan), Dr. Wen-Chan Tsai (Taiwan), Dr. Yukitaka Ueki (Japan), Dr. Sarath Chandra Mouli Veeravalli (India), Dr. Shrikant Wagh (India), Dr. Hisashi Yamanaka (Japan), Dr. Bin Yoo (Korea).

Australia. Assoc. Prof. Stephen Hall, Dr. David Nicholls, Dr. Maureen Rischmueller.

Canada. Dr. Milton F. Baker, Dr. Louis Bessette, Dr. Alfred A. Cividin, Dr. Boulos Haraoui, Dr. Henry Niall Jones, Dr. Edward C. Keystone, Dr. Majed Khraishi, Dr. J. Thorne.

Europe. Dr. Anastas Batalov (Bulgaria), Dr. Daniela Bichovska (Bulgaria), Dr. Zdenek Dvorak (Czech Republic), Dr. Ivan Goranov (Bulgaria), Dr. Halyna M. Hrytsenko (Ukraine), Dr. Jana Kopackova (Czech Republic), Dr. Zdenka Mosterova (Czech Republic), Dr. Boycho Oparanov (Bulgaria), Dr. Andriy Petrov (Ukraine), Dr. Ines Pokrzywnicka-Gajek (Poland), Prof. Vladyslav V. Povoroznyuk (Ukraine), Dr. Jan Rosa (Czech Republic), Dr. Zofia Ruzga (Poland), Prof. Loukas Settas (Greece), Prof. Mykola A. Stanislavchuk (Ukraine), Dr. Dana Tegzova (Czech Republic), Dr. Vira Iosypivna Tseluyko (Ukraine), Dr. Petr Vitek (Czech Republic).

Latin America. Dr. Joao Carlos Tavares Brenol (Brazil), Dr. Mario H. Cardiel-Rios (Mexico), Dr. William Jose Otero Escalante (Colombia), Dr. Javier Dario Marquez Hernandez (Colombia), Dr. Edwin Antonio Jauregui (Colombia), Dr. Mauro W. Keiserman (Brazil), Dr. Ana Claudia Cauceglia Melazzi (Brazil), Dr. Virginia Pascual-Ramos (Mexico), Dr. Luciana Teixeira Pinto (Brazil), Dr. Juan Jose Jaller Raad (Colombia), Dr. Sebastiao C. Radominski (Brazil), Dr. Antonio Carlos Ximenes (Brazil), Dr. Cristiano Augusto de Freitas Zerbini (Brazil).

US. Dr. Herbert Stuart Block Baraf, Dr. Joan Marie Bathon, Dr. Charles Allen Birbara, Dr. Alan Lawrence Brodsky, Dr. John Joseph Cush, Dr. Ara Hagop Dikranian, Dr. Erdal Diri, Dr. Paul Andrew Dura, Dr. Roy Mitchell Fleischmann, Dr. Robert Michael Griffin, Jr., Dr. Dale George Halter, Dr. Jody Kay Hargrove, Dr. Geneva Louise Hill, Dr. Raymond Edward Jackson, Dr. Shelly Pearl Kafka, Dr. Jeffrey Louis Kaine, Dr. Paul L. Katzenstein, Dr. Kevin James Kempf, Dr. Karen Sue Kolba, Dr. Joel Marc Kremer, Dr. Selden Longley III, Dr. Steven D. Mathews, Dr. Ami Charise Milton, Dr. Richard James Misischia, Dr. Haydon Anthony Moorman, Dr. Larry W. Moreland, Dr. Mark William Niemer, Dr. William Rodney Palmer, Dr. Michael Eugene Sayers, Dr. Patrick Thomas Schuette, Dr. Talha Shamim, Dr. William Julius Shergy, Dr. David Hilton Sikes, Dr. Joel Charles Silverfield, Dr. Chokkalingam Siva, Dr. James D. Taborn, Dr. Bridget Tyrell Walsh, Dr. Alvin Francis Wells, Dr. Sanford Mayer Wolfe.