



## ORIGINAL ARTICLE

# Patient-reported outcomes for tofacitinib with and without methotrexate, or adalimumab with methotrexate, in rheumatoid arthritis: a phase IIIB/IV trial

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## ABSTRACT

**Objective** To provide the first direct comparison of patient-reported outcomes (PROs) following treatment with tofacitinib monotherapy versus tofacitinib or adalimumab (ADA) in combination with methotrexate (MTX) in patients with rheumatoid arthritis (RA) with inadequate response to MTX (MTX-IR).

**Methods** ORAL Strategy (NCT02187055), a phase IIIB/IV, head-to-head, randomised controlled trial, assessed non-inferiority between tofacitinib 5 mg two times per day monotherapy, tofacitinib 5 mg two times per day+MTX and ADA 40 mg every other week+MTX. PROs assessed included the following: Patient Global Assessment of disease activity (PtGA), Pain, Health Assessment Questionnaire-Disability Index, Functional Assessment of Chronic Illness Therapy-Fatigue and 36-Item Short-Form Health Survey (SF-36) summary and domain scores.

**Results** Substantial improvements from baseline were reported across all PROs in all treatment arms, which, in the majority, met or exceeded minimum clinically important differences. Compared with tofacitinib monotherapy, tofacitinib+MTX combination treatment conferred significantly greater improvements in PtGA, Pain and SF-36 physical component summary scores at month 6. Statistically or numerically greater improvements were often, but not uniformly, reported for combination treatments compared with tofacitinib monotherapy at other time points.

**Conclusion** Treatment with tofacitinib+MTX, ADA+MTX and tofacitinib monotherapy resulted in clinically meaningful improvements in PROs in MTX-IR patients with RA. These were comparatively greater with combination treatments versus tofacitinib monotherapy, although differences between treatment arms were small, limiting our ability to confer clinical meaning.

**Trial registration number** NCT02187055.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease characterised by systemic inflammation, persistent synovitis

## Key messages

### What is already known about this subject?

- Primary efficacy data from the phase IIIB/IV study ORAL Strategy in patients with rheumatoid arthritis (RA) supported a preference for adding tofacitinib to methotrexate (MTX) rather than switching to tofacitinib monotherapy, which has shown efficacy versus placebo.
- Improvements in patient-reported outcomes (PROs) are a priority for patients with RA.

### What does this study add?

- Using data from ORAL Strategy, this analysis is the first adequately powered direct comparison of PROs associated with tofacitinib monotherapy, tofacitinib+MTX and adalimumab (ADA)+MTX.
- Tofacitinib+MTX, ADA+MTX and tofacitinib monotherapy improved PROs in patients with RA and an inadequate response to MTX; improvements were generally greater with both combination arms than with monotherapy.

### How might this impact on clinical practice?

- These data show that tofacitinib administered as monotherapy is a suitable treatment for patients with a previous inadequate response to MTX, although combination therapy remains the most effective treatment strategy.

and joint destruction, and affects approximately 0.24% of the global population.<sup>1</sup>

When patients with RA are inadequate responders (IR) to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX), the next treatment step is either to switch or add therapies.<sup>2,3</sup> First-choice add-on therapies include biologic DMARDs (bDMARDs), usually tumour necrosis factor inhibitors (TNFi), and



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Janus kinase inhibitors, all approved in RA.<sup>2–4</sup> The TNFi adalimumab (ADA) is a recombinant human monoclonal antibody applied at 40 mg every other week (Q2W), with demonstrated efficacy in MTX-IR patients with active RA<sup>5–12</sup> and an acceptable safety profile in long-term extension studies of over 10 years' duration.<sup>13</sup> The efficacy and safety of the oral Janus kinase inhibitor tofacitinib 5 mg and 10 mg two times per day administered as monotherapy or in combination with csDMARDs in patients with active RA have been demonstrated in phase III<sup>14–24</sup> randomised controlled trials (RCTs) of up to 24 months' duration, and in long-term extension studies with as long as 9.5 years of observation.<sup>25–27</sup>

ORAL Strategy (NCT02187055) was a head-to-head, phase IIIB/IV RCT that directly compared the efficacy and safety of tofacitinib monotherapy, tofacitinib in combination with MTX and ADA in combination with MTX in MTX-IR patients with active RA.<sup>28</sup> In this trial, American College of Rheumatology 50% (ACR50) responses at month 6 (primary endpoint) were achieved by 38% of patients receiving tofacitinib monotherapy, 46% receiving tofacitinib+MTX and 44% receiving ADA+MTX. At month 6, tofacitinib+MTX was non-inferior to ADA+MTX; the non-inferiority of tofacitinib monotherapy relative to either combination therapy was inconclusive. Rates of remission and low disease activity were numerically similar between the three treatment arms, no new or unexpected safety issues were observed, and overall adverse event rates and discontinuations due to adverse events were similar between combination and monotherapy arms.

Improvements in pain, physical function, fatigue and overall health-related quality of life (HRQoL) are a priority for patients and, in accordance with clinical guidelines, treatment decisions should be shared between rheumatologists and patients.<sup>2,3</sup> Treatment with tofacitinib or ADA in combination with MTX has previously demonstrated improvements versus placebo across patient-reported outcomes (PROs) in the phase III ORAL Standard RCT of MTX-IR patients with moderately to severely active RA; however, this trial was not powered for direct comparisons between active treatment arms.<sup>22</sup> Here, we present the first adequately powered direct comparison of PROs associated with tofacitinib monotherapy, tofacitinib+MTX and ADA+MTX in the ORAL Strategy RCT.

## METHODS

### Study design

ORAL Strategy was a 1-year, triple-dummy, active comparator head-to-head RCT (see online supplementary figure S1, available at *RMD Open* online, for the study design). It was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Declaration of Helsinki and the Good Clinical Practice Guidelines, along with applicable local regulatory requirements and laws. All patients provided written, informed consent.

## Randomisation and treatment

Patients were randomised 1:1:1 in a blinded fashion to receive tofacitinib monotherapy, tofacitinib+MTX or ADA+MTX. Oral tofacitinib was dosed at 5 mg two times per day and subcutaneous ADA was dosed at 40 mg Q2W. All patients were required to have been treated for  $\geq 4$  months with MTX at a stable dosage of 15–25 mg/week for  $\geq 6$  weeks prior to baseline (MTX doses  $< 15$  mg/week were permitted if intolerance/toxicity to higher doses was documented). Further details of the randomisation procedures are provided in the primary publication.<sup>28</sup>

## Patients

Patient inclusion and exclusion criteria are provided in the primary publication.<sup>28</sup> Briefly, eligible patients were  $\geq 18$  years of age and met ACR/European League Against Rheumatism classification criteria for active RA.<sup>29</sup> They were required to discontinue all csDMARDs except MTX for  $\geq 4$  weeks or five half-lives, whichever was longer, prior to baseline, but could continue to receive stable non-steroidal anti-inflammatory drugs, analgesics and/or  $\leq 10$  mg prednisone or equivalent per day throughout the trial. Prior TNFi use was not allowed if patients had failed any for either lack of efficacy or a related adverse event.

## Assessments

Reported PROs included least squares mean (LSM) changes from baseline in the following: Patient Global Assessment of disease activity (PtGA), arthritis pain (Pain), Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and 36-Item Short-Form Health Survey version 2 (SF-36), physical component summary (PCS) and mental component summary (MCS) and domain scores (Physical Functioning [PF], Role Physical [RP], Bodily Pain [BP], General Health, Vitality [VT], Social Functioning, Role Emotional and Mental Health). Details of PRO measures are in online supplementary figure S1, available at *RMD Open* online.

The proportions of patients reporting improvements  $\geq$  minimum clinically important differences (MCIDs) in PtGA, Pain, HAQ-DI, FACIT-F and SF-36 summary and domain scores are reported, as well as those reporting scores in HAQ-DI, FACIT-F and SF-36 domains within normative values. MCIDs have been defined previously as follows:  $\geq 10$  mm decreases from baseline in PtGA and Pain,<sup>30</sup>  $\geq 0.22$ -point decrease from baseline in HAQ-DI score,<sup>31</sup>  $\geq 4$ -point increase in FACIT-F score,<sup>31</sup> and increases from baseline  $\geq 2.5$  points in SF-36 PCS and MCS and  $\geq 5$  points in SF-36 domain (0–100) scores.<sup>31</sup> Normative values for HAQ-DI are  $\leq 0.25$ <sup>32</sup> and normative values for FACIT-F have been reported as  $\geq 40.1$ <sup>33</sup> or, more recently,  $\geq 43.5$ <sup>34</sup>; we also report functional remission as previously defined by a HAQ-DI value of  $< 0.5$ .<sup>35</sup>

Normative values for SF-36 domain scores (see online supplementary table S1, available at *RMD Open* online) are based on age-matched and gender-matched norms

reported in the SF-36 Scoring Manual<sup>36,37</sup> according to the population enrolled in ORAL Strategy. The proportions of patients reporting Pain scores <20 mm<sup>38–40</sup> (considered to represent mild pain<sup>41</sup>), and ≥20% (mild), ≥30% (moderate), ≥50% (substantial) and ≥70% (extensive) improvements in Pain,<sup>38–40</sup> are also reported.

### Statistical analyses

All PRO analyses were based on the full analysis set (all patients randomised who received ≥1 dose of study drug [tofacitinib or ADA]). Descriptive statistics were provided for baseline and scheduled post-baseline measurements (month 0, week 6 [except SF-36 and FACIT-F endpoints], and months 3, 6, 9 and 12). Analysis of continuous data (eg, change from baseline in HAQ-DI) was conducted using a mixed-effects model of repeated measures, with fixed effects including treatment, geographical region, visit and treatment-by-visit interaction, and baseline as a covariate. This approach implicitly imputes any missing values. Binary variables (eg, % patients reporting improvements ≥MCIDs) were compared using the normal approximation to the binomial distribution. For this approach, missing values were ignored and response rates were calculated for patients with non-missing values at that visit. Analyses included 95% confidence intervals (CIs). Statistical significance was set at ≤0.05 with no correction for multiple comparisons. Statistically significant results are only reported in the text if present at ≥2 time points (months), or at an early time point, that is, at week 6 and/or month 3. SF-36 domain scores at baseline and scores at months 0, 3, 6, 9 and 12 (mean values expressed on the 0–100 scale) are displayed using spidergrams, where higher scores indicate improved HRQoL.

Statistical analyses not prespecified in the study statistical analysis protocol were as follows: descriptive statistics of baseline Pain, PtGA, HAQ-DI, FACIT-F and SF-36 summary scores; descriptive statistics of baseline and post-baseline SF-36 domain scores; age/gender adjustments of norms for domain scores used in the construction of the spidergrams; rates (and statistical tests) of reported improvements ≥MCID; reported scores within normative values; reported scores below function remission for HAQ-DI; and reported 20%, 30%, 50% and 70% improvements in Pain scores, and the percentage achieving a target Pain score of <20 mm. The statistical tests are comparisons of rates using the normal approximation to the binomial, with differences and 95% CIs formed.

## RESULTS

### Patients

In all, 1152 patients were randomised at 194 centres worldwide (located in North America, Latin America, Europe, the Middle East, Africa and the Asia-Pacific region), of whom 1146 were included in the full analysis set (tofacitinib monotherapy, n=384; tofacitinib+MTX, n=376; ADA+MTX, n=386). Patient disposition and baseline disease and demographic characteristics are included in the primary publication.<sup>28</sup> Key baseline disease

characteristics included the following: mean disease duration from 7.5 to 8.4 years; mean (standard deviation [SD]) tender joint counts (28-joint count) from 15.2 (6.7) to 15.6 (6.5); mean swollen joint counts (28-joint count) from 11.0 (5.4) to 11.8 (5.7); and mean (SD) Disease Activity Scores 28–4 using erythrocyte sedimentation rate from 6.5 (0.9) to 6.6 (0.9). A similar proportion of patients in each treatment arm completed the trial (tofacitinib monotherapy, n=315 [82.0%]; tofacitinib+MTX, n=303 [80.6%]; ADA+MTX, n=312, [80.8%]), with comparable reasons for discontinuation.<sup>28</sup>

### PROs at baseline

Baseline PROs were similar between treatment arms (table 1). Mean scores ranged from 60.1 to 61.7 for PtGA, 60.6 to 61.2 for Pain, 1.6 for HAQ-DI (all groups), 26.2 to 27.1 for FACIT-F, 31.7 to 32.4 for SF-36 PCS and 38.8 to 39.8 for SF-36 MCS, indicating the substantial impact of disease on patients across all parameters.

### PROs over time

Substantial improvements from baseline were reported across all PROs across all treatment arms (figure 1A–F), and the majority of patients reported improvements ≥MCID (figure 2A–F).

### PtGA

Clinically meaningful improvements from baseline were reported across all treatment groups at week 6 (tofacitinib monotherapy LSM change, –26.1; tofacitinib+MTX, –28.2; ADA+MTX, –26.6). At month 3, these approximated maximal values were greater with tofacitinib+MTX versus monotherapy (p<0.05) (figure 1A). Greater improvements from baseline in PtGA were reported in both combination arms versus tofacitinib monotherapy at month 6 (tofacitinib monotherapy LSM change, –35.7; tofacitinib+MTX, –38.4; ADA+MTX, –38.8; both comparisons, p<0.05), which were sustained through to month 9 (p<0.05) and month 12 (p<0.01) (table 1; figure 1A). The proportions of patients reporting improvements ≥MCID were similar between all treatment arms at all time points (ranges: 71%–77% at month 3, 72%–76% at month 6, 72%–78% at month 9 and 73%–79% at month 12) (figure 2A).

### Arthritis pain

Clinically meaningful improvements in Pain were reported across all treatment groups at week 6 (tofacitinib monotherapy LSM change, –22.6; tofacitinib+MTX, –22.8; ADA+MTX, –23.0), which generally approached maximal values by month 3 (figure 1B). Tofacitinib+MTX resulted in greater improvements from baseline versus tofacitinib monotherapy at month 3 (p<0.01), and this was sustained at month 6 (tofacitinib LSM change, –26.6; tofacitinib+MTX, –30.7; ADA+MTX, –28.1; p<0.05) and month 12 (p<0.05) (table 1; figure 1B). Greater improvements from baseline with ADA+MTX were reported versus tofacitinib monotherapy at month 3 (p<0.05) and again at month 9 (p<0.05) (figure 1B). The proportions of patients reporting improvements ≥MCID were similar between all

**Table 1** Baseline patient-reported outcomes and changes from baseline at month 6 (FAS)

	Baseline, mean (SE) score			LSM changes from baseline ( $\pm$ SE) at month 6		
	Tofacitinib 5 mg two times per day (n=384)	Tofacitinib 5 mg two times per day+MTX (n=376)	ADA+MTX (n=386)	Tofacitinib 5 mg two times per day (n=384)	Tofacitinib 5 mg two times per day+MTX (n=376)	ADA+MTX (n=386)
PtGA	(n=383) 60.1 (1.09)	(n=376) 61.7 (1.14)	(n=383) 60.2 (1.20)	(n=357) -35.7 (0.98)	(n=346) -38.4 (0.99)*	(n=348) -38.8 (0.98)†
Pain	(n=383) 61.2 (1.11)	(n=376) 60.7 (1.15)	(n=383) 60.6 (1.15)	(n=357) -26.6 (1.26)	(n=347) -30.7 (1.26)*	(n=351) -28.1 (1.26)
HAQ-DI	(n=383) 1.6 (0.03)	(n=376) 1.6 (0.03)	(n=382) 1.6 (0.03)	(n=356) -0.52 (0.03)	(n=348) -0.58 (0.03)	(n=350) -0.54 (0.03)
FACIT-F	(n=383) 27.1 (0.52)	(n=376) 26.2 (0.53)	(n=384) 27.1 (0.52)	(n=357) 7.14 (0.50)	(n=348) 7.59 (0.50)‡	(n=352) 6.07 (0.50)
SF-36 PCS	(n=381) 32.4 (0.38)	(n=375) 31.7 (0.36)	(n=382) 31.7 (0.38)	(n=355) 6.7 (0.44)	(n=346) 7.9 (0.43)*	(n=349) 7.8 (0.43)
SF-36 MCS	(n=381) 39.3 (0.59)	(n=375) 38.8 (0.57)	(n=382) 39.8 (0.58)	(n=355) 5.2 (0.52)	(n=346) 5.7 (0.51)	(n=349) 4.4 (0.51)

\* $p < 0.05$  for tofacitinib+MTX versus tofacitinib monotherapy.

† $p < 0.05$  for ADA+MTX versus tofacitinib monotherapy.

‡ $p < 0.05$  for tofacitinib+MTX versus ADA+MTX.

ADA, adalimumab; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; LSM, least squares mean; MCS, mental component summary; MTX, methotrexate; Pain, arthritis pain; PCS, physical component summary; PtGA, Patient Global Assessment of disease activity; SE, standard error; SF-36, 36-Item Short-Form Health Survey.

treatment arms at all time points (ranges: 71%–76% at month 3, 73%–78% at month 6, 74%–80% at month 9 and 76%–78% at month 12) (figure 2B).

As many as 45% of patients reported Pain scores  $< 20$  mm in any treatment arm at any time point, with greater proportions in both combination arms (tofacitinib+MTX [ $p < 0.01$ ] and ADA+MTX [ $p < 0.05$ ]) at month 3 versus tofacitinib monotherapy (figure 3A).

The majority of patients reported  $\geq 20\%$  (all  $> 69\%$ ) or  $\geq 30\%$  improvements in Pain (all  $> 59\%$ ). The proportions of patients reporting  $\geq 30\%$  improvements in Pain were greater in both combination arms (tofacitinib+MTX and ADA+MTX) at month 3 (both  $p < 0.01$ ), and with tofacitinib+MTX at month 6 ( $p < 0.05$ ), versus tofacitinib monotherapy (figure 3B).

### HAQ-DI

No statistically significant differences in LSM changes from baseline in HAQ-DI between treatment arms were reported at any time point, with improvements generally approaching maximal values by month 3 and continuing to month 12 for all treatments (table 1; figure 1C). In all treatment arms, the majority of patients reported improvements  $\geq$ MCID (figure 2C; all  $> 68\%$ ). Scores  $\leq$ normative HAQ-DI values ranged from 17% to 25%, and scores below functional remission ( $< 0.5$  HAQ-DI) ranged from 19% to 32% (online supplementary table S1, available at *RMD Open* online).

### FACIT-F

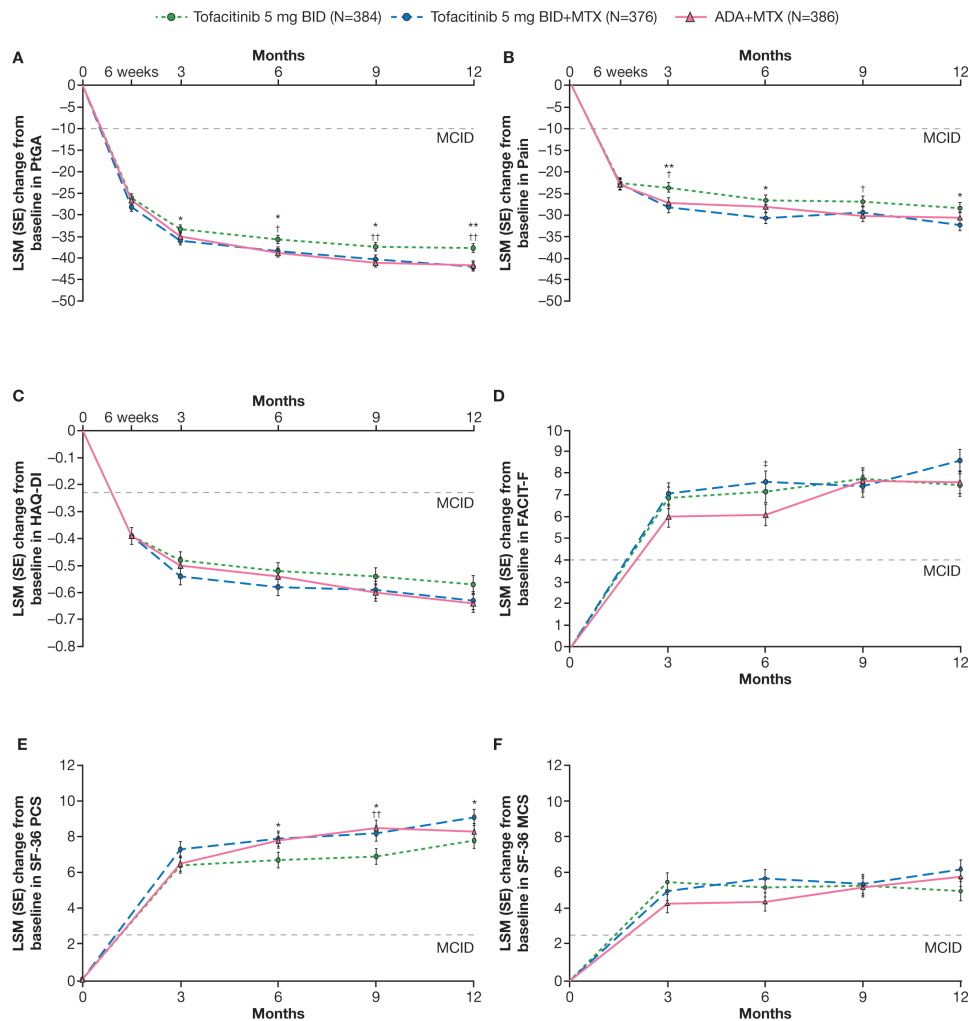
LSM changes from baseline and improvements  $\geq$ MCID in FACIT-F were similar between tofacitinib+MTX and

tofacitinib monotherapy at all time points (all  $p > 0.05$ ; table 1; figure 1D; figure 2D); improvements were comparatively lower for ADA+MTX at months 3 and 6, but this did not reach statistical significance at both time points. The proportions of patients reporting scores  $\geq$ normative values ( $\geq 40.1$ ) were greater with tofacitinib monotherapy versus ADA+MTX at month 3 ( $p < 0.05$ ); no statistically significant differences were observed between treatment groups when considering  $\geq$ normative values to be  $\geq 43.5$  (online supplementary table S1, available at *RMD Open* online).

### SF-36

Tofacitinib+MTX treatment resulted in greater improvements from baseline in SF-36 PCS versus tofacitinib monotherapy, sustained through months 6, 9 and 12 ( $p < 0.05$  for all) (table 1; figure 1E). The proportions of patients reporting improvements  $\geq$ MCID in SF-36 PCS with tofacitinib+MTX were greater than ADA+MTX at month 3 ( $p < 0.05$ ), and versus tofacitinib monotherapy at month 3 ( $p < 0.01$ ) and again at month 12 ( $p < 0.05$ ) (figure 2E). No statistically significant differences in LSM change from baseline between treatment arms were reported in SF-36 MCS scores at any time point (table 1; figure 1F).

With respect to SF-36 domains, the largest improvements were reported at month 3, with continuing incremental increases generally observed at months 6, 9 and 12. These improvements were generally similar across treatment arms at month 6 (online supplementary table S2, available at *RMD Open* online). At month 3, mean SF-36 domain scores were numerically higher with tofacitinib monotherapy versus both combination therapy arms for the RP and VT



**Figure 1** PRO scores over time for (A) PtGA, (B) Pain, (C) HAQ-DI, (D) FACIT-F, (E) SF-36 PCS and (F) SF-36 MCS (FAS). PtGA and Pain were assessed using 0–100 mm VAS. N numbers evaluable for each outcome may be  $\leq$  those reported for the FAS. \* $p < 0.05$  tofacitinib+MTX versus tofacitinib monotherapy; \*\* $p < 0.01$  tofacitinib+MTX versus tofacitinib monotherapy; † $p < 0.05$  ADA+MTX versus tofacitinib monotherapy; †† $p < 0.01$  ADA+MTX versus tofacitinib monotherapy; ‡ $p < 0.05$  tofacitinib+MTX versus ADA+MTX. ADA, adalimumab; BID, two times per day; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; LSM, least squares mean; MCID, minimum clinically important difference; MCS, mental component summary; MTX, methotrexate; Pain, arthritis pain; PCS, physical component summary; PtGA, Patient Global Assessment of Disease Activity; PRO, patient-reported outcome; SE, standard error; SF-36, 36-Item Short-Form Health Survey; VAS, visual analogue scale.

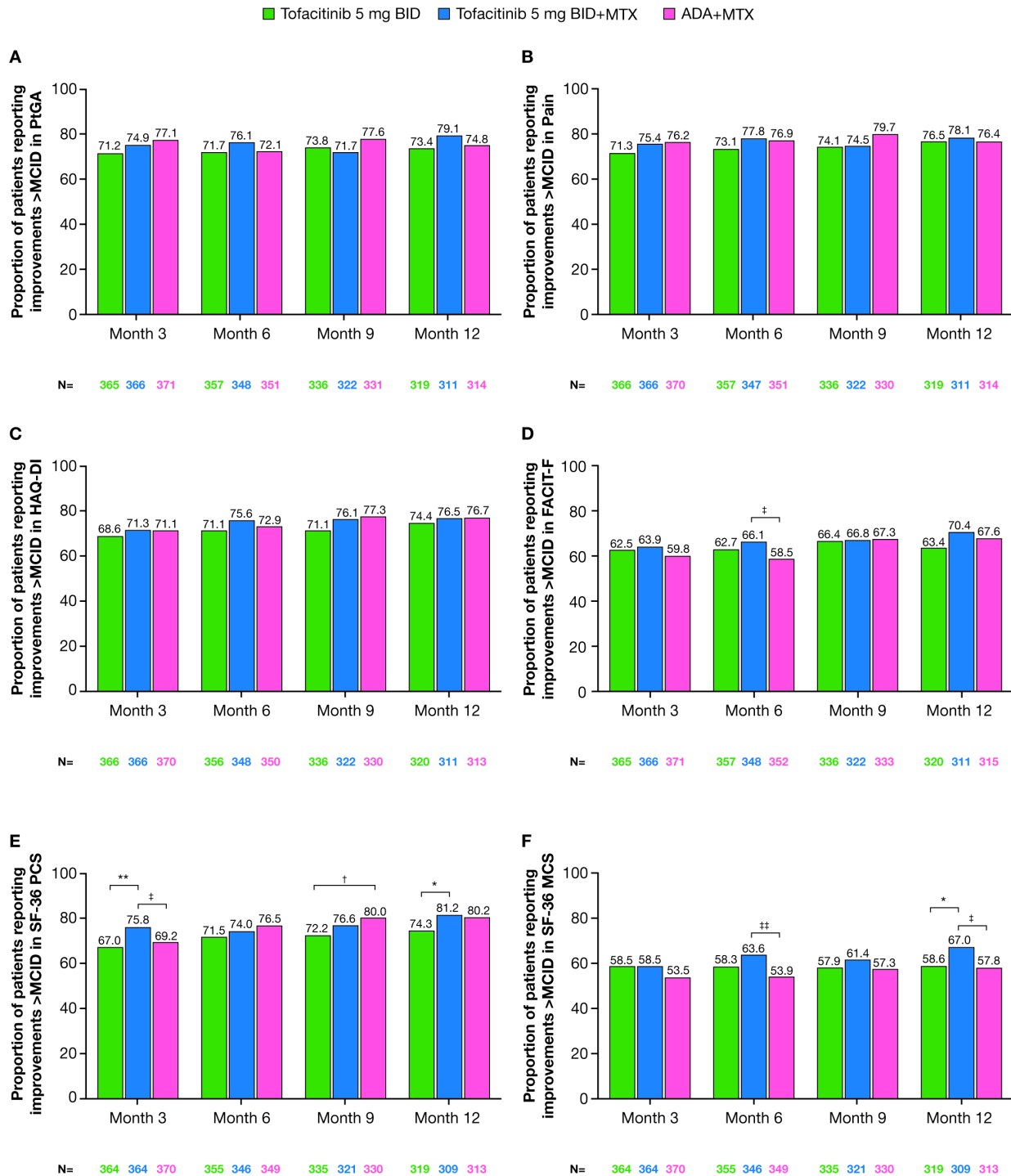
domains, and with tofacitinib+MTX versus tofacitinib monotherapy and ADA+MTX for the BP domain (figure 4). By month 12, mean VT scores approximated age-matched and gender-matched norms (differences from the VT normative score of 57.2 for tofacitinib monotherapy, tofacitinib+MTX and ADA+MTX were  $-3.5, -2.8$  and  $-1.2$ , respectively). The proportions of patients reporting scores  $\geq$  normative values and improvements  $\geq$  MCID in SF-36 domains are reported in online supplementary tables S1 and S3, respectively, available at *RMD Open* online.

## DISCUSSION

ORAL Strategy was the first head-to-head, non-inferiority RCT directly comparing a Janus kinase inhibitor (tofacitinib), as monotherapy or in combination with MTX, with a

TNFi (ADA) in combination with MTX, in MTX-IR patients with RA.

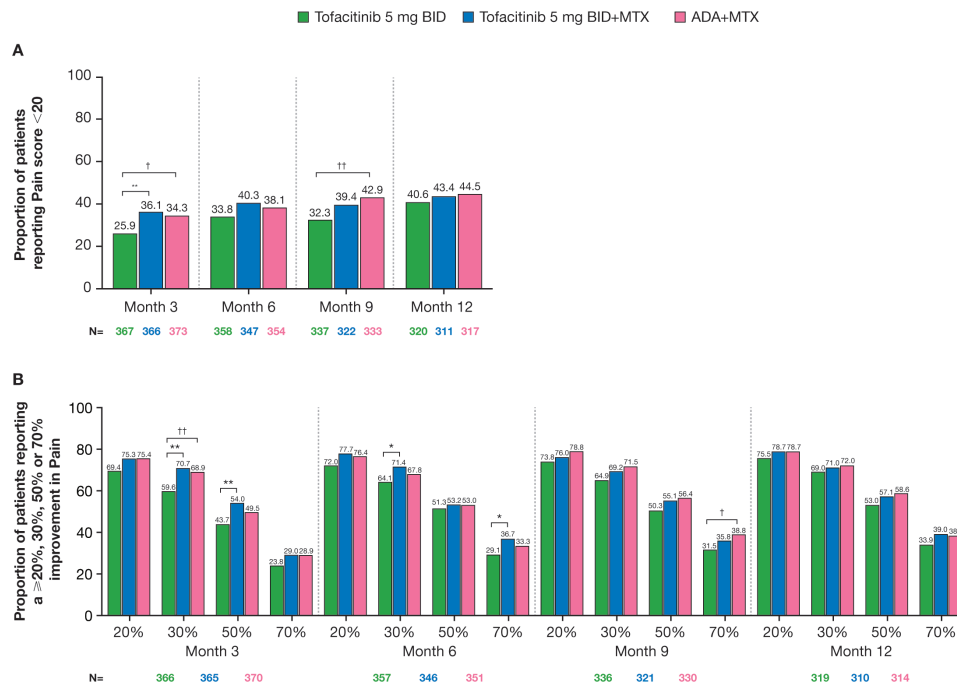
PRO data in ORAL Strategy support the conclusions of the primary publication,<sup>28</sup> with improvements in all three treatment arms reported as early as 3 months after initiation (clinically meaningful improvements [ $\geq$ MCID] at 6 weeks in PtGA and Pain), that were generally comparable with tofacitinib+MTX and ADA+MTX. Statistically (nominal p values) or numerically greater improvements were often, but not uniformly, reported with either combination therapy compared with tofacitinib monotherapy. Differences between treatment arms in reported PROs in ORAL Strategy are acknowledged to be small. Although it was not possible to formally determine whether these differences were clinically meaningful, and it must be noted that the study was designed to assess non-inferiority of treatment



**Figure 2** Proportion of patients reporting improvements  $\geq$ MCID in (A) PtGA, (B) Pain, (C) HAQ-DI, (D) FACIT-F, (E) SF-36 PCS and (F) SF-36 MCS (FAS). MCID:  $\geq 10$  mm decrease from baseline in PtGA and Pain;  $\geq 0.22$ -point decrease from baseline in HAQ-DI score;  $\geq 2.5$ -point increase from baseline in SF-36 PCS and MCS scores;  $\geq 4$ -point increase from baseline in FACIT-F score. \* $p < 0.05$  tofacitinib+MTX versus tofacitinib monotherapy; \*\* $p < 0.01$  tofacitinib+MTX versus tofacitinib monotherapy; † $p < 0.05$  ADA+MTX versus tofacitinib monotherapy; ‡ $p < 0.05$  tofacitinib+MTX versus ADA+MTX; †† $p < 0.01$  tofacitinib+MTX versus ADA+MTX. ADA, adalimumab; BID, two times per day; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCID, minimum clinically important difference; MCS, mental component summary; MTX, methotrexate; Pain, arthritis pain; PCS, physical component summary; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short-Form Health Survey.

arms by the primary clinical endpoint of ACR50 responses at month 6, these results are consistent with those of the primary outcomes.

Both combination treatments conferred statistically significant improvements from baseline versus tofacitinib monotherapy in PtGA and Pain, although this was



**Figure 3** The proportion of patients reporting (A) Pain scores <20 mm over time, and (B)  $\geq 20\%$ , 30%, 50% or 70% improvements in Pain at month 6 (FAS). \* $p < 0.05$  tofacitinib+MTX versus tofacitinib monotherapy; \*\* $p < 0.01$  tofacitinib+MTX versus tofacitinib monotherapy; † $p < 0.05$  ADA+MTX versus tofacitinib monotherapy; †† $p < 0.01$  ADA+MTX versus tofacitinib monotherapy. ADA, adalimumab; BID, two times per day; FAS, full analysis set; MTX, methotrexate; Pain, arthritis pain.

consistently maintained only with tofacitinib+MTX (from 3 to 12 months). The majority of patients reported clinically meaningful improvements ( $\geq$ MCID), and while these proportions were generally similar between all treatment arms at all time points in PtGA and Pain, they were numerically greater in Pain in both combination arms versus tofacitinib monotherapy from months 3 to 9.

Thresholds of pain improvement used in these analyses were chosen based on recommendations made by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) public-private consortium, whereby a 10%–20% decrease in pain intensity was considered ‘minimal’ improvement,  $\geq 30\%$  was ‘moderate’ and  $\geq 50\%$  ‘substantial’<sup>39 40</sup>; the higher threshold of  $\geq 70\%$  (‘extensive’ improvement) was defined in a meta-analysis of seven RCTs.<sup>38</sup> In patient surveys conducted across America and Europe, daily pain was highlighted as a paramount issue in terms of disease burden.<sup>42</sup> In ORAL Strategy, as many as 45% of patients reported Pain scores <20 mm in any treatment arm at any time point, and a majority reported  $\geq 20\%$  (all >69%) or  $\geq 30\%$  improvements in Pain (all >59%). Both combination treatments resulted in significantly greater proportions of patients reporting mild pain (Pain scores <20 mm) at 3 months, and moderate ( $\geq 30\%$ ) and extensive ( $\geq 70\%$ ) improvements in Pain scores at varying time points. With discrepancies observed between physician-reported and patient-reported disease activity largely driven by pain,<sup>43 44</sup> it follows that these observations deserve particular attention.

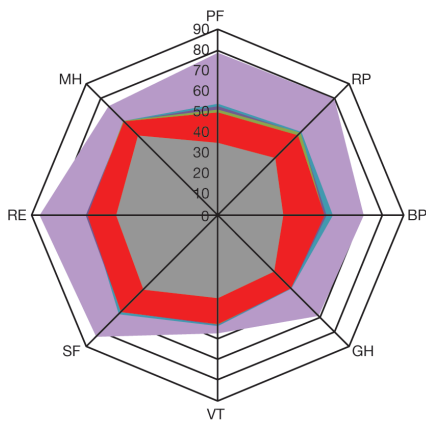
All treatment arms reported similar improvements from baseline in HAQ-DI and FACIT-F at all time points, such that the proportions of patients reporting clinically meaningful improvements ( $\geq$ MCID) and scores within normative values were generally similar between all treatment arms at all time points. Thus, tofacitinib monotherapy was as effective in improving physical function and alleviating fatigue as both combination therapies, with early improvements in FACIT-F reported in both tofacitinib treatment arms.

Diminished HRQoL was evident by the differences observed between baseline SF-36 domain scores compared with a US age-matched and gender-matched normative population. Both combination treatment groups reported statistically significant improvements from baseline in SF-36 PCS versus tofacitinib monotherapy, evident with tofacitinib+MTX at 6, 9 and 12 months. The proportions of patients reporting improvements  $\geq$ MCID in SF-36 PCS generally favoured combination treatments, although differences between combination arms (favouring tofacitinib+MTX vs ADA+MTX) were also observed at certain time points. With regards to domain scores, it is notable that the largest improvements were reported at month 3 and generally similar across treatment arms, although improvements were numerically higher with tofacitinib monotherapy compared with both combination arms at month 3 for the RP and VT domains, and with tofacitinib+MTX compared with tofacitinib monotherapy and ADA+MTX for the BP domain.

Recently, treatment with another targeted synthetic DMARD, baricitinib+MTX, demonstrated significantly

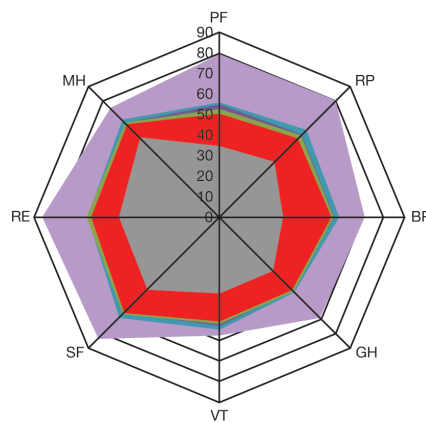
AG norms Baseline Month 3 Month 6 Month 9 Month 12

**A** Tofacitinib 5 mg BID



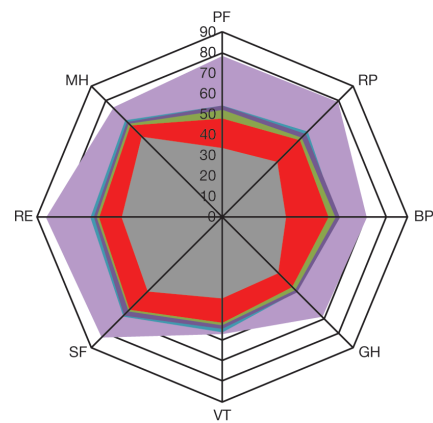
	PF	RP	BP	GH	VT	SF	RE	MH
AG norms	79	80	71	69	57	83	86	75
Baseline (n=383)	35	39	32	39	40	51	49	55
Month 3 (n=367)	50	55	52	50	53	66	63	64
Month 6 (n=358)	51	57	51	50	53	65	63	65
Month 9 (n=337)	53	56	53	50	53	66	64	64
Month 12 (n=321)	54	57	56	50	54	68	62	65

**B** Tofacitinib 5 mg BID+MTX



	PF	RP	BP	GH	VT	SF	RE	MH
AG norms	79	80	71	69	57	83	86	75
Baseline (n=376)	34	38	31	37	37	50	49	55
Month 3 (n=366)	50	54	54	50	50	66	63	64
Month 6 (n=348)	52	56	56	51	52	67	65	65
Month 9 (n=322)	55	56	56	50	53	66	64	65
Month 12 (n=311)	55	60	58	52	54	69	64	67

**C** ADA+MTX



	PF	RP	BP	GH	VT	SF	RE	MH
AG norms	79	80	71	69	57	83	86	75
Baseline (n=382)	34	38	31	38	40	51	49	56
Month 3 (n=374)	48	54	52	48	51	64	60	64
Month 6 (n=354)	53	55	55	50	53	65	62	65
Month 9 (n=335)	55	58	57	52	55	68	63	66
Month 12 (n=317)	55	59	56	52	56	68	65	67

**Figure 4** Spidergrams representing mean SF-36 domain scores over time for (A) tofacitinib 5 mg two times per day, (B) tofacitinib 5 mg two times per day+MTX and (C) ADA+MTX. The sample sizes indicated represent the number of patients who took the SF-36 at that visit. Some domains may have had one to two patients fail to respond. ADA, adalimumab; AG norms, age-matched and gender-matched norms; BID, two times per day; BP, Bodily Pain; GH, General Health; MH, Mental Health; MTX, methotrexate; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; SF-36, 36-Item Short-Form Health Survey; VT, Vitality.

greater improvements in PROs including physical function, pain, fatigue and HRQoL, compared with placebo or ADA+MTX, in the head-to-head RA-BEAM trial in MTX-IR patients with RA.<sup>45</sup> Baricitinib monotherapy was

not evaluated in RA-BEAM. Taken together, ORAL Standard, ORAL Strategy and RA-BEAM provide consistent support for the benefits of a targeted synthetic DMARD (tofacitinib or baricitinib) and csDMARD combination for



the treatment of RA, with at least similar efficacy to a TNFi (such as ADA)+MTX.

The limitations of ORAL Strategy are discussed in detail in the primary publication.<sup>28</sup> Of note, although TNFi share a common mechanism of action, the generalisability of observations in patients receiving ADA+MTX in ORAL Strategy to other TNFi is limited. In this analysis, nominal *p* values were not controlled for multiple comparisons, so must be interpreted with caution. Data were not collected at time points earlier than 6 weeks, so an evaluation of early PRO benefits, as previously reported with tofacitinib monotherapy and combination therapy versus placebo, is not possible.

In addition, the majority of patients were enrolled from countries or regions with low accessibility to bDMARDs and RCTs, and regional differences may therefore occur in outcomes. Further research into reported PRO results across different regions is warranted to determine approaches to best meet local patient needs.

In conclusion, treatment with tofacitinib+MTX, ADA+MTX and tofacitinib monotherapy resulted in clinically meaningful improvements ( $\geq$ MCID) and scores approaching normative values across a broad range of PROs in MTX-IR patients with RA. These improvements were generally, but not uniformly, greater with both combination arms than with monotherapy; however, it was not possible to determine the clinical value of these differences between treatment groups. Primary efficacy data from ORAL Strategy supported a preference for adding tofacitinib to MTX rather than switching to tofacitinib monotherapy,<sup>28</sup> which has shown efficacy versus placebo.<sup>22</sup> These PRO data suggest that in patients without sufficient responses to, or who are intolerant to, MTX, tofacitinib monotherapy can be an effective alternative treatment. Future research to identify subsets of patients that consistently show improvements in all, or specific, PROs, warrants consideration, to determine tailored treatment approaches for MTX-IR patients with RA.

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