Running head: ACR subscores in RA

Impact of Tofacitinib on Components of the ACR Response Criteria: Posthoc Analysis of Phase III and Phase IIIb/IV Trials

Louis Bessette[1], Eduardo Mysler[2], Cassandra D Kinch[3], Kenneth Kwok[4], Tatjana Lukic[4], Phu Vinh On[3], and Ronald F van Vollenhoven[5,6]

Funding

This study was sponsored by Pfizer Inc. Medical writing support, under the guidance of the authors, was provided by Jennifer Arnold, PhD, CMC Connect, McCann Health Medical Communications and was funded by Pfizer Inc, New York, NY, USA in accordance with Good Publication Practice (GPP3) guidelines (Ann Intern Med 2015;163:461–464).

[1]L. Bessette, MD, MSc, Associate Professor, Department of Medicine, Laval University, Quebec, Quebec, Canada; [2]E. Mysler, MD, Director, Organización Médica de Investigación, Buenos Aires, Argentina; [3]C.D. Kinch, PhD, Medical Advisor, P.V. On, MSc, Senior Manager Access, Pfizer Canada ULC, Kirkland, Quebec, Canada; [4]K. Kwok, MS, Senior Director, T. Lukic, MD, MSc, Global Clinical Lead, Pfizer Inc, New York, New York, USA; [5]R.F. van Vollenhoven, MD, PhD, Director, Amsterdam Rheumatology and Immunology Center, Amsterdam, The Netherlands; [6]R.F. van Vollenhoven, MD, PhD, Professor and Chair, Department of Rheumatology and Clinical Immunology, Amsterdam University Medical Centres, Amsterdam, The Netherlands

Conflict of Interest

LB has received grants and/or research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Gilead Sciences, Novartis, Pfizer Inc, Roche, Sanofi, and UCB; and has acted as a consultant or speaker for AbbVie, Celgene, Eli Lilly, Fresenius Kabi, Gilead Sciences, Novartis, Pfizer Inc, and Sandoz. EM has received research grants from Eli Lilly, Pfizer Inc, and Roche; and serves on speakers' bureaus for AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer Inc, Roche, and Sanofi. CDK, KK, TL, and PVO are employees and stockholders of Pfizer Inc. RFvV has received grants and/or research support from AbbVie, Amgen, Bristol-Myers Squibb, GSK, Pfizer Inc, Roche, and UCB; and has acted as a consultant for AbbVie, AstraZeneca, Biotest, Bristol-Myers Squibb, Celgene, Crescendo, Eli Lilly, GSK, Janssen, Merck, Novartis, Pfizer Inc, Roche, UCB, and Vertex.

Address correspondence to C. D Kinch, Pfizer Canada ULC, 17300 Trans-Canada Hwy, Kirkland, QC, Canada H9J2M5.

Telephone: 403-827-3347.

Email: Cassandra.Kinch@pfizer.com.

Key Indexing Terms

ACR improvement criteria, clinical trials, rheumatoid arthritis

ABSTRACT

Objective. Evaluate the impact of tofacitinib on American College of Rheumatology (ACR) response criteria components in patients with rheumatoid arthritis (RA).

Methods. This posthoc analysis pooled data from RA phase III randomized controlled trials (RCTs) assessing tofacitinib 5 or 10 mg twice daily (BID), adalimumab, or placebo, with conventional synthetic disease-modifying antirheumatic drugs, and a phase IIIb/IV RCT assessing tofacitinib 5 mg BID monotherapy, tofacitinib 5 mg BID with methotrexate, or adalimumab with methotrexate. Outcomes included: proportions of patients achieving ACR20/50/70 responses and ≥20/50/70% improvement rates in ACR components at Week 2 and Months 1, 3, and 6; mean percent improvement in ACR components and Clinical or Simplified Disease Activity Index (CDAI or SDAI) low disease activity or remission rates, at Month 3, for ACR20/50/70 responders.

Results. Across treatment groups, ≥20/50/70% improvement rates were numerically higher for most physician- versus patient-reported measures. In phase III RCTs, at earlier timepoints, ≥50/70% improvements in Patient Global Assessment of Disease Activity, Pain and Clinician Global Assessment were similar. Among ACR20 responders receiving tofacitinib, mean percent improvements for tender and swollen joint counts were >70% at Month 3. CDAI/SDAI remission was achieved by 27.8–45.0% of ACR70 responders receiving tofacitinib at Month 3.

Conclusion. Among ACR20 responders treated with tofacitinib, physician-reported components particularly exceeded 20% response improvement. At Month 3, disease state generally did not corroborate ACR70 response criteria. Divergences between physician- and

patient-reported measures highlight the importance of identifying appropriate patient-reported outcome targets to manage RA symptoms in clinical practice.

NCT00847613/NCT00856544/NCT00853385/NCT02187055

INTRODUCTION

Composite measures of disease activity and treatment response are key efficacy outcomes in rheumatoid arthritis (RA) clinical trials. Common measures include the American College of Rheumatology (ACR) response criteria (1), which require meeting a threshold of ≥20/50/70% improvement (ACR20/50/70, respectively) in several physician- and patient-reported measures, including tender and swollen joint counts (TJC and SJC, respectively; primary criteria) and at least three of five secondary criteria: Clinician Global Assessment (CGA), Patient Global Assessment of Disease Activity (PtGA), patient-reported pain (Pain), Health Assessment Questionnaire-Disability Index (HAQ-DI), and C-reactive protein (CRP) (2,3). The ACR20 response rate is commonly used as the primary outcome measure in RA trials because it can discriminate between active treatment and placebo (1,3). However, ACR response outcomes are not typically calculated in real-world practice (4).

Other composite measures assessed in RA trials and the clinic include the Simplified Disease Activity Index (SDAI; numerical sum of TJC, SJC, CGA, PtGA, and CRP) (5), and the Clinical Disease Activity Index (CDAI; numerical sum of TJC, SJC, CGA, and PtGA) (6). Cut-offs of both indices have been established to classify disease state (remission or low, moderate, or high disease activity) in patients with RA (7).

Using a treat-to-target approach for RA, physicians are recommended to tailor treatment plans to pre-specified goals (e.g., remission or low disease activity [LDA]), and to use composite disease activity measures to monitor treatment response (8). However, there is no standard composite measure used across clinics. Therefore, a comprehensive understanding of the impact of RA treatments on the individual components, which are

typically assessed in the clinic, and the resulting impact on composite measures, may help inform physicians regarding a patient's response to treatment.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. The efficacy and safety of tofacitinib immediate-release 5 and 10 mg twice daily (BID), administered as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), predominantly methotrexate (MTX), in patients with moderately to severely active RA, have been previously reported in phase II (9-13), phase III (14-20), and phase IIIb/IV (21) randomized controlled trials (RCTs) of up to 24 months' duration and in long-term extension (LTE) studies with up to 114 months' observation (22-24). The long-term safety of tofacitinib has been reported in an integrated safety analysis of RCTs and LTE studies spanning 114 months' cumulative tofacitinib exposure (25).

To provide further insight for clinicians regarding expected outcomes with tofacitinib, we examined the impact of tofacitinib 5 or 10 mg BID, adalimumab (ADA) 40 mg every 2 weeks (Q2W), or placebo, with background csDMARDs, or tofacitinib 5 mg BID monotherapy, on the ACR components via a posthoc analysis of phase III and phase IIIb/IV trials. To further explore the ACR components that are most (and least) likely to be improved by treatment, and meet the improvement thresholds (≥20/50/70%) required for inclusion in the ACR response calculation, we evaluated the relative contribution of the secondary ACR components (CGA, PtGA, Pain, HAQ-DI, and CRP) to the overall ACR20/50/70 response rates. Furthermore, to provide insight into expected disease state outcomes in patients achieving ACR20/50/70 responses in clinical trials, we show the proportions of responders achieving SDAI- and CDAI-defined LDA and remission.

MATERIALS AND METHODS

Study design and patients. This posthoc analysis included two cohorts. The placebo-controlled cohort comprised pooled data from three phase III RCTs (ORAL Scan [NCT00847613], ORAL Standard [NCT00853385], ORAL Sync [NCT00856544]) of tofacitinib in patients with active RA. The head-to-head cohort comprised data from a phase IIIb/IV RCT (ORAL Strategy [NCT02187055]) of tofacitinib versus ADA in patients with active RA. Study designs and patient inclusion/exclusion criteria were reported previously (16,17,19-21), and are summarized in Table 1.

Each study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practice, and local country regulations, and was approved by the Institutional Review Board and Independent Ethics Committee at each center (16,17,19-21). Patients provided written informed consent. No further ethical approval was required for this posthoc analysis in accordance with the policies of our institutions.

Outcomes. Outcomes assessed included: proportions of patients achieving overall ACR20/50/70 responses and ≥20/50/70% improvements from baseline in ACR components (improvement rates; TJC, SJC, CGA, PtGA, Pain, HAQ-DI, and CRP) at Week 2 (ORAL Sync only), 6 (head-to-head cohort only), Months 1 (placebo-controlled cohort only), 3 (all studies; end of placebo-controlled period for placebo-controlled cohort), and 6 (all studies); the relative contribution of the secondary ACR components (CGA, PtGA, Pain, HAQ-DI, and CRP) to overall ACR20/50/70 response rates at Month 3; and the relative contribution of SDAI components (TJC, SJC, CGA, PtGA, and CRP) and CDAI components (TJC, SJC,

CGA, and PtGA) to mean change from baseline in SDAI and CDAI scores, respectively, at Month 3.

Additional outcomes assessed in subgroups of patients achieving ACR20/50/70 responses (ACR20/50/70 responders) at Month 3 included: mean percent improvement from baseline in ACR components, SDAI score, and CDAI score; and proportions of patients achieving LDA and remission as defined by SDAI (≤11 and ≤3.3, respectively) and CDAI (≤10 and ≤2.8, respectively) (7).

Statistical analyses. Data are presented for the full analysis set, which comprised all patients who were randomized and received ≥1 dose of study treatment. Analyses are based on observed case data in patients with all seven ACR components assessed at the analyzed time point. No imputation was performed for missing data. Outcomes were summarized descriptively and numerical differences (with no formal statistical comparisons) between treatments are reported.

To assess the relative contribution of each secondary ACR component to the attainment of the overall ACR20 response rate, each component was sequentially set to 'no improvement' (i.e., value of 0 in change from baseline) and the ACR20 response rate was recalculated. The resulting response rates were then rank-ordered from 1–5, with 1 representing the largest contribution (largest decrease in ACR20 response rate); and 5 representing the smallest contribution (smallest decrease in ACR20 response rate). This approach was used to assess the relative contribution of each secondary ACR component to the attainment of the overall ACR50 and ACR70 response rates. The relative contributions of TJC and SJC to the attainment of ACR20/50/70 response rates were not considered in this analysis as these are primary components, with ≥20/50/70% improvement in these

components required to achieve an ACR20/50/70 response rate, respectively. The relative contribution of each SDAI and CDAI component to the mean change from baseline in SDAI and CDAI, respectively, was assessed using a similar approach.

RESULTS

Patients. The placebo-controlled cohort comprised 2117 patients receiving tofacitinib 5 mg BID + csDMARDs (N=769), tofacitinib 10 mg BID + csDMARDs (N=767), ADA + csDMARDs (N=191), or placebo + csDMARDs (N=390). The head-to-head cohort comprised 1088 patients receiving tofacitinib 5 mg BID monotherapy (N=359), tofacitinib 5 mg BID + MTX (N=363), or ADA + MTX (N=366). Demographics and baseline characteristics for each study were previously reported (16,17,19,21).

ACR20/50/70 response rates and ≥20/50/70% improvement rates in ACR components. In the placebo-controlled cohort, ACR20/50/70 response rates and ≥20/50/70% improvement rates in ACR components at Month 3 (end of placebo-controlled period) were similar with tofacitinib 5 or 10 mg BID + csDMARDs and ADA + csDMARDs, but were higher with active treatment versus placebo (Figure 1A–C). Notably, ACR20/50/70 response rates and ≥20/50/70% improvement rates in ACR components were higher beginning at Week 2 and Month 1 with tofacitinib and ADA, respectively, versus placebo.

Across treatments, ACR20/50/70 response rates and ≥20/50/70% improvement rates in ACR components mostly increased through Month 6, and improvement rates for most ACR components surpassed ACR20/50/70 response rates (Figure 1A–C). Typically, through Month 6, ≥20/50/70% improvement rates were higher in physician-reported measures (TJC, SJC, and CGA) versus patient-reported measures (PtGA, Pain, and HAQ-DI) across

treatments. However, ≥20/50/70% improvement rates in CRP were highest versus the other components at Week 2 with active treatment and tended to remain stable over time. Differences between improvement rates in CGA versus the patient-reported measures were generally greater when considering ≥20% versus ≥50/70% improvement rates through Month 6 across treatments, particularly at earlier time points; indeed, ≥50/70% improvement rates in PtGA and Pain were similar to CGA at Week 2, Month 1, and Month 3 (≥70% improvement rates only). Generally, ≥20/50/70% improvement rates in PtGA and Pain were comparable and followed a similar pattern through Month 6, irrespective of treatment. Across treatments, ≥20/50/70% improvement rates in HAQ-DI showed the least improvement of all ACR components through Month 6.

In the head-to-head cohort, ACR20/50/70 response rates and ≥20/50/70% improvement rates in ACR components were comparable through Month 6 in patients receiving tofacitinib 5 mg BID monotherapy, tofacitinib 5 mg BID + MTX, or ADA + MTX (Supplementary Figure 1A–C). Across treatments, ≥20/50/70% improvement rates for most ACR components surpassed ACR20/50/70 response rates; however, ≥20/50/70% improvement rates for HAQ-DI were generally similar to or lower than the ACR20/50/70 response rates.

Similar to the placebo-controlled cohort, ≥20/50/70% improvement rates in ACR components were higher in physician-reported versus patient-reported measures. Across treatments, ≥20/50/70% improvement rates in PtGA and Pain were typically comparable and followed a similar pattern through Month 6. Unlike the placebo-controlled cohort, ≥50/70% improvement rates in PtGA and Pain were not similar to CGA through Month 6.

Relative contribution of the secondary ACR components to ACR20/50/70 response rates at Month 3. Generally, in the placebo-controlled cohort, CGA contributed most, while HAQ-DI contributed least, to ACR20/50/70 response rates at Month 3, across treatments (Table 2A–C). Exceptions with active treatment included ACR70 response rates with tofacitinib 5 mg BID + csDMARDs, wherein Pain contributed most, ACR50 response rates with tofacitinib 10 mg BID + csDMARDs, wherein PtGA contributed least, and ACR70 response rates with ADA + csDMARDs, wherein CGA and PtGA contributed most and Pain and CRP contributed least (Table 2B–C).

In the head-to-head cohort, results aligned with the placebo-controlled cohort, as CGA generally contributed most, while HAQ-DI generally contributed least, to ACR20/50/70 response rates at Month 3, across treatments (Supplementary Table 1A–C).

Percent improvement from baseline in ACR components, SDAI score, and CDAI score in ACR20/50/70 responders at Month 3. Among ACR20/50/70 responders in the placebo-controlled cohort, mean percent improvements from baseline in ACR components typically exceeded 20/50/70%, respectively, at Month 3, across treatments (Figure 2A–C). Mean percent improvement from baseline was higher for TJC and SJC versus CGA, PtGA, Pain, HAQ-DI, and CRP in ACR20/50/70 responders across treatments, and greater differences were observed between physician-reported and patient-reported measures in ACR20 versus ACR50/70 responders. Mean percent improvement from baseline in Pain was comparable in ACR20/50 responders receiving tofacitinib versus ADA; however, mean percent improvement from baseline in Pain was 10.4% higher in ACR70 responders receiving tofacitinib 5 mg BID + csDMARDs versus ADA + csDMARDs. Mean percent improvements from baseline in CRP appeared lower with tofacitinib versus ADA due to

outliers in the tofacitinib groups; median percent improvements from baseline in CRP were similar across active treatment groups for ACR20 (73.8–81.6%), ACR50 (76.1–85.3%), and ACR70 responders (75.9–85.9%). Notably, for ACR20 responders receiving tofacitinib, mean percent improvement from baseline in TJC and SJC exceeded 70%.

Across ACR20/50/70 responders, mean percent improvements from baseline in SDAI and CDAI scores to Month 3 were generally similar to improvements observed for TJC and SJC with all treatments, and exceeded 65% in ACR20 responders receiving tofacitinib (Figure 2A–C).

In the head-to-head cohort, mean percent improvements in ACR components, SDAI score, and CDAI score in ACR20/50/70 responders at Month 3 were comparable across treatments and mostly similar to the placebo-controlled cohort (Supplementary Figure 2A–C).

Proportions of ACR20/50/70 responders achieving SDAI- or CDAI-defined LDA or remission at Month 3. In the placebo-controlled cohort, the proportions of ACR20/50/70 responders achieving SDAI- or CDAI-defined LDA or remission at Month 3 were higher with active treatment versus placebo, with the largest differences observed in ACR70 responders receiving active treatment versus placebo (Figure 3). At Month 3, the proportions of ACR20/50/70 responders in the active treatment groups achieving CDAI LDA ranged from 38.2–49.1%, 61.4–73.6%, and 88.2–95.0%, respectively, versus 28.8%, 60.6%, and 62.5%, for placebo; those achieving CDAI remission ranged from 3.6–9.0%, 9.1–16.7%, and 23.5–45.0%, respectively, versus 0.9%, 3.0%, and 12.5%, for placebo. Overall, SDAI and CDAI LDA and remission rates were numerically higher in ACR20/50/70 responders receiving tofacitinib versus ADA.

In the head-to-head cohort, the proportions of ACR20/50/70 responders across treatments achieving CDAI LDA at Month 3 were mostly comparable with the placebo-controlled cohort (Supplementary Figure 3). The proportions of ACR20/50/70 responders across treatments achieving CDAI remission at Month 3 were generally higher than the placebo-controlled cohort, ranging from 10.0–10.8%, 17.9–18.8%, and 30.6–40.0%, respectively. Across treatments, SDAI and CDAI LDA and remission rates were generally similar (Supplementary Figure 3).

Relative contribution of SDAI or CDAI components to mean change from baseline in SDAI or CDAI scores at Month 3. In the placebo-controlled cohort, TJC, followed by SJC, contributed most to mean change from baseline in SDAI at Month 3, whereas CRP contributed least, across treatments (Table 3). Similarly, across treatments, TJC, followed by SJC, contributed most to mean change from baseline in CDAI at Month 3, whereas PtGA contributed least (Table 3). Similar results were observed in the head-to-head cohort (Supplementary Table 2).

DISCUSSION

Many RA clinical trials use ACR response criteria, generally ACR20/50, as the primary outcome measure, while only the individual ACR components are commonly assessed in clinical practice (1,26). Therefore, to guide clinical decision making, it is important for physicians to have a comprehensive understanding of the impact of RA treatments on the composite measures and individual components. This posthoc analysis investigated the impact of treatments in phase III and phase IIIb/IV tofacitinib RA RCTs on ACR components, SDAI score, and CDAI score; the relative contribution of each component to the

ACR20/50/70 response rates, SDAI score, and CDAI score; and the proportions of patients achieving SDAI and CDAI LDA and remission stratified by ACR20/50/70 response.

In the placebo-controlled cohort, ACR20/50/70 response rates and ≥20/50/70% improvement rates in ACR components at Month 3 were higher with active treatment versus placebo, aligning with previous findings (16,17,19). These improvements were observed from the earliest time point for tofacitinib-treated and ADA-treated patients (Week 2 and Month 1, respectively), versus placebo-treated patients. In the head-to-head cohort, ACR20/50/70 response rates and ≥20/50/70% improvement rates in ACR components were typically similar across time points and treatments. In ACR20/50/70 responders in both cohorts, mean percent improvements from baseline in the ACR components typically exceeded 20/50/70%, respectively, at Month 3. These findings provide insight into the impact that tofacitinib or ADA have on the ACR components at Month 3, a key time point for treatment target assessments, according to the treat-to-target approach for RA (8).

Generally, in both cohorts, ≥20/50/70% improvement rates were higher in physician-reported versus patient-reported measures through Month 6. However, in the placebo-controlled cohort, ≥20/50/70% improvement rates in CRP were highest versus the other components at the earliest time point for tofacitinib-treated and ADA-treated patients (Week 2 and Month 1, respectively) and tended to remain consistent over time. This corresponds with prior findings that tofacitinib results in a rapid, early reduction in CRP that stabilizes by Month 1 (27,28). Overall, however, mean percent improvements from baseline in CRP appeared to be lower in tofacitinib-treated patients compared with ADA-treated patients. This was likely due to outliers in the tofacitinib groups, in which the majority of patients in this analysis were randomized, as median improvements from baseline were

similar across treatments. However, there remains a possibility that this could also be reflective of mechanistic differences between JAK inhibitors and tumor necrosis factor inhibitors in the modulation of inflammatory mediators. Interestingly, ≥70% improvement rates in CGA, PtGA, and Pain were similar through Month 3 in the placebo-controlled cohort, suggesting that patient and physician perceptions of disease status may be more closely aligned for patients achieving LDA following RA treatment. These results may also provide insight into the impact of tofacitinib on other composite measures assessed in RA trials and clinics, including Disease Activity Score in 28 joints using erythrocyte sedimentation rate (29), which was previously reported in tofacitinib-treated versus placebo-treated patients (16,17,19,20).

In both cohorts, physician-reported measures typically contributed more to ACR20/50/70 response rates, SDAI score, and CDAI score than patient-reported measures at Month 3. This may be due to differences in the type of information collected between physician-reported and patient-reported measures (30), or discrepancies in disease or symptom perceptions between the physician and patient, as reported previously for RA (31-34) and other inflammatory diseases (35). Additionally, the divergence of ≥50/70% improvement rates in CGA versus PtGA and Pain at later time points in the placebo-controlled cohort may highlight an unintentional overestimation of treatment response by physicians who wish to retain patients in clinical trials despite only achieving mild symptomatic resolution. Interestingly, differences in ≥20/50/70% improvement rates in CGA versus PtGA and Pain were observed across most time points and treatments in the head-to-head cohort, potentially due to physicians' higher expectations of improvement in the absence of placebo. These results further highlight the need to identify appropriate patient-reported outcome targets that help assess RA symptoms in clinical practice. In both cohorts,

HAQ-DI generally contributed least to the achievement of ACR20/50/70 response rates, which may be attributed to pre-existing functional restrictions of the patients in these trials. While these results may indicate that HAQ-DI is not a reliable measure of treatment response, it is unclear how these results translate into clinical practice. However, a previous study showed no statistical differences in HAQ-DI between RCTs and observational studies (36). Future analyses could focus on an earlier RA patient population to identify if HAQ-DI contributes more to the achievement of ACR response rates in those patients versus the cohorts studied here.

Analysis of ACR20/50/70 responders achieving SDAI- or CDAI-defined LDA or remission at Month 3 showed that 38.2–52.0% of ACR20 responders and 61.4–79.5% of ACR50 responders receiving active treatment across both cohorts achieved SDAI or CDAI LDA. Furthermore, while many physicians consider the ACR70 response rate to correspond with a state of remission, these results showed that 23.5–45.0% of ACR70 responders receiving active treatment across both cohorts achieved SDAI or CDAI remission. This suggests that ACR response rates, which measure treatment response between two time points (37), may not corroborate achievement of disease state thresholds when assessing the effectiveness of RA treatments in a clinical setting.

Accumulating evidence indicates that JAK inhibitors may be more effective in improving patient pain than other advanced therapies (38,39). This analysis showed that ≥20/50/70% improvement rates in Pain were generally comparable in tofacitinib-treated and ADA-treated patients in both cohorts, as previously reported (40). However, there was a small improvement in Pain in ACR70 responders receiving tofacitinib versus ADA at Month 3. Therefore, a specific effect on pain, other than through the established

antirheumatic efficacy of tofacitinib, cannot be concluded from this analysis. The finding that ≥20/50/70% improvement rates in PtGA and Pain were similar across treatments through Month 6 confirm previous results over 3 months, and identify a close concordance of PtGA and Pain outcomes (41). Physicians base their overall assessment of patients' disease activity on joint counts (TJC and SJC), while PtGA is greatly influenced by non-inflammatory patient factors (42), which might explain the lower improvement rate in PtGA versus CGA.

Limitations include the posthoc nature of this evaluation, the lack of formal statistical testing, and the small sample size for ACR70 responders. In the placebo-controlled cohort, comparisons between active treatments were limited, as data for tofacitinib were pooled across three studies versus one study for ADA. Furthermore, responses in the tofacitinib groups at Month 6 may have been impacted by the advancement of non-responder patients to tofacitinib at Month 3. This analysis was conducted over six months; further studies would be required to determine the impact of long-term treatment and disease status on the components of the composite measures. Finally, interpretation of these data in a real-world context is limited by the clinical trial setting.

In conclusion, this posthoc analysis of data from phase III and phase IIIb/IV tofacitinib RA RCTs provides insight into patient responses to tofacitinib or ADA in terms of the composite measures and their individual components. In particular, the higher weighting of physician-reported versus patient-reported components to overall response and remission highlights the importance of considering the patient’s perspective when making treatment decisions. Despite different modes of action, tofacitinib and ADA did not show differentiated efficacy across the composite measures studied. Although ACR20 response rate is typically thought of as a ‘low’ threshold to meet, these findings demonstrate that in patients meeting

composite score criteria, tofacitinib-induced improvements in clinically measured signs and symptoms, especially those reported by the physician, far exceed what would be considered a 20% improvement in response. Lastly, these data show that changes in disease state do not generally corroborate ACR70 response criteria. Taken together, these findings may help clinicians to interpret clinical study results, and to define expected responses to advanced therapies, to assist in setting treatment goals for patients during routine practice.

ACKNOWLEDGMENTS

The authors would like to acknowledge Tanya Girard, PhD, a former employee and stockholder of Pfizer Canada ULC, for her significant intellectual and scientific contributions to this work.

Some data reported in this manuscript were previously presented at the American College of Rheumatology Annual Scientific Meeting, Atlanta, GA, USA, November 8–13, 2019, Bessette L, Dougados M, Mysler E, et al. Impact of tofacitinib on the individual components of the ACR composite score in patients with rheumatoid arthritis: a post hoc analysis of phase 3 trials [abstract]. Arthritis Rheumatol 2019;71(suppl 10):1348.

AUTHOR CONTRIBUTIONS

LB, CDK, TL, and RFvV conceived or designed the study. LB, CK, and TL acquired data. LB, EM, CDK, KK, TL, and RFvV analyzed the data. All authors were involved in interpretation of data, and reviewed and approved the final version of the manuscript.

DATA AVAILABILITY

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data.
See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

REFERENCES

1. Ward MM, Guthrie LC, Alba MI. Brief report: rheumatoid arthritis response criteria and patient-reported improvement in arthritis activity: is an American College of Rheumatology twenty percent response meaningful to patients? Arthritis Rheumatol 2014;66:2339–43.

2. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.

3. Felson DT, Anderson JJ, Lange ML, Wells G, LaValley MP. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? Arthritis Rheum 1998;41:1564–70.

4. Pincus T, Yazici Y, Sokka T. Quantitative measures of rheumatic diseases for clinical research versus standard clinical care: differences, advantages and limitations. Best Pract Res Clin Rheumatol 2007;21:601–28.

5. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42:244–57.

6. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.

7. Smolen JS, Aletaha D. Scores for all seasons: SDAI and CDAI. Clin Exp Rheumatol 2014;32 (Suppl 85):S75–9.

8. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.

9. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum 2009;60:1895–905.

10. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH, 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.

11. Fleischmann R, Cutolo M, Genovese MC, 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.

12. Kremer JM, Cohen S, Wilkinson BE, 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.

13. Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyoizumi S, Zwillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. Mod Rheumatol 2015;25:514–21.

14. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367:495–507.

15. Burmester GR, Blanco R, Charles-Schoeman C, et al. 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;381:451–60.

16. Kremer J, Li Z-G, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013;159:253–61.

17. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013;65:559–70.

18. Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014;370:2377–86.

19. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19.

20. van der Heijde D, Strand V, Tanaka Y, et al. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic, and safety outcomes from a twenty-four-month, phase III study. Arthritis Rheumatol 2019;71:878–91.

21. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients

with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017;390:457–68.

22. Wollenhaupt J, Silverfield J, Lee EB, et al. Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. J Rheumatol 2014;41:837–52.

23. Yamanaka H, Tanaka Y, Takeuchi T, et al. Tofacitinib, an oral Janus kinase inhibitor, as monotherapy or with background methotrexate, in Japanese patients with rheumatoid arthritis: an open-label, long-term extension study. Arthritis Res Ther 2016;18:34.

24. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther 2019;21:89.

25. Cohen SB, Tanaka Y, Mariette X, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. RMD Open 2020;6:e001395.

26. Aletaha D, Landewe R, Karonitsch T, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. Arthritis Rheum 2008;59:1371–7.

27. Hodge JA, Kawabata TT, Krishnaswami S, et al. The mechanism of action of tofacitinib - an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clin Exp Rheumatol 2016;34:318–28.

28. Rigby WF, Burmester GR, FitzGerald O, et al. Changes in key laboratory values with tofacitinib 5mg BID treatment in patients with psoriatic arthritis and rheumatoid arthritis [abstract]. Arthritis Rheumatol. 2018;70:685.

29. Canhão H, Rodrigues AM, Gregório MJ, et al. Common evaluations of disease activity in rheumatoid arthritis reach discordant classifications across different populations. Front Med (Lausanne) 2018;5:40.

30. Gossec L, Dougados M, Dixon W. Patient-reported outcomes as end points in clinical trials in rheumatoid arthritis. RMD Open 2015;1:e000019.

31. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814–23.

32. Challa DN, Kvrgic Z, Cheville AL, et al. Patient-provider discordance between global assessments of disease activity in rheumatoid arthritis: a comprehensive clinical evaluation. Arthritis Res Ther 2017;19: 212.

33. Smolen JS, Strand V, Koenig AS, Szumski A, Kotak S, Jones TV. Discordance between patient and physician assessments of global disease activity in rheumatoid arthritis and association with work productivity. Arthritis Res Ther 2016;18:114.

34. Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D. Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010;62:857–64.

35. Wei W, Anderson P, Gadkari A, et al. Discordance between physician- and patient-reported disease severity in adults with atopic dermatitis: a US cross-sectional survey. Am J Clin Dermatol 2017;18:825–35.

36. Kilcher G, Hummel N, Didden EM, Egger M, Reichenbach S, GetReal Work Package 4. Rheumatoid arthritis patients treated in trial and real world settings: comparison of randomized trials with registries. Rheumatology (Oxford) 2018;57:354–69.

37. Fleischmann R, Strand V, Wilkinson B, Kwok K, Bananis E. Relationship between clinical and patient-reported outcomes in a phase 3 trial of tofacitinib or MTX in MTX-naïve patients with rheumatoid arthritis. RMD Open 2016;2:e000232.

38. Fautrel B, Kirkham B, Pope JE, et al. Effect of baricitinib and adalimumab in reducing pain and improving function in patients with rheumatoid arthritis in low disease activity: exploratory analyses from RA-BEAM. J Clin Med 2019;8:1394.

39. Fautrel B, Zhu B, Taylor PC, et al. Comparative effectiveness of improvement in pain and physical function for baricitinib versus adalimumab, tocilizumab and tofacitinib monotherapies in rheumatoid arthritis patients who are naïve to treatment with biologic or conventional synthetic disease-modifying antirheumatic drugs: a matching-adjusted indirect comparison. RMD Open 2020;6:e001131.

40. Strand V, Mysler E, Moots RJ, et al. Patient-reported outcomes for tofacitinib with and without methotrexate, or adalimumab with methotrexate, in rheumatoid arthritis: a Phase IIIB/IV trial. RMD Open 2019;5:e001040.

41. Strand V, Kaine J, Alten R, et al. Associations between Patient Global Assessment scores and pain, physical function, and fatigue in rheumatoid arthritis: a post hoc analysis of data from Phase 3 trials of tofacitinib. Arthritis Res Ther 2020;22:243.

42. Masri KR, Shaver TS, Shahouri SH, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139–45.

FIGURE LEGENDS

Figure 1. Placebo-controlled cohort[a]: proportions of patients treated with tofacitinib 5 mg BID + csDMARDs, tofacitinib 10 mg BID + csDMARDs, ADA + csDMARDs[b], or placebo + csDMARDs[c] who reported an (A) overall ACR20 response or ≥ 20% improvement from baseline in each ACR component, an (B) overall ACR50 response or ≥ 50% improvement from baseline in each ACR component, and an (C) overall ACR70 response or ≥ 70% improvement from baseline in each ACR component, up to Month 6 (FAS)

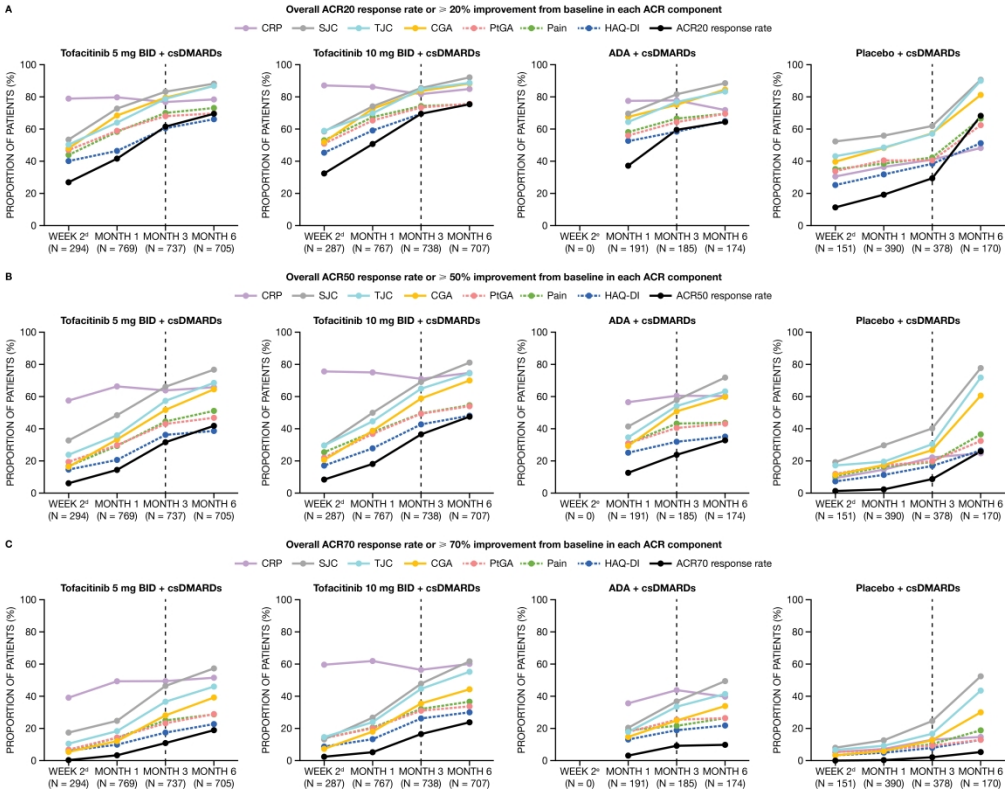
Analyses are based on observed case data in patients with all seven ACR components assessed at the analyzed time point. [a] Data were pooled from three phase III studies: ORAL Scan (NCT00847613); ORAL Sync (NCT00856544); ORAL Standard (NCT00853385). [b] ORAL Standard only. [c] Placebo-treated patients received placebo from Study Day 1 up to either Month 3 (non-responders) or Month 6 (responders). At Month 3, placebo non-responders were advanced to active tofacitinib treatment (represented by dashed vertical line); therefore, all patients reported under placebo at Month 6 would have been placebo responders at Month 3. Patients who did not achieve ≥ 20% reduction from baseline in both SJC and TJC at Month 3 were considered non-responders. [d] ORAL Sync only. [e] Week 2 data not assessed in ORAL Standard. ACR: American College of Rheumatology; ACR20/50/70: American College of Rheumatology ≥ 20/50/70% response rates; ADA: adalimumab; BID: twice daily; CGA: Clinician Global Assessment; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; N: number of evaluable patients; Pain: patient-reported pain (Visual Analog Scale); PtGA: Patient Global Assessment of Disease Activity; SJC: swollen joint count; TJC: tender joint count.

Figure 2. Placebo-controlled cohort[a]: mean percent improvement from baseline in the ACR components, SDAI score, and CDAI score in patients treated with tofacitinib 5 mg BID + csDMARDs, tofacitinib 10 mg BID + csDMARDs, ADA + csDMARDs[b], or placebo + csDMARDs achieving overall (A) ACR20, (B) ACR50, and (C) ACR70 responses at Month 3 (FAS)

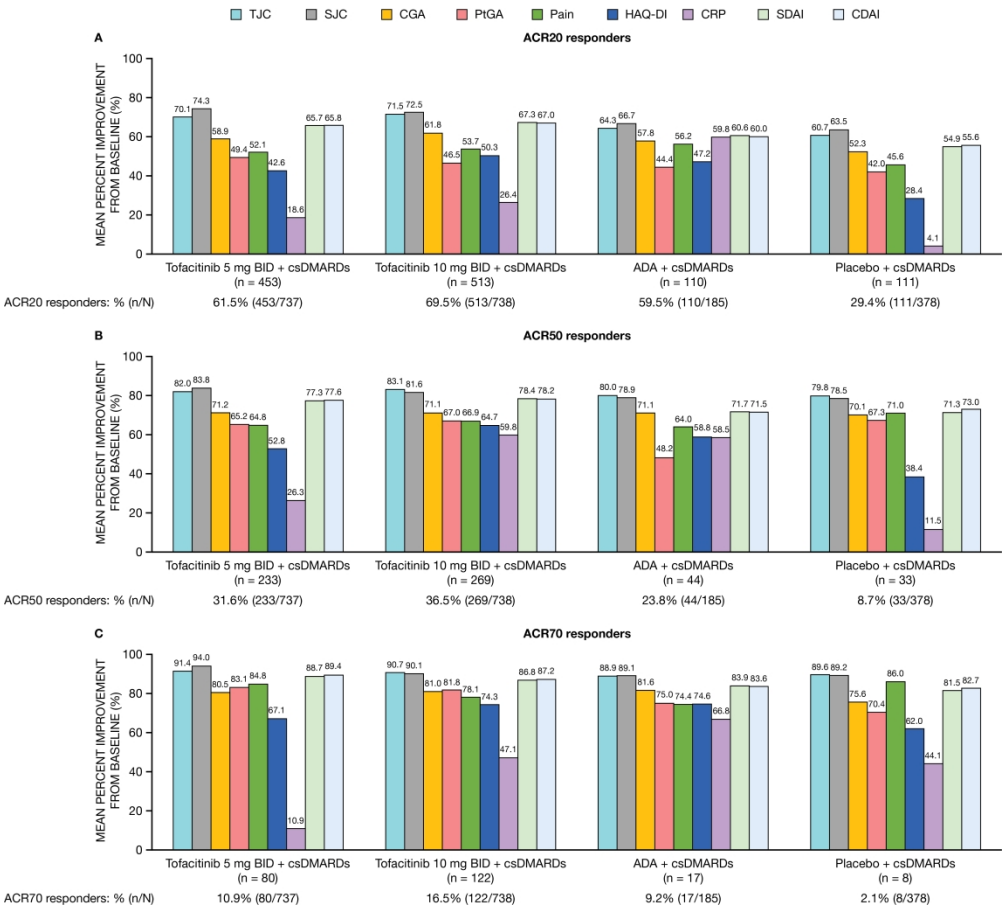
Analyses are based on observed case data in patients with all seven ACR components assessed at the analyzed time point. [a] Data were pooled from three phase III studies: ORAL Scan (NCT00847613); ORAL Sync (NCT00856544); ORAL Standard (NCT00853385). [b] ORAL Standard only.
ACR: American College of Rheumatology; ACR20/50/70: American College of Rheumatology ≥ 20/50/70% response rates; ADA: adalimumab; BID: twice daily; CDAI: Clinical Disease Activity Index; CGA: Clinician Global Assessment; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; n: number of patients achieving overall ACR20/50/70 responses at Month 3; N: number of evaluable patients; Pain: patient-reported pain (Visual Analog Scale); PtGA: Patient Global Assessment of Disease Activity; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.

Figure 3. Placebo-controlled cohort[a]: proportions of (A) ACR20, (B) ACR50, and (C) ACR70 responders treated with tofacitinib 5 mg BID + csDMARDs, tofacitinib 10 mg BID + csDMARDs, ADA + csDMARDs[b], or placebo + csDMARDs achieving SDAI- or CDAI-defined LDA or remission at Month 3 (FAS)

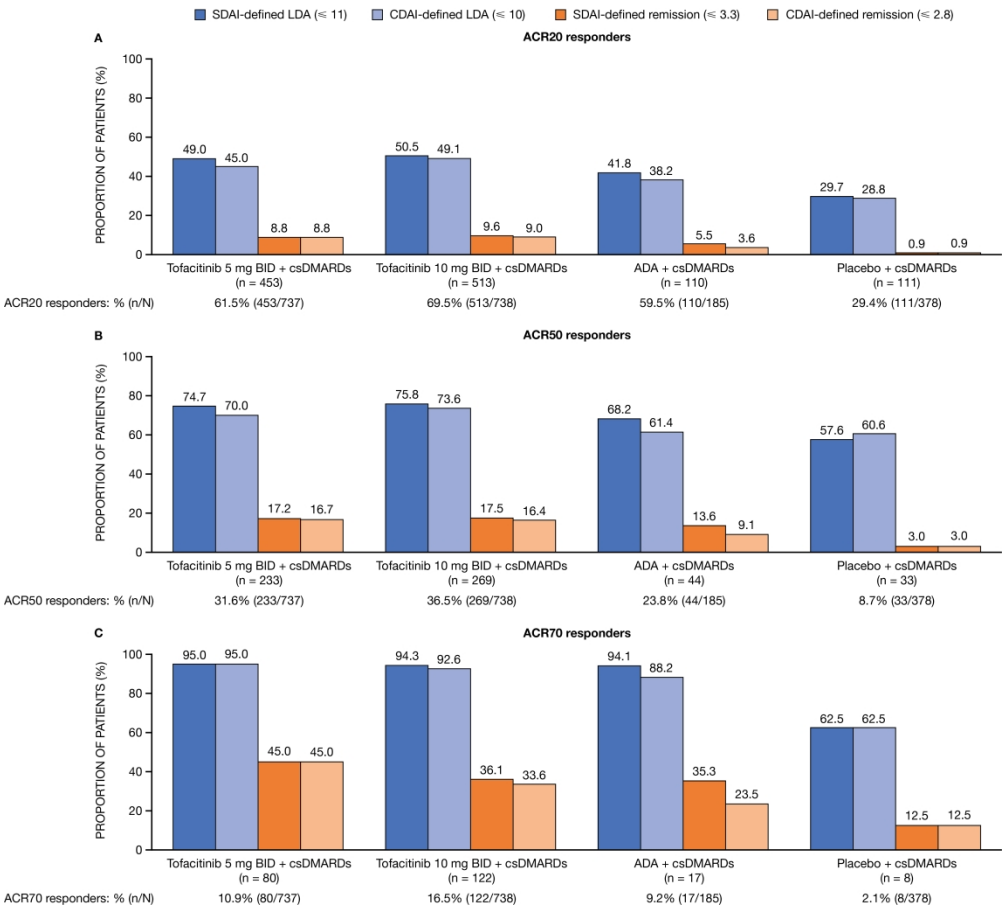
Analyses are based on observed case data in patients with all seven ACR components assessed at the analyzed time point. ACR20/50/70 responders were defined as patients achieving improvements in ACR criteria ≥ 20/50/70%, respectively. [a] Data were pooled from three phase III studies: ORAL Scan (NCT00847613); ORAL Sync (NCT00856544); ORAL Standard (NCT00853385). [b] ORAL Standard only. ACR: American College of Rheumatology; ACR20/50/70: American College of Rheumatology ≥ 20/50/70% response rates; ADA: adalimumab; BID: twice daily; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; FAS: full analysis set; LDA: low disease activity; n: number of ACR20/50/70 responders; N: number of evaluable patients; SDAI: Simplified Disease Activity Index.



247x193mm (600 x 600 DPI)



204x183mm (600 x 600 DPI)



204x183mm (600 x 600 DPI)

Table 1. Summary of the study designs, patients, and treatments for the RCTs included in the posthoc analysis

ClinicalTrials.gov identifier	**Study name/ protocol number**	**Total number of patients treated, N**	**Patient population**	**Randomization and interventions**	**Study duration**
Placebo-controlled cohort (phase III studies)					
NCT00847613 (17,20)	ORAL Scan, A3921044	797	Aged ≥ 18 years with a diagnosis of active RA[a] and an inadequate response to MTX	Patients were randomized 4:4:1:1 to receive one of the following with background MTX: Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo advanced to tofacitinib 5 mg BID[b] Placebo advanced to tofacitinib 10 mg BID[b]	24 months
NCT00853385 (19)	ORAL Standard, A3921064	717	Aged ≥ 18 years with a diagnosis of active RA[a] and an inadequate response to MTX	Patients were randomized 4:4:4:1:1 to receive one of the following with background MTX: Tofacitinib 5 mg BID Tofacitinib 10 mg BID ADA 40 mg Q2W	12 months

				Placebo advanced to tofacitinib 5 mg BID[b] Placebo advanced to tofacitinib 10 mg BID[b]	
NCT00856544 (16)	ORAL Sync, A3921046	792	Aged ≥ 18 years with a diagnosis of active RA[c] and an inadequate response to ≥ 1 non-biologic or biologic DMARDs	Patients were randomized 4:4:1:1 to receive one of the following with background csDMARDs: Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo advanced to tofacitinib 5 mg BID[b] Placebo advanced to tofacitinib 10 mg BID[b]	12 months
Head-to-head cohort (phase IIIb/IV study)					
NCT02187055 (21)	ORAL Strategy, A3921187	1146	Aged ≥ 18 years with a diagnosis of active RA[d] and an inadequate response to MTX	Patients were randomized 1:1:1 to receive one of the following: Tofacitinib 5 mg BID monotherapy Tofacitinib 5 mg BID with background MTX ADA 40 mg Q2W with background MTX	12 months

[a] Based on the ACR 1987 revised criteria (26). Active disease was defined as ≥ 6 tender/painful joints (68-joint count) and ≥ 6 swollen joints (66-joint count), and by an ESR (Westergren method) > 28 mm/hr or a CRP level of > 7 mg/L (reference range 0–10 mg/L). [b] At Month 3, placebo non-responders (i.e., those not achieving ≥ 20% reduction from baseline in SJC and TJC) were advanced in a blinded manner to tofacitinib 5 or 10 mg BID. At Month 6,

all remaining placebo-treated patients were advanced to tofacitinib. [c] Based on the ACR 1987 revised criteria (26). Active disease was defined as ≥ 4 tender/painful joints (68-joint count) and ≥ 4 swollen joints (66-joint count), and by an ESR (Westergren method) > 28 mm/hr or a CRP level > 66.7 nmol/L. [d] Based on the 2010 ACR and EULAR classification criteria (27). Active disease was defined as ≥ 4 tender/painful joints on motion (28-joint count) and ≥ 4 swollen joints (28-joint count) at baseline, despite treatment with methotrexate 15–25 mg/week, high-sensitivity CRP ≥ 3 mg/L in a central laboratory, and class I–III functional capacity as classified by the ACR 1991 revised criteria for global functioning status in RA (28).

ACR: American College of Rheumatology; ADA: adalimumab; BID: twice daily; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; EULAR: European Alliance of Associations for Rheumatology; MTX: methotrexate; Q2W: every 2 weeks; RA: rheumatoid arthritis; RCT: randomized controlled trial; SJC: swollen joint count; TJC: tender joint count.

Table 2A. Placebo-controlled cohort[a]: relative contribution of the secondary ACR components (CGA, PtGA, Pain, HAQ-DI, and CRP) to the overall ACR20 response rates in patients treated with tofacitinib 5 mg BID + csDMARDs, tofacitinib 10 mg BID + csDMARDs, ADA + csDMARDs[b], or placebo + csDMARDs at Month 3 (FAS)

Tofacitinib 5 mg BID + csDMARDs (N = 737)		**Tofacitinib 10 mg BID + csDMARDs (N = 738)**		**ADA + csDMARDs (N = 185)**		**Placebo + csDMARDs (N = 378)**	
ACR component (by rank)	**n (%)**	**ACR component (by rank)**	**n (%)**	**ACR component (by rank)**	**n (%)**	**ACR component (by rank)**	**n (%)**
1. CGA	383 (52.0)	1. CGA	449 (60.8)	1. CGA	94 (50.8)	1. CGA	74 (19.6)
2. CRP	401 (54.4)	2. CRP	462 (62.6)	1. CRP	94 (50.8)	2. PtGA	86 (22.8)
3. Pain	406 (55.1)	3. Pain	469 (63.6)	3. Pain	99 (53.5)	2. Pain	86 (22.8)
4. PtGA	414 (56.2)	3. PtGA	469 (63.6)	4. PtGA	100 (54.1)	4. HAQ-DI	90 (23.8)
5. HAQ-DI	418 (56.7)	5. HAQ-DI	470 (63.7)	5. HAQ-DI	103 (55.7)	5. CRP	93 (24.6)

Table 2B. Placebo-controlled cohort[a]: relative contribution of the secondary ACR components (CGA, PtGA, Pain, HAQ-DI, and CRP) to the overall ACR50 response rates in patients treated with tofacitinib 5 mg BID + csDMARDs, tofacitinib 10 mg BID + csDMARDs, ADA + csDMARDs[b], or placebo + csDMARDs at Month 3 (FAS)

Tofacitinib 5 mg BID + csDMARDs (N = 737)		**Tofacitinib 10 mg BID + csDMARDs (N = 738)**		**ADA + csDMARDs (N = 185)**		**Placebo + csDMARDs (N = 378)**	
ACR component (by rank)	**n (%)**	**ACR component (by rank)**	**n (%)**	**ACR component (by rank)**	**n (%)**	**ACR component (by rank)**	**n (%)**
1. CGA	189 (25.6)	1. CGA	225 (30.5)	1. CGA	30 (16.2)	1. CGA	18 (4.8)
2. PtGA	195 (26.5)	2. CRP	226 (30.6)	2. Pain	32 (17.3)	1. PtGA	18 (4.8)
3. CRP	196 (26.6)	3. Pain	235 (31.8)	3. CRP	33 (17.8)	1. Pain	18 (4.8)
4. Pain	198 (26.9)	4. HAQ-DI	238 (32.3)	4. PtGA	35 (18.9)	4. HAQ-DI	28 (7.4)
5. HAQ-DI	204 (27.7)	5. PtGA	241 (32.7)	5. HAQ-DI	36 (19.5)	5. CRP	29 (7.7)

Table 2C. Placebo-controlled cohort[a]: relative contribution of the secondary ACR components (CGA, PtGA, Pain, HAQ-DI, and CRP) to the overall ACR70 response rates in patients treated with tofacitinib 5 mg BID + csDMARDs, tofacitinib 10 mg BID + csDMARDs, ADA + csDMARDs[b], or placebo + csDMARDs at Month 3 (FAS)

Tofacitinib 5 mg BID + csDMARDs (N = 737)		**Tofacitinib 10 mg BID + csDMARDs (N = 738)**		**ADA + csDMARDs (N = 185)**		**Placebo + csDMARDs (N = 378)**	
ACR component (by rank)	**n (%)**	**ACR component (by rank)**	**n (%)**	**ACR component (by rank)**	**n (%)**	**ACR component (by rank)**	**n (%)**
1. Pain	59 (8.0)	1. CGA	91 (12.3)	1. CGA	10 (5.4)	1. Pain	1 (0.3)
2. PtGA	60 (8.1)	2. Pain	92 (12.5)	1. PtGA	10 (5.4)	2. PtGA	3 (0.8)
3. CGA	62 (8.4)	3. PtGA	97 (13.1)	3. HAQ-DI	12 (6.5)	3. CGA	4 (1.1)
4. CRP	70 (9.5)	4. CRP	107 (14.5)	4. Pain	13 (7.0)	4. HAQ-DI	5 (1.3)
5. HAQ-DI	71 (9.6)	5. HAQ-DI	109 (14.8)	4. CRP	13 (7.0)	5. CRP	6 (1.6)

To assess the relative contribution of each secondary ACR component (CGA, PtGA, Pain, HAQ-DI, and CRP) to the attainment of the overall ACR20 response rate, each component was sequentially set to 'no improvement' (i.e., value of 0 in change from baseline) and the ACR20 response rate was recalculated. The resulting response rates were then rank-ordered from 1–5, with 1 representing the largest contribution, corresponding to the largest decrease in ACR20 response rate; and 5 representing the smallest contribution, corresponding to the smallest decrease

in ACR20 response rate. The same approach was used to assess the relative contribution of each secondary ACR component to the attainment of the overall ACR50 and ACR70 response rates. Analyses are based on observed case data in patients with all seven ACR components assessed at the analyzed time point. [a] Data were pooled from three phase III studies: ORAL Scan (NCT00847613); ORAL Sync (NCT00856544); ORAL Standard (NCT00853385). [b] ORAL Standard only. ACR: American College of Rheumatology; ACR20/50/70: American College of Rheumatology ≥ 20/50/70% response rates; ADA: adalimumab; BID: twice daily; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CGA: Clinician Global Assessment; CRP: C-reactive protein; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; n: number of patients achieving ≥ 20/50/70% improvement when each secondary ACR component is set to 'no improvement' (i.e., value of 0 in change from baseline) and the ACR20/50/70 response rate was recalculated; N: number of evaluable patients; Pain: patient-reported pain (Visual Analog Scale); PtGA: Patient Global Assessment of Disease Activity.

Table 3. Placebo-controlled cohort[a]: relative contribution of SDAI or CDAI components to the mean change from baseline in SDAI or CDAI scores, respectively, in patients treated with tofacitinib 5 mg BID + csDMARDs, tofacitinib 10 mg BID + csDMARDs, ADA + csDMARDs[b], or placebo + csDMARDs at Month 3 (FAS)

Tofacitinib 5 mg BID + csDMARDs (N = 737)		**Tofacitinib 10 mg BID + csDMARDs (N = 738)**		**ADA + csDMARDs (N = 185)**		**Placebo + csDMARDs (N = 378)**	
Component (by rank)	**Change from baseline, mean (SD)**	**Component (by rank)**	**Change from baseline, mean (SD)**	**Component (by rank)**	**Change from baseline, mean (SD)**	**Component (by rank)**	**Change from baseline, mean (SD)**
SDAI components							
1. TJC	-11.8 (9.3)	1.TJC	-13.1 (8.9)	1. TJC	-11.0 (9.2)	1.TJC	-4.3 (10.4)
2. SJC	-13.2 (10.3)	2. SJC	-15.0 (10.3)	2. SJC	-12.0 (9.5)	2. SJC	-5.0 (11.5)
3. CGA	-16.3 (12.7)	3. CGA	-18.1 (12.4)	3. CGA	-15.3 (12.3)	3. CGA	-7.2 (13.5)
4. PtGA	-16.7 (12.9)	4. PtGA	-18.5 (12.5)	4. PtGA	-15.8 (12.2)	4. PtGA	-7.7 (13.7)
5. CRP	-18.1 (13.5)	5. CRP	-20.1 (13.1)	5. CRP	-17.0 (12.9)	5. CRP	-8.6 (14.3)

CDAI components							
1. TJC	-10.8 (8.7)	1.TJC	-11.8 (8.2)	1. TJC	-10.1 (8.6)	1.TJC	-4.4 (9.9)
2. SJC	-12.2 (9.9)	2. SJC	-13.8 (9.7)	2. SJC	-11.1 (9.0)	2. SJC	-5.0 (11.0)
3. CGA	-15.3 (12.4)	3. CGA	-16.9 (11.9)	3. CGA	-14.4 (11.9)	3. CGA	-7.3 (13.0)
4. PtGA	-15.7 (12.5)	4. PtGA	-17.2 (12.0)	4. PtGA	-14.9 (11.8)	4. PtGA	-7.8 (13.3)

To assess the relative contribution of each SDAI component (TJC, SJC, CGA, PtGA, and CRP) to mean change from baseline in SDAI, each component was sequentially set to 'no improvement' (i.e., value of 0 in change from baseline for each component) and the mean change from baseline in SDAI was recalculated. The resulting mean change from baseline in SDAI was compared numerically with the overall SDAI score and then rank-ordered from 1–5, with 1 representing the largest decrease in improvement compared with the overall SDAI score; and 5 representing the smallest decrease in improvement compared with the overall SDAI score. To assess the relative contribution of each CDAI component (TJC, SJC, CGA, and PtGA) to mean change from baseline in CDAI, each component was sequentially set to 'no improvement' (i.e., value of 0 in change from baseline for each component) and the mean change from baseline in CDAI was recalculated. The resulting mean change from baseline in CDAI was compared numerically with the overall CDAI score and then rank-ordered from 1–4, with 1 representing the largest decrease in improvement compared with the overall CDAI score; and 4 representing the smallest decrease in improvement compared with the overall CDAI score. Analyses are based on observed case data in patients with all seven ACR components assessed at the analyzed time point. [a] Data were pooled from three phase III studies: ORAL Scan (NCT00847613); ORAL Sync (NCT00856544); ORAL Standard (NCT00853385). [b] ORAL Standard only. ACR: American College of Rheumatology; ADA: adalimumab; BID: twice

daily; CDAI: Clinical Disease Activity Index; CGA: Clinician Global Assessment; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; FAS: full analysis set; N: number of evaluable patients; PtGA: Patient Global Assessment of Disease Activity; SD: standard deviation; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.