ORIGINAL ARTICLE
Tofacitinib versus methotrexate in rheumatoid arthritis: patient-reported outcomes from the randomised phase III ORAL Start trial

Vibeke Strand,1 Eun Bong Lee,2 Roy Fleischmann,3 Rieke E Alten,4 Tamas Koncz,5 Samuel H Zwillich,6 David Gruben,6 Bethanie Wilkinson,6 Sriram Krishnaswami,6 Gene Wallenstein6


ABSTRACT

Objectives: To compare patient-reported outcomes (PROs) in methotrexate (MTX)-naive patients (defined as no prior treatment or ≤3 doses) receiving tofacitinib versus MTX.

Methods: In the 24-month, phase III, randomised, controlled, ORAL Start trial (NCT01039688), patients were randomised 2:2:1 to receive tofacitinib 5 mg two times per day (n=373), tofacitinib 10 mg two times per day (n=397) or MTX (n=186). PROs assessed included Patient Global Assessment of disease (PtGA), pain, Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and health-related quality of life (Short Form-36 [SF-36]).

Results: PROs improved following tofacitinib and MTX treatment: benefits were sustained over 24 months. Patients receiving tofacitinib reported earlier responses which were significantly different between each tofacitinib dose and MTX at month 3 through month 24. At month 6 (primary end point), significant improvements versus MTX were observed in PtGA, pain, HAQ-DI, SF-36 Physical Component Summary (PCS), 5/8 domain scores and FACIT-F with tofacitinib 5 mg two times per day; all PROs, except SF-36 Mental Component Summary Score and Medical Outcomes Survey-Sleep, with tofacitinib 10 mg two times per day. At month 6, the proportion of patients reporting improvements ≥minimal clinically important difference were significant versus MTX with tofacitinib 5 mg two times per day in PtGA and 3/8 SF-36 domains; and with tofacitinib 10 mg two times per day in PtGA, pain, HAQ-DI, SF-36 PCS, 4/8 domains and FACIT-F.

Conclusions: Patients with rheumatoid arthritis receiving tofacitinib 5 and 10 mg two times per day monotherapy versus MTX reported statistically significant and clinically meaningful improvements in multiple PROs over 24 months; onset of benefit with tofacitinib treatment occurred earlier.

Trial registration number: NCT01039688.

Key messages
▸ Both tofacitinib monotherapy doses and MTX improved PROs; however, patients treated with tofacitinib reported earlier responses.
▸ Significant differences in improvement between tofacitinib and MTX were evident by month 3 and persisted.
▸ Improvements ≥MCID at month 6 were significant with tofacitinib versus MTX for multiple PROs.

INTRODUCTION
Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease characterised by systemic inflammation, persistent synovitis and joint destruction. RA affects all aspects of health-related quality of life (HRQoL).1,2 Patients and physicians rate RA disease differently—while physicians focus on RA-specific clinical and radiographic outcomes, patients focus on how their General Health (GH) is affected by RA, which may lead to discordance.3–6 Patient-reported outcomes (PROs) reflect how patients with RA feel and function;7,8 therefore, an effective treatment for RA should offer benefits in terms of Physical Functioning (PF), Emotional Functioning and Social Functioning (SF), as well as clinical and radiographic end points.3–11 Furthermore, the importance of incorporating PROs into the design of randomised controlled trials (RCTs) has been emphasised by Outcome Measures in Rheumatology (OMERACT) international consensus effort, American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR).7,12–15


Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2016-000308).

Received 12 May 2016
Revised 28 July 2016
Accepted 5 August 2016

For numbered affiliations see end of article.

Correspondence to
Dr Gene Wallenstein;
Gene.wallenstein@pfizer.com
Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. Tofacitinib preferentially inhibits signalling by heterodimeric receptors associated with JAK3 and JAK1, with functional selectivity over receptors that signal via pairs of JAK2.16 17 Tofacitinib 5 and 10 mg two times per day have been investigated in six phase III RCTs as monotherapy or in combination with conventional disease-modifying antirheumatic drugs (DMARDs), predominantly methotrexate (MTX), in patients with RA.18–25

This RCT, ORAL Start, was designed to investigate the effects of tofacitinib monotherapy versus MTX in patients who were MTX-naive (defined as no prior treatment or ≤3 doses) over 24 months. This phase III RCT (ClinicalTrials.gov ID NCT01039688; Pfizer protocol A3921069) demonstrated that tofacitinib monotherapy resulted in clinically and statistically significant reductions in signs and symptoms of RA, improvements in physical function and statistically significant inhibition of progression of structural damage compared with MTX, reported previously.21 The safety profile was similar to that previously reported in tofacitinib trials. Here we report the PRO data from this RCT.

METHODS

Trial design and patients

This RCT was conducted across 151 centres worldwide; full details have been reported previously.21 Patients were ≥18 years of age with a diagnosis of RA according to the ACR 1987 Revised Criteria24 and active disease, defined as ≥6 tender and swollen joints (of 68/66 joints examined), with either erythrocyte sedimentation rate >28 mm/hour (Westergren method) or C reactive protein >7 mg/L. Patients were randomised (2:2:1) to receive tofacitinib 5 mg two times per day or tofacitinib 10 mg two times per day monotherapy (hereafter referred to as tofacitinib 5 mg and tofacitinib 10 mg), or MTX starting at 10 mg/week, increasing in increments of 5 mg/week every month to 20 mg/week by week 8.

The trial was designed to detect differences between MTX and tofacitinib 5 or 10 mg in two primary efficacy end points at month 6: ACR70 response rates (at least 90% power) and inhibition of structural damage, measured by change from baseline in modified total Sharp score. All other (efficacy) assessments were predefined as secondary end points. After the publication of the results, one of its study sites (eight patients randomised) was found non-compliant to study procedures and those patients have been removed from the PRO analyses presented here.

The trial was approved by Institutional Review Boards (IRBs) and/or Independent Ethics Committees at each investigational centre or a central IRB, and conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent.

Assessment of PROs

The following PROs (components of the ACR response criteria) were included as predefined end points: Patient Global Assessment of disease (PtGA), pain (assessed by 100 mm visual analogue scales (VAS)) and physical function by Health Assessment Questionnaire-Disability Index (HAQ-DI). Other predefined secondary end points included HRQoL using Medical Outcomes Survey (MOS) Short Form-36 (SF-36; V2, acute) questionnaire, fatigue by Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F) scale and quality of sleep using MOS-Sleep scale.25 26

Minimum clinically important differences (MCIDs) were defined as: >0.10 mm decreases from baseline in PtGA and pain VAS scores;27 ≥0.22 point decrease from baseline in HAQ-DI;15 25 ≥2.5 point increases from baseline in SF-36 Physical Component Summary (PCS) and MCS scores; ≥6.5 point increases from baseline in SF-36 domain scores;15 25 and a 4-point increase from baseline in FACT-F.25 MCID is not available for MOS-Sleep.28

PtGA, pain, HAQ-DI and SF-36 scores were measured at all time points (baseline, months 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24); FACT-F and MOS-Sleep at baseline, months 1, 2, 3, 6, 12, 18 and 24. The proportion of patients reporting improvements ≥MCID were compared between tofacitinib and MTX treatment groups at months 3, 6, 12 and 24.

Statistical analyses

End points were expressed as mean changes from baseline and analysed using a linear mixed-effects repeated-measures model. This model was based on the full analysis set (FAS; all patients who received ≥1 dose of study drug and with ≥1 postbaseline assessment). Treatment, visit, treatment-by-visit interaction and baseline were included as fixed effects, as well as disease duration at baseline and region of investigative site; patients were included as random effects, employing the method of maximum likelihood using least squares (LS) estimates for parameters such as mean changes from baseline (for each treatment) as well as mean differences (each tofacitinib treatment vs MTX), hereafter LS mean (LSM). Corresponding SEs for these estimates were also derived.

The percentage of patients reporting improvements ≥MCID and scores meeting or exceeding normative values were compared between tofacitinib and MTX treatment groups using the normal approximation to the binomial (FAS, no imputation). All end points presented were prespecified, except for percentages of patients reporting improvements ≥MCID for FACT-F and percentages of patients whose scores met or exceeded normative values.

Statistical significance was declared at p<0.05, with no correction for multiple comparisons.

Number needed to treat (NNT; the number of patients who need to be treated for one patient to achieve an improvement in outcome) was calculated as 1/(proportion of patients in the tofacitinib group...
<table>
<thead>
<tr>
<th>PRO</th>
<th>Baseline mean (SD)</th>
<th>Month 3 LSM change from baseline (SE)</th>
<th>Month 6 LSM change from baseline (SE)</th>
<th>Month 12 LSM change from baseline (SE)</th>
<th>Month 24 LSM change from baseline (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tofacitinib 5 mg two times per day</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>60.42 (24.49)</td>
<td>60.86 (22.55)*</td>
<td>60.67 (22.50)*</td>
<td>60.86 (22.33)</td>
<td>60.67 (22.50)*</td>
</tr>
<tr>
<td>SF-36</td>
<td>32.82 (7.25)</td>
<td>33.19 (7.33)*</td>
<td>33.51 (7.83)*</td>
<td>32.82 (7.25)</td>
<td>33.19 (7.33)*</td>
</tr>
<tr>
<td>MCS</td>
<td>40.47 (12.09)</td>
<td>40.69 (11.76)*</td>
<td>40.86 (11.30)*</td>
<td>40.47 (12.09)</td>
<td>40.69 (11.76)*</td>
</tr>
<tr>
<td>RP</td>
<td>30.13 (9.44)</td>
<td>31.58 (9.88)*</td>
<td>32.04 (9.59)*</td>
<td>30.13 (9.44)</td>
<td>31.58 (9.88)*</td>
</tr>
<tr>
<td>SF</td>
<td>36.38 (11.30)</td>
<td>36.67 (11.10)</td>
<td>37.52 (11.33)</td>
<td>36.38 (11.30)</td>
<td>36.67 (11.10)</td>
</tr>
<tr>
<td>RE</td>
<td>33.98 (13.36)</td>
<td>34.73 (13.09)</td>
<td>34.67 (12.61)</td>
<td>33.98 (13.36)</td>
<td>34.73 (13.09)</td>
</tr>
<tr>
<td>MH</td>
<td>38.85 (11.92)</td>
<td>39.42 (11.77)</td>
<td>39.72 (11.35)</td>
<td>38.85 (11.92)</td>
<td>39.42 (11.77)</td>
</tr>
<tr>
<td>FACIT-F</td>
<td>28.43 (10.94)</td>
<td>29.01 (10.73)</td>
<td>28.49 (10.57)</td>
<td>28.43 (10.94)</td>
<td>29.01 (10.73)</td>
</tr>
<tr>
<td>MOS-Sleep</td>
<td>42.68 (19.50)</td>
<td>42.86 (20.56)</td>
<td>42.99 (18.09)</td>
<td>42.68 (19.50)</td>
<td>42.86 (20.56)</td>
</tr>
<tr>
<td>MTX</td>
<td>N=184</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=132</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=132</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=132</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=156</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
reporting improvements \( \geq \)MCID minus the proportion of patients in the MTX group reporting improvements \( \geq \)MCID).^{29}

**RESULTS**

**Patients**

Of 958 patients randomised, 373 received tofacitinib 5 mg, 397 tofacitinib 10 mg and 186 MTX (total=956). Two hundred and ninety-eight patients discontinued treatment: 80 (43.0%) with MTX compared with 107 (28.7%) and 111 (28.0%) for tofacitinib 5 and 10 mg, respectively. Most common reasons for discontinuation were adverse events with tofacitinib 5 mg (n=38) and tofacitinib 10 mg (n=39), and lack of efficacy with MTX (n=26).

**Baseline values**

Prior treatments, patient demographics and baseline disease characteristics were similar across treatment groups.^{21} Mean disease duration was 2.7–3.4 years; 65.5% and 53.9% of patients had disease duration <2 years and <1 year, respectively. Baseline mean PtGA, pain and HAQ-DI scores indicated impaired physical function (table 1). Large decrements in reported

---

**Figure 1** Spydergrams displaying SF-36 domains at months 3, 6, 12 and 24. Study values were normed using population mean and SDs.\(^{51,52}\) BID, twice a day; BP, Bodily Pain; GH, General Health; MH, Mental Health; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; SF-36, Short Form-36; VT, Vitality.
HRQoL were evident by PCS scores ~1.5–2.0 SDs below the normative score of 50, and lower domain scores compared with an age-matched and gender-matched US non-disease population (figure 1).

**Patient-reported outcomes**

**Patient Global Assessment of Disease activity**

Patients who received tofacitinib 5 or 10 mg reported improvements from baseline in PtGA that were significant (p<0.05) versus MTX at all time points from month 1 to month 24 (table 1 and figure 2A); maximal effects were observed by month 6. Compared with MTX, significantly more (p<0.05) patients who received tofacitinib reported improvements ≥MCID at months 3, 6, 12 and 24 (figure 3A). NNTs ranged from 7.2 to 10.4 with tofacitinib 5 mg and from 5.9 to 9.7 with tofacitinib 10 mg (figure 3).

**Pain**

Significant improvements from baseline in pain (p<0.05) versus MTX were seen at all time points from month 1 for patients who received tofacitinib 10 mg and at all time points with the exception of month 6 for those receiving tofacitinib 5 mg (table 1 and figure 2B). At months 3, 6 and 12, more patients (p<0.05) receiving tofacitinib 10 mg reported improvements ≥MCID versus MTX. NNTs were lower with tofacitinib 10 mg compared with tofacitinib 5 mg, ranging from 7.3 to 10.2 (figure 3B).

**Health Assessment Questionnaire-Disability Index**

Patients receiving tofacitinib reported improvements from baseline in HAQ-DI that were significant (p<0.05) versus MTX at all time points from month 1 to month 24 (table 1 and figure 3C). Significantly (p<0.05) more...
patients reported improvements ≥MCID in HAQ-DI with tofacitinib 10 mg versus MTX at months 3 and 6, with NNTs of 8.7 and 11.6, respectively (figure 3C). The proportions of patients who reported HAQ-DI values meeting or exceeding normative values were significantly greater with tofacitinib versus MTX at month 6 (p<0.001; table 2), month 12 and month 24 (p<0.05; data not shown).

Functional Assessment of Chronic Illness Therapy-Fatigue
Patients who received tofacitinib reported significant (p<0.05) improvements from baseline in FACIT-F versus MTX at all time points from month 1 (table 1 and figure 2). At month 3, significantly more patients in both tofacitinib groups reported improvements ≥MCID in FACIT-F versus MTX (p<0.05); at month 6, significant improvements were evident with tofacitinib 10 mg but not with tofacitinib 5 mg (figure 3D). NNTs at all time points were lower with tofacitinib 10 mg than with tofacitinib 5 mg (figure 3D). At months 6, 12 and 24, significantly (p<0.05) more patients receiving tofacitinib 10 mg two times per day versus MTX reported scores ≥normative values for FACIT-F (table 2); significant improvement was evident with tofacitinib 5 mg two times per day at month 12.

HRQoL by SF-36
Patients in both tofacitinib treatment arms reported LSM changes from baseline in PCS scores that were significant (p<0.001) versus MTX at months 3, 6, 12 and 24. The proportion of patients reporting improvements ≥MCID in PCS scores was significant (p<0.05) versus MTX at month 3 for both tofacitinib doses and months 6, 12 and 24 for tofacitinib 10 mg (table 1). LSM

Figure 2  Continued
changes from baseline in MCS scores with tofacitinib exceeded MTX at months 3, 6, 12 and 24, but were significant (p<0.05) versus MTX at month 3 for tofacitinib 5 mg and month 12 for tofacitinib 10 mg (table 1). The proportion of patients receiving tofacitinib 10 mg who reported improvements ≥MCID in MCS scores was significant (p<0.05) versus MTX at months 12 and 24 (figure 3E). NNTs were therefore lower with tofacitinib 10 mg versus tofacitinib 5 mg for PCS and MCS scores.

Significant (p<0.05) improvements versus MTX were reported with tofacitinib 5 mg in PF, Role Physical (RP) and Bodily Pain (BP; months 3, 6, 12 and 24), GH (months 3 and 24), Vitality (VT) and Mental Health (MH) (months 3, 6 and 12), SF (months 3, 12 and 24) and Role Emotional (RE; month 3) domains (table 1). Patients who received tofacitinib 10 mg reported significant improvements versus MTX in PF, RP, BP, GH, VT, SF and RE (months 3, 6, 12 and 24), and MH (months 6 and 12) domains (table 1). Significantly more (p<0.05) patients who received tofacitinib 5 or 10 mg (vs MTX) reported improvements ≥MCID in all SF-36 domains at month 3. Additionally, significantly more patients reported improvements ≥MCID with tofacitinib 5 mg in PF, BP and MH domains at month 6, PF, BP and SF domains at month 12 and PF domain at month 24; and with tofacitinib 10 mg in PF, RP, BP and RE domains at month 6, PF, BP, SF, RE and MH domains at month 12 and PF, BP, VT, SF and MH at month 24 (figure 3E). Across SF-36 domains, NNTs were generally lower with tofacitinib 10 mg than with tofacitinib 5 mg (figure 3E). Significantly more (p<0.05) patients reported scores ≥normative values with tofacitinib 5 and 10 mg two times per day in PF, RP, BP, VT and MH domains at month 6 (table 2), PF, RP, SF and BP domains at month 12, and PF and BP domains at month 24 compared with MTX.

Medical Outcomes Survey-Sleep

In general, compared with MTX, patients in both tofacitinib treatment arms reported numerically greater improvements from baseline in MOS-Sleep scores at all

![Figure 3](http://rmdopen.bmj.com)
time points. These changes were statistically significant versus MTX with tofacitinib 5 mg at months 3 and 12, but were not statistically significant versus MTX with tofacitinib 10 mg (table 1).

**Discussion**

In this paper, we report PROs from the phase III ORAL Start trial, which investigated the effects of tofacitinib monotherapy at two doses versus MTX in patients with
active RA. This is the first investigation of tofacitinib mono-
therapy versus MTX in patients who were predominantly
MTX-naive. Improvements in PROs in this ORAL Start
trial were consistent with those reported in other tofaciti-
nib phase III RCTs in DMARD and tumour necrosis factor
inhibitor-inadequate responder populations.30

Patients in all active treatment groups reported
improvements across multiple PROs. However, onset of
treatment effect occurred earlier with tofacitinib than
with MTX. Statistically significant differences between
both tofacitinib doses and MTX were first evident as
early as month 1 in the case of PtGA, pain, HAQ-DI and
both tofacitinib doses and MTX were

Table 2 Percentage of patients reporting scores
>normative values for PROs at month 6

<table>
<thead>
<tr>
<th>Tofacitinib</th>
<th>Tofacitinib</th>
<th>MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg two</td>
<td>10 mg two</td>
<td></td>
</tr>
<tr>
<td>times per day</td>
<td>times per day</td>
<td></td>
</tr>
<tr>
<td>N=337</td>
<td>N=363</td>
<td>N=156</td>
</tr>
<tr>
<td>HAQ-DI, n (%)</td>
<td>149 (44.21)**</td>
<td>195 (53.72)***</td>
</tr>
<tr>
<td>SF-36 domain, n (%)</td>
<td>99 (29.38)***</td>
<td>133 (36.64)***</td>
</tr>
<tr>
<td>PF</td>
<td>104 (30.86)*</td>
<td>133 (36.64)**</td>
</tr>
<tr>
<td>RP</td>
<td>122 (36.20)*</td>
<td>153 (42.15)***</td>
</tr>
<tr>
<td>BP</td>
<td>109 (32.34)</td>
<td>111 (30.58)</td>
</tr>
<tr>
<td>GH</td>
<td>192 (56.97)*</td>
<td>209 (57.58)*</td>
</tr>
<tr>
<td>VT</td>
<td>144 (42.73)</td>
<td>166 (45.73)</td>
</tr>
<tr>
<td>RE</td>
<td>113 (33.53)</td>
<td>138 (38.02)</td>
</tr>
<tr>
<td>MH</td>
<td>142 (42.14)*</td>
<td>157 (43.25)*</td>
</tr>
<tr>
<td>FACIT-F, n (%)</td>
<td>147 (43.62)*</td>
<td>183 (50.41)***</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.001; ***p<0.0001 vs MTX.
BP, Bodily Pain; FACIT-F, Functional Assessment of Chronic
Illness Therapy-Fatigue; GH, General Health; HAQ-DI, Health
Assessment Questionnaire-Disability Index; MH, Mental Health;
MTX, methotrexate; PF, Physical Functioning; PROs, patient-reported outcomes; RE, Role Emotional; RP, Role
Physical; SF, Social Functioning; SF-36, Short Form-36; VT,
Vitality.

In general, NNT values over time were numerically
lower with tofacitinib 10 mg compared with tofacitinib
5 mg. It must be noted that although it is usual for
NNTs to be calculated against a placebo control, in this
analysis, NNT values were calculated in relation to the
active control MTX. For most PRO measures, NNT values increased over time, which may be a reflection of
the improvement in PRO outcomes with MTX generally occurring later than with tofacitinib.

Data from RCTs have demonstrated that the onset of
benefit with MTX treatment is most evident 6 months
after treatment initiation, with maximal benefit observed
at 9–12 months;36–39 patients with earlier disease treated
aggressively are more likely to respond. As this trial popu-
lation included a majority of patients with disease of
<1 year duration, and those randomised to MTX received
aggressive treatment (10 mg/week titrated to 20 mg/
week by month 2), clinically meaningful responses would
be expected with MTX. Onset of benefit with tofacitinib
treatment was more rapid than with MTX, reflected by
statistically significant LSM changes from baseline
≥MCID in tofacitinib-treated patients at month 3, except the MH domain with
tofacinib 10 mg. LSM changes from baseline reported
by tofacitinib-treated patients at subsequent time points
were sustained through month 24, although not neces-
sarily statistically significant versus MTX at later time
points, when additional later improvements with MTX
were evident—consistent with the known time course of
benefit of MTX.

Improvements in HRQoL observed in this trial were of
similar magnitude and tempo of onset as observed in
biological agents plus MTX compared with MTX mono-
therapy in MTX-naive patients, as reported with adali-
mumab, etanercept, golimumab and in

In a phase III clinical trial of adalimumab, PROs includ-
ing HAQ-DI, SF-36 PCS and FACIT-F scores were significa-
cantly improved with adalimumab 40 mg every other
week plus MTX versus MTX monotherapy.46 A higher
percentage of patients reported improvements in
HAQ-DI ≥MCID with rituximab plus MTX (30%) com-
pared with placebo plus MTX (15%) at year 2.47
Similarly, treatment with abatacept 10 mg/kg plus MTX
resulted in greater improvements in SF-36 PCS and

Rheumatoid arthritis

| FACIT-F, n (%) | 147 (43.62)* | 183 (50.41)***| 55 (35.26) |
| FACIT-F, n (%) | 147 (43.62)* | 183 (50.41)***| 55 (35.26) |
Patients enrolled in the GO-BEFORE RCT reported similar improvements in HAQ-DI and SF-36 PCS regardless of whether they received golimumab 50 mg plus MTX or MTX monotherapy.⁴⁹ The limitations of this study have been reported previously.²¹

In summary, in the ORAL Start phase III RCT, patients with moderately to severely active RA who were MTX-naive reported improvements in PROs with tofacitinib 5 and 10 mg monotherapy that were statistically superior to MTX at month 3, occurred earlier and persisted through 24 months' treatment. These results provide further evidence that tofacitinib monotherapy not only improves signs and symptoms and inhibits progression of structural damage in RA but also improves pain, physical function, HRQoL and fatigue in a range of patient populations, and with more rapid onset of these benefits than MTX.

Author affiliations
Division of Immunology/Rheumatology, Stanford University School of Medicine, Palo Alto, California, USA
²Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea
³Department of Medicine, University of Texas Southwestern Medical Center, Metroplex Clinical Research Center, Dallas, Texas, USA
⁴Department of Internal Medicine, Rheumatology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany
⁵Global Innovative Pharmaceuticals, Pfizer, New York, New York, USA
⁶Global Innovative Pharmaceuticals, Pfizer, Groton, Connecticut, USA

Acknowledgements
Anne Marie Reid, PhD, of Complete Medical Communications provided editorial support under the direction of authors, funded by Pfizer. Andrew Anisefeld, Elaine Hoffman, Ryan DeMasi and Lisy Wang, all employees of Pfizer, provided intellectual input during the manuscript development.

Funding
This work was supported by Pfizer.

Competing interests
VS and EBL are consultants for Pfizer. REA and RF have received research grants and are consultants for Pfizer. TK, SHZ, DG, BW, SK and GW are shareholders and employees of Pfizer.

Ethics approval
The trial was approved by Institutional Review Boards (IRBs) and/or Independent Ethics Committees at each investigational centre or a central IRB.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
No additional data are available.

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES
15. Strand V, Boers M, Idzerda L, et al. It’s good to feel better but it’s better to feel good and even better to feel good as soon as possible. Response criteria and the importance of change at OMERACT 10. J Rheumatol 2011;38:1720–7.


