**ORAL Strategy: a Phase 3b/4 head-to-head randomised trial comparing the efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis**

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**Target journal**: *The Lancet*

**Research in context**

**Evidence before this study**

PubMed MEDLINE was searched up to February 2017, to identify randomised controlled trials (RCTs) published in the English language assessing the efficacy and safety of tofacitinib and adalimumab specifically in patients with rheumatoid arthritis (RA) in the same clinical trial who had an incomplete response to conventional synthetic disease modifying antirheumatic drugs (csDMARDs), either as monotherapy or in combination. Two comparator, but not head-to-head, trials were found which are discussed in the Introduction. We also searched for head-to-head comparator clinical trials assessing the efficacy and safety of a Janus kinase (JAK) inhibitor and a tumour necrosis factor inhibitor (TNFi) therapy; the RA-BEAM trial suggested a statistical advantage of JAK inhibition in combination with methotrexate (MTX) over TNF inhibition in combination with MTX in the treatment of RA and is also described in the Introduction and Discussion. However, we did not find any comparative RCTs comparing JAK inhibitor monotherapy versus TNFi in combination with MTX. We also found no comparative RCTs assessing the efficacy or safety of tofacitinib monotherapy versus tofacitinib in combination with MTX.

**Added value of this study**

This is the first head-to-head non-inferiority trial assessing a JAK inhibitor with or without MTX directly compared with a TNFi therapy plus MTX in RA, and the first head-to-head non-inferiority comparison of tofacitinib monotherapy versus tofacitinib in combination with MTX. The primary endpoint selected was the American College of Rheumatology 50% (ACR50) response rate at 6 months based on prior evidence of the suitability of this composite endpoint in head-to-head trials comparing active treatment arms. A non-inferiority margin was selected based on a systematic review reporting ACR50 response of adalimumab compared with placebo, supplemented with data from one subsequent relevant trial. The treatment arms in this trial reflect the treatment choices facing rheumatologists when confronted with a patient who has had an inadequate response to a csDMARD such as MTX, either alone or in combination with other csDMARDs, and has markers of poor prognosis. Current practice is to add a biologic DMARD (bDMARD) such as adalimumab to MTX, but the most recent EULAR recommendations propose that the addition of a targeted synthetic DMARD (tsDMARD) such as tofacitinib to MTX may be an alternative. If csDMARDs are contraindicated, then EULAR recommends JAK inhibitor or IL6 inhibitor monotherapy as options. ORAL Strategy provides evidence that the addition of either a bDMARD or a tsDMARD can be considered and both are more likely to be effective than switching to tofacitinib monotherapy.

**Implications of all the available evidence**

This trial reports that tofacitinib plus MTX was non-inferior to adalimumab plus MTX when assessing the ACR50 response at 6 months. Although the monotherapy tofacitinib arm also achieved meaningful benefit in clinical and functional responses, non-inferiority relative to the two combination arms could not be demonstrated for the primary endpoint.

**Word count/limit:** 4886/4500

**References/limit:** 30/30

# Summary (word count/limit: 300/300)

**Background**: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA).

**Methods**: ORAL Strategy was a 1-year, double-blind, Phase 3b/4, controlled head-to-head trial in patients aged ≥18 years with active RA despite methotrexate therapy who received tofacitinib 5 mg twice daily (BID) monotherapy, tofacitinib 5 mg BID plus methotrexate (‘tofacitinib + MTX’) or adalimumab 40 mg every other week plus methotrexate (‘adalimumab + MTX’). Eligible patients received live zoster vaccine at investigators’ discretion. The primary endpoint was the proportion of patients achieving American College of Rheumatology 50% (ACR50) response at Month 6; non-inferiority between groups was declared if the lower bound of the 98·34% confidence interval (CI) of the difference between comparators was larger than -13·0%. Secondary efficacy endpoints assessed included ACR20/50/70 responses, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and Disease Activity Score - 28, erythrocyte sedimentation rate (DAS28-4[ESR]) at several timepoints, and adverse events and laboratory parameters throughout. (ClinicalTrials.gov: NCT02187055.)

**Findings**: A total of 1146 patients received treatment (tofacitinib monotherapy: n=384; tofacitinib + MTX: n=376; adalimumab + MTX: n=386). At 6 months, ACR50 response rates were achieved in 38·3% with tofacitinib monotherapy, 46·0% with tofacitinib + MTX, and 43·8% with adalimumab + MTX. Non-inferiority was declared for tofacitinib + MTX versus adalimumab + MTX (difference [98·34% CI]: 2·2% [−6·4 to 10·9]) but not for tofacitinib monotherapy versus either adalimumab + MTX (−5·5 [−14·0 to 3·0]) or tofacitinib + MTX (−7·7 [−16·3 to 0·8]). Secondary endpoints supported primary observations. No new or unexpected safety issues were observed for either treatment in this study of limited duration.

**Interpretation**: Tofacitinib + MTX was non-inferior to adalimumab + MTX in the treatment of RA in patients with an inadequate response to MTX in this trial. Tofacitinib monotherapy could not be declared non-inferior to either combination.

# Funded by:Pfizer Inc.

# Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterised by inflammation, persistent synovitis, and eventual joint destruction.1 In patients who have an inadequate response (IR) to therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), either as monotherapy or in combination with other csDMARDs, the addition of either a biologic DMARD (bDMARD), such as a tumour necrosis factor inhibitor (TNFi) or a targeted synthetic DMARD (tsDMARD), such as a Janus kinase (JAK) inhibitor, is recommended by both the ACR and EULAR.2,3

Tofacitinib is an oral JAK inhibitor approved for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) administered as monotherapy or in combination with csDMARDs (mainly MTX) in patients with active RA, have been demonstrated in Phase 34–9 studies of up to 24 months’ duration and in long-term extension (LTE) studies with up to 105 months of observation10,11 The TNFi adalimumab is a recombinant human monoclonal antibody approved as a 40 mg dose every other week (Q2W) that has demonstrated efficacy in patients with active RA who had an IR to MTX12–16 and an acceptable safety profile demonstrated in LTE studies of over 10 years’ duration.17

Tofacitinib is approved worldwide either as monotherapy or in combination with csDMARDs. No prospective, randomized clinical trial has compared the clinical efficacy of tofacitinib monotherapy with tofacitinib in combination with a csDMARD; post-hoc analyses suggest similar efficacy between the two approaches.18 Conversely, as with all bDMARDs, enhanced clinical efficacy has been demonstrated for adalimumab with concomitant MTX compared with adalimumab monotherapy.19

Only two studies have compared tofacitinib and adalimumab (one with and one without background MTX) in patients with active RA; neither was appropriately designed as a head-to-head study to compare treatment arms.9,16 This Phase 3b/4 trial (ORAL Strategy) directly compared the efficacy and safety of tofacitinib monotherapy, tofacitinib in combination with MTX, and adalimumab in combination with MTX in an adequately powered head-to-head trial in patients with active RA and an IR to prior MTX treatment.

# Methods

# Study design

ORAL Strategy (NCT02187055) was a 1-year, double-blind, triple-dummy, Phase 3b/4, active comparator, head-to-head controlled trial assessing non-inferiority between treatment arms of tofacitinib 5 mg BID monotherapy, tofacitinib 5 mg BID in combination with MTX, and adalimumab 40 mg Q2W with MTX, in patients with active RA despite MTX treatment. The study was conducted at 194 centres in 25 countries. All procedures were performed in accordance with the Declaration of Helsinki and all patients provided written informed consent; a full list of contributing investigators is provided as supplementary material.

## Randomisation and masking

Between 11 September 2014 and 28 December 2015, patients were blindly randomised 1:1:1 to receive oral tofacitinib 5 mg BID monotherapy (‘tofacitinib monotherapy’), oral tofacitinib 5 mg BID in combination with MTX (‘tofacitinib + MTX’), or subcutaneous adalimumab 40 mg Q2W in combination with MTX (‘adalimumab + MTX’); all patients enrolled in the study were required to have been treated for a minimum of 4 months with a stable MTX dose of 15–25 mg/week for at least 6 weeks prior to baseline. At the time of randomisation (Baseline/Visit 2), patients discontinued their own MTX and were switched to one of 3 groups: (1) tofacitinib monotherapy with concomitant placebo MTX and placebo adalimumab; (2) tofacitinib plus MTX with concomitant placebo adalimumab or; (3) adalimumab plus MTX with concomitant placebo tofacitinib. The pre-study stable dose of MTX was continued in all patients taking combination therapy.

Randomisation was achieved by an interactive voice response system (IVRS): an automated internet-/telephone-based system with which investigators enrolled patients using minimal identification criteria (such as date of birth and initials), and received a patient identification number which was then used to determine the patient treatment according to a predetermined randomisation schedule.

## Patients

The study population consisted of individuals ≥18 years of age who met the 2010 ACR/EULAR classification criteria for RA20 with active RA defined as having ≥4 tender/painful joints on motion and ≥4 swollen joints (based on 28 joint count) at baseline in spite of treatment with MTX 15–25 mg per week, high-sensitivity C-reactive protein (hsCRP) ≥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.21 Patients were required to discontinue all csDMARDs other than MTX, for at least 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 oral corticosteroids (≤10 mg prednisone or equivalent per day) throughout the trial. Patients who had not failed or had an adverse event (AE) secondary to a bDMARD could be included but had to have discontinued the bDMARD for a minimum period of time prior to randomisation (rituximab or other selective B lymphocyte depleting agents: 52 weeks; abatacept, certolizumab pegol, tocilizumab: 4 weeks; golimumab: 10 weeks; infliximab: 8 weeks; anakinra, etanercept: 4 weeks).

Patients were excluded if they had: contraindications for any study treatment; a history of infections requiring treatment within 2 weeks, or hospitalisation within the 6 months prior to randomisation; had exclusionary morbidities, HIV, hepatitis B or C, inadequately treated or undocumented treatment of tuberculosis; experienced more than one episode of herpes zoster, one episode of disseminated herpes zoster or herpes simplex; any clinically significant laboratory abnormalities; or were pregnant. Patients who had previously failed treatment with a bDMARD (due to lack of efficacy or bDMARD--related AEs) or who had previously received tofacitinib, adalimumab, glucocorticoids (>10 mg/day within the previous 4 weeks), or live attenuated vaccines other than the herpes zoster vaccine (within 6 weeks prior to study initiation, or planned within 6 weeks after discontinuation of study treatment) were also excluded. A complete list of inclusion and exclusion criteria are provided as supplementary material.

## Procedures

All treatments (except herpes vaccination) were self-administered. To maintain the blinding of treatment in this triple-dummy trial, patients in each treatment group received the appropriate placebo, whether MTX, tofacitinib or adalimumab, to ensure identical dose burden between groups. In patients who were eligible (based on vaccine availability at site and age ≥50 years), live zoster vaccine was administered approximately 4 weeks in advance of study treatment at the investigator’s discretion. Physical examinations were performed at screening, baseline and Month 12, and laboratory observations, and AE assessments were performed at each visit and at a follow-up visit 28 (±14) days after the end of the study treatment period.

## Outcomes

The primary endpoint was the proportion of patients achieving an American College of Rheumatology 50% (ACR50) response at 6 months. Secondary efficacy endpoints included achievement of ACR20/50/70 response rates at various time points; the proportion of patients achieving low disease activity (LDA) (as defined by the Simplified Disease Activity Index [SDAI] ≤11, Clinical Disease Activity Index [CDAI] ≤10, Disease Activity Score in 28 joints, erythrocyte sedimentation rate [DAS28-4(ESR)] <3·2 and Disease Activity Score in 28 joints, C-reactive protein [DAS28-4(CRP)] <3·2), remission (as defined by SDAI ≤3·3, CDAI ≤2·8, DAS28-4[ESR], DAS28-4[CRP] <2·6, and ACR-EULAR Boolean remission criteria); the proportion of patients achieving a HAQ-DI response (improvement of ≥0·22 compared with baseline); and least squares mean (LSM) change from baseline for SDAI, CDAI, DAS28-4(ESR), and HAQ-DI.

Safety was assessed by evaluating AEs, serious AEs (SAEs), discontinuations due to AEs, and laboratory observations. External adjudication committees were established to standardise the assessment of selected safety events of special interest (cardiovascular events, hepatic events, opportunistic infections, malignancy, and gastrointestinal perforation). Occurrences of interstitial lung disease were determined by an internal adjudication committee.

## Statistical analysis

For the primary outcome (non-inferiority in ACR50 at Month 6) there were three independent comparisons: tofacitinib 5 mg BID + MTX was compared with adalimumab 40 mg Q2W + MTX; and tofacitinib 5 mg BID monotherapy was compared with both adalimumab + MTX and with tofacitinib + MTX. A sample size calculation, assuming an ACR50 response rate of 35% in all groups, determined that 360 patients in each treatment arm were required to demonstrate non-inferiority with a power of 90% in each comparison. A non-inferiority margin of 13% was chosen as it represents approximately half of the observed treatment difference between adalimumab + background MTX and placebo (based on a meta-analysis of adalimumab trials22 supplemented with data from an additional recent trial9). For the primary endpoint, an alpha value of 0·0166 was calculated using a Bonferroni procedure to preserve the overall type I error rate of 5% for multiple comparisons; non-inferiority was declared if the lower bound of the 98·34% confidence interval (CI) for the difference was larger than ˗13%. For any comparison between primary endpoints, if non-inferiority was demonstrated, superiority could be declared if the lower bound of the 98·34% CI of the difference was greater than zero. Nominal p values and nominal 95% CIs for secondary analyses were calculated. These additional analyses were not type I error controlled.

Primary and secondary efficacy endpoints were assessed using the full analysis set (FAS), which included all patients who were randomised and received at least one dose of the study treatment; this was also the definition for the safety analysis set (SAS). A sensitivity analysis was performed assessing the primary endpoint in all patients who completed 6 months with no substantial protocol deviations (the per protocol set). Non-responder imputation for patient withdrawal and last observation carried forward for patients with missing data before withdrawal were used to handle missing data for binary endpoints, which were then analysed using normal approximation to proportions. Continuous endpoints were analysed using a linear mixed-effects model of repeated measurements including fixed-effect terms (treatment group, visit, treatment group by visit interaction, and geographical region), covariate (baseline value), and patient as a random effect with autoregressive covariance.

***Role of the funding source***

This study was sponsored by Pfizer Inc. The study was designed by Pfizer Inc in collaboration with the lead author. Pfizer Inc was responsible for the collection of the data. All authors had full access to all data and all were involved in the analysis and interpretation of data and in the writing of the report. The lead author had final responsibility for the decision to submit for publication. All authors meet ICMJE criteria for authorship. Zhen Luo, Richard Zhang, Ryan DeMasi, Koshika Soma, Liza Takiya, Svitlana Tatulych, Christopher Mojcik, Sriram Krishnaswami, and Sujatha Menon are employees of Pfizer Inc. Medical writing support, under the guidance of the authors, was provided by Martin Bell, PhD, of Complete Medical Communications and was funded by Pfizer Inc.

# Results

## Patients

A total of 1152 patients were randomised and 1146 were treated (FAS: tofacitinib monotherapy: n=384; tofacitinib + MTX: n=376; adalimumab + MTX: n=386). Patient disposition is presented in figure 1; discontinuation rates were similar between all three treatment arms. Baseline demographics, disease characteristics, and disease severity for all patients included in the FAS were comparable between groups (table 1).

## Outcomes

### Clinical efficacy

At 6 months, ACR50 response was achieved in 38·3% of tofacitinib monotherapy patients, 46·0% of tofacitinib + MTX patients, and 43·8% of adalimumab + MTX patients (figure 2A; table 2). Tofacitinib + MTX was deemed non-inferior to adalimumab + MTX: the difference (98·34% CI) in ACR50 response rates for tofacitinib + MTX compared with adalimumab + MTX was 2·2% (−6·4% to 10·9%), with the lower bound of the 98·34% CI (−6·4%) was above the pre-specified non-inferiority boundary (−13%) (figure 2B). Non-inferiority of the ACR50 response at 6 months could not be declared for tofacitinib monotherapy versus tofacitinib + MTX (difference [98·34% CI]: −7·7% [−16·3% to 0·8%]) or versus adalimumab + MTX (difference [98·34% CI]: −5·5% [−14·0% to 3·0%]); superiority could not be claimed for any comparison between the treatment arms. ACR50 response was maintained in all treatment groups through Month 12 (tofacitinib monotherapy: 39·3%; tofacitinib + MTX: 47·6%; adalimumab + MTX: 45·9%) (figure 2A). ACR20 and ACR70 response rates in each treatment arm showed similar trends to those observed for ACR50, and were maintained over 12 months (figures 2C and 2D). Over 12 months, ACR20/50/70 response rates were higher in both combination treatment arms compared with the tofacitinib monotherapy arm, and were similar between both combination treatment arms (figure 2A, 2C and 2D; table 2). A sensitivity analysis, assessing non-inferiority of the primary endpoint in the per protocol set, provided similar observations to the main analysis. The per protocol ACR50 response rates for tofacitinib monotherapy, tofacitinib + MTX, and adalimumab + MTX were 41·1%, 50·9%, and 47·3%, respectively. The difference (98·34% CI) in per protocol ACR50 response rates for tofacitinib + MTX compared with adalimumab + MTX was 3.7% (−5·7% to 13·1%), with the lower bound above the non-inferiority boundary. Per protocol comparisons for tofacitinib monotherapy versus tofacitinib + MTX (−9·8% [−19·1% to −0·5%]) or versus adalimumab + MTX (−6·2% [−15·3% to 3·0%]) could not be declared non-inferior.

Multiple secondary efficacy endpoints supported the results from the primary analyses results; in general, responses were similar between combination arms, which were higher than in the tofacitinib monotherapy arm. The proportion of patients achieving LDA at 6 months, as indicated by SDAI (≤11), was comparable between combination therapy groups (tofacitinib + MTX: 49·7%; adalimumab + MTX: 47·2%), which were higher than in the tofacitinib monotherapy group (43·5%); these were maintained at 12 months in each treatment arm (table 2). The proportions of patients achieving LDA at 6 and 12 months in all treatment arms, as indicated by CDAI, DAS28-4(ESR), and DAS28-4(CRP), were consistent with those seen when assessing LDA as indicated by SDAI.

The proportion of patients achieving remission at 6 months, as assessed by SDAI (≤3·3), was comparable between combination therapy groups (tofacitinib + MTX: 13·3%; adalimumab + MTX: 13·0%), which were higher than in the tofacitinib monotherapy group (9·9%); these were maintained at 12 months in each treatment arm (table 2). The proportions of patients achieving remission at 6 and 12 months in all treatment arms, as indicated by CDAI, DAS28-4(ESR), DAS28-4(CRP), and ACR-EULAR Boolean remission criteria, were consistent with those seen when assessing remission as indicated by SDAI. The proportion of patients achieving a HAQ-DI response (i.e., improvement from baseline greater than 0·22) at 6 months was comparable between treatment arms (tofacitinib monotherapy: 66·2%; tofacitinib + MTX: 70.2%; adalimumab + MTX: 67.4%); these response rates were broadly maintained at 12 months in each treatment arm (table 2).

The absolute LSM changes from baseline in SDAI, CDAI, DAS28-ESR, and DAS28-4(CRP) at Months 6 and 12, although clinically relevant in all groups, were significantly greater in patients receiving tofacitinib + MTX or adalimumab + MTX than in those receiving tofacitinib monotherapy (figure 3A, 3B, 3C, 3D). There was no appreciable difference between the treatment groups in the LSM changes from baseline in HAQ-DI, either at Month 6 or 12 (figure 3E). For all outcomes and for all study treatment arms, the LSM changes from baseline observed at Month 6 were maintained through Month 12.

### Safety

A summary of treatment emergent AEs is provided in table 3. Overall, 7·5% of patients discontinued treatment due to AEs; rates were similar between treatment arms. Although more patients developed an SAE in either tofacitinib group, discontinuations due to AEs were higher in the adalimumab + MTX group (9·3%) than in the tofacitinib monotherapy group (6·0%) or the tofacitinib + MTX group (6·9%) (table 3). In this limited sample of patients monitored over one year, no new or unexpected safety issues were observed in any treatment arm. A full list of AEs responsible for discontinuation is provided as supplementary material. Most AEs were mild-to-moderate, and the most common (occurring in >3·5% of patients overall) investigator-reported AEs occurring overall across all treatment arms were upper respiratory tract infections (6·5%, 9·8%, and 7·5% of patients in the tofacitinib monotherapy, tofacitinib + MTX, and adalimumab + MTX groups, respectively), alanine aminotransferase (ALT) elevation (2.1%, 6.1% and 6.7%, respectively), nasopharyngitis (5·7%, 4·3%, and 4·7%, respectively), urinary tract infections (2·9%, 4·0%, and 4·1%, respectively), and nausea (2·9%, 3·5%, and 4·1%, respectively). Herpes zoster was documented in 18 patients (1·6%) overall; 4 (1·0%), 8 (2·1%), and 6 (1·6%) in the tofacitinib monotherapy, tofacitinib + MTX, and adalimumab + MTX groups, respectively. Of the 216 patients who received herpes zoster vaccination, three patients (1·4%) developed mild cases of herpes zoster. Of the 930 patients who did not receive vaccination, fifteen patients (1·6%) developed herpes zoster. Four multidermatomal cases were reported (two in the tofacitinib monotherapy group and one each in the tofacitinib + MTX, and adalimumab + MTX groups). There was one serious varicella zoster event in the tofacitinib monotherapy group and one serious herpes zoster event in each of the tofacitinib + MTX group and adalimumab + MTX groups. Two cases of tuberculosis were seen, both in the tofacitinib + MTX group. One white female patient from Mexico aged 32 years (with a negative QuantiFERON-TB Gold ® test at screening) experienced headaches and nausea on Day 117, after which the study drug was permanently withdrawn. A lumber puncture on Day 122 indicated probable bacterial infection, and meningitis tuberculosis was confirmed by adenosine deaminase test. The patient was hospitalised from Day 122 until Day 144, and went on to recover. Another white female from Mexico aged 45 years, with a history of diabetes mellitus and hypertension and receiving isoniazid therapy after a positive QuantiFERON-TB Gold ® test at screening, developed probable pulmonary tuberculosis on Day 233, and the study drug was permanently withdrawn on Day 240. Sputum smear microscopy and culture were negative; anti-tuberculosis therapy was initiated based on the judgement of an infectious disease specialist and on radiographic evidence of alveolar infiltrates, and the patient went on to recover. One patient in the tofacitinib monotherapy arm (0·3%) and one patient in the adalimumab + MTX arm (0·3%) experienced probable drug-induced liver injury as determined by adjudication; it was not clear whether this was due to other concomitant therapy or study medication. No gastrointestinal perforations occurred in any treatment arm.

Increases from baseline in laboratory parameters, including total cholesterol, low-and high-density lipoprotein-cholesterol, serum creatinine, haemoglobin, ALT, aspartate aminotransferase (AST), and bilirubin, and decreases from baseline in absolute neutrophil counts, were observed in all treatment arms. An increase in absolute lymphocyte count was seen in the adalimumab + MTX arm, with no appreciable difference in the tofacitinib arms. Liver function observations are shown in Table 4; the incidence of any elevation of LFT was lower in the tofacitinib monotherapy group than in the combination arms.

Two patients died during the study, both in the tofacitinib monotherapy group. In Chile, a white female aged 71 years completed the study on Day 337 and was admitted to an emergency unit with fever and signs of urosepsis on Day 363, culminating in her death on Day 368, despite antibiotic therapy. No urinary culture was available to confirm this diagnosis. In Mexico, a mixed-race female aged 48 years developed symptoms of an upper respiratory tract infection on Day 59, which subsequently deteriorated and the patient was admitted to hospital on Day 69. Viral tests confirmed H1N1 influenza and the patient died from septic shock and cardiopulmonary arrest on Day 71; an autopsy confirmed H1N1 influenza A.

# Discussion

This was the first prospective, blinded head-to-head controlled trial comparing tofacitinib monotherapy versus tofacitinib plus MTX, or comparing tofacitinib as monotherapy or combination therapy versus any TNFi therapy in patients with active RA and an IR to MTX. The trial evaluated clinical and functional measures of efficacy and safety. The primary endpoint, non-inferiority of achieving an ACR50 response at 6 months, was met for tofacitinib 5 mg BID + MTX compared with adalimumab + MTX, with both achieving clinically meaningful responses. This observation of comparable efficacy in the tofacitinib + MTX and adalimumab + MTX groups was not surprising considering previous studies. In ORAL Standard, a Phase 3 randomised controlled trial, ACR20 response rates at 6 months (the primary endpoint) were similar in patients receiving tofacitinib + MTX (52%) or adalimumab + MTX (47%) for the treatment of RA; the ACR50 response was higher with tofacitinib plus MTX (37%) compared to adalimumab plus MTX (28%) but with overlapping CIs.9 The present analysis suggests that adding tofacitinib 5 mg BID to MTX is as effective as adding adalimumab, a TNFi, to MTX.

Recently, it has been shown that adding another JAK inhibitor, baricitinib, to MTX is statistically superior to adding adalimumab in a similar patient population. In a head-to-head trial comparing adalimumab in combination with MTX and baricitinib in combination with MTX (RA-BEAM), baricitinib plus MTX was found to be superior in terms of ACR20 response and change from baseline in DAS28(CRP) at week 12.23 In this trial, however, baricitinib monotherapy was not tested. Of additional note, the primary endpoint used in RA-BEAM was ACR20, compared with the more conservative use of ACR50 in ORAL Strategy.

In the RA-BEGIN Phase 3 trial, baricitinib 4 mg once daily (QD) monotherapy was found to be similar to baricitinib 4 mg QD in combination with MTX with respect to clinical and functional outcomes in an MTX-naïve population.24 Of note, radiographic progression was significantly attenuated in the baricitinib combination group only. As the population studied in RA-BEGIN was MTX-naïve (in contrast to the patients included in ORAL Strategy), it is currently unclear whether baricitinib monotherapy is non-inferior to baricitinib in combination with MTX in an MTX inadequate response (MTX-IR) population. In addition, neither RA-BEAM nor RA-BEGIN compared baricitinib monotherapy with adalimumab in combination with MTX. Thus, it is unknown whether baricitinib monotherapy is non-inferior to adalimumab plus MTX. Taking these studies collectively (ORAL Standard, ORAL Strategy, RA-BEGIN, and RA-BEAM) provides further support for the therapeutic potential of JAK inhibition for the treatment of RA. Inferences on the differential efficacy of baricitinib and tofacitinib, however, cannot be made in the absence of a head-to-head comparison of the two therapies.

This is the first trial directly comparing tofacitinib monotherapy with tofacitinib in combination with MTX. Non-inferiority could not be demonstrated for tofacitinib monotherapy compared with either combination arm. In this study, however, tofacitinib monotherapy demonstrated ACR20/50/70 responses and improvements in composite measures of disease activity and HAQ-DI similar to those previously reported in the Phase 3 tofacitinib monotherapy placebo-controlled trials.5 Of interest, across the tofacitinib Phase 3 trial program, ACR response rates were higher in trials of tofacitinib monotherapy than in trials of tofacitinib in combination with a csDMARD; this was found not to be true in ORAL Strategy. This highlights the importance of comparing efficacy between two treatment strategies only in a powered head-to-head trial, rather than comparing between different source populations, even when baseline demographics appear to be similar.

 When treating a patient with active RA, it is important to not only control clinical symptoms, as measured by ACR responses and change in DAS28-4(ESR), SDAI, and CDAI, but also to improve patient function, which is reflected by patient reported outcomes such as the HAQ-DI. Of note, in this trial, improvements in HAQ-DI among the three groups were comparable. Taking the clinical and functional results of this trial together, it appears that, in the population assessed, patients in general will respond better to the addition of tofacitinib 5 mg BID or adalimumab 40 mg Q2W to MTX rather than switching from MTX directly to tofacitinib 5 mg BID monotherapy. In clinical practice, a csDMARD (or combination of csDMARDs) or a bDMARD is added to MTX in a patient with an inadequate response to MTX, consistent with the most recently updated ACR and EULAR recommendations for the treatment of RA.2,3 Thus, in accordance with both sets of recommendations, patients should start treatment with a csDMARD such as MTX. If the patient does not reach the desired treatment target with the csDMARD, or combination of csDMARDs, within a reasonable time, then a tsDMARD such as tofacitinib, or a bDMARD such as adalimumab, can be added with an equal likelihood of achieving the treatment target. The results of this trial would also support this concept; in this group of patients, higher efficacy was seen with either combination therapy arm compared with tofacitinib monotherapy. A missing piece of information is whether MTX can be withdrawn in patients treated with tofacitinib in combination with MTX who have achieved low disease activity; this question is being evaluated in an ongoing clinical trial (clinicaltrials.gov: NCT02831855).

The patients enrolled in ORAL Strategy had active disease despite MTX therapy with almost 60% also having received glucocorticoids. A majority of the patients came from countries or regions with low accessibility to bDMARDs and hence may not have received optimal therapy prior to enrolment into this trial. The population is quite similar to those of many other trials of MTX-IR patients.23,25

Owing to the active comparator trial design and the absence of a placebo group, ACR50 was selected as the primary endpoint in this study. This composite measure of disease activity has been shown to be a more valid endpoint than ACR20 in head-to-head trials comparing active treatment arms.26 The majority of previous clinical trials assessing tofacitinib have contained a placebo group and, accordingly, used an appropriate primary endpoint of ACR20 response.

Although this study was of limited duration and sample size, no new or unexpected safety issues were noted. Data from this trial will be incorporated into the combined safety data of ongoing observational studies to continue to assess the safety of tofacitinib in these patients. Overall AEs rates, including rates of the most common AEs, were comparable between treatment arms; the majority of AEs were mild to moderate in severity. Rates of serious AEs (SAEs) and discontinuations due to AEs were generally similar between treatment arms. Previous studies have demonstrated that the risk of herpes zoster is increased with tofacitinib therapy.27 In the present analysis, incidence of herpes zoster was comparable between the tofacitinib monotherapy group (1·0% [4/384 patients]) and the adalimumab + MTX group (1·6% [6/386 patients]) but was somewhat higher in the tofacitinib + MTX group (2·1% [8/376 patients]). This is in line with previous findings that concomitant csDMARDS augment the risk of herpes zoster with tofacitinib.27–29 There were 216 patients who received live zoster vaccination; 3 of these patients developed mild cases of herpes zoster. There was one case of injection site erythema in the tofacitinib monotherapy group within 42 days of the vaccination. The incidence of herpes zoster was similar in the group of patients who did (1·4%) and did not (1·6%) receive prior vaccination. It is important to note that in the Shingles Prevention Study, the overall efficacy of the live zoster vaccine was determined to be 51%.30 Since vaccination was left to the discretion of the investigators, the present study did not formally evaluate the efficacy of herpes zoster vaccination. However, if one assumes that patients at high risk of herpes zoster infection may have received the vaccine more frequently than patients with lower risk then it is possible a channeling bias is present. Thus, further studies are required to assess the risk of herpes zoster infection, and the clinical benefit of herpes vaccination, in patients receiving tofacitinib.

ORAL Strategy was designed to answer clinically relevant questions faced by clinicians in routine clinical practice when confronted with a patient with RA and an IR to MTX who may have also failed other csDMARDs: to either add tofacitinib or a TNFi, such as adalimumab, to the MTX regimen, or to switch MTX to tofacitinib monotherapy. The study was sufficiently powered to assess differences in the treatment arms and included clear, pre-specified endpoints. The results of ORAL Strategy suggest that it is preferable to add tofacitinib to MTX rather than switching to tofacitinib monotherapy.

Limitations of this study include the fact that, although TNFi therapies share a common mechanism of action, the degree to which the observations among patients receiving adalimumab + MTX in the present study are generalisable to other TNFi therapies, or to therapies using another mechanism of action, is unclear. Additionally, radiographic follow-up, which may have assisted clinical interpretation, was not evaluated in this trial, because all patients had active therapies which inhibit progression of joint damage12 and no major differences were to be expected during the short course of the study. The lack of a placebo arm precluded a statistical demonstration of the clinically important efficacy of tofacitinib monotherapy in the present study. It is also possible that owing to the lack of a placebo arm, an expectation of efficacy from patients and investigators alike may have been responsible for improved clinical and functional observations in all groups. However, the responses are consistent with those seen in Phase 3 trials of tofacitinib as monotherapy or in combination with a csDMARD. This study does not formally answer whether the addition of a tsDMARD or bDMARD is superior to adding combination csDMARDs, even though approximately one-third of patients met the inclusion criteria of active disease in spite of previous treatment with combination csDMARDs. Finally, although nominal p values for secondary endpoints were reported for reference, they must be interpreted with caution as they were not controlled for multiple comparisons.

In conclusion, tofacitinib 5 mg BID with MTX demonstrated efficacy and safety comparable to adalimumab with MTX in patients with RA who had an IR to MTX therapy. Tofacitinib monotherapy did not achieve statistical non-inferiority to either combination regimen. These results suggest that in patients with an inadequate response to MTX, the addition of tofacitinib or adalimumab is equally efficacious and more likely to be effective than switching to tofacitinib monotherapy.

# Author contributions

All authors had full access to all data and all were involved in the analysis and interpretation of data and in the writing of the report. The lead author had final responsibility for the decision to submit for publication.

# Declaration of interests

R Fleischmann has received grants and/or research support from, and has acted as a consultant for, AbbVie, Amgen, Bristol‑Myers Squibb, Celgene, Glaxo, Eli Lilly, Janssen, Novartis, Pfizer Inc, Sanofi-Genzyme, and UCB. E Mysler has received research grants, consultancy, and speaker’s fees from AbbVie, Bristol‑Myers Squibb, Eli Lilly, Janssen, Medimmune, Pfizer Inc, and Roche. S Hall has acted as a consultant for AbbVie, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, and UCB Pharma. RJ Moots has received research grant support or speaking fees from, and/or has acted as a consultant for, AKL, Biogen, BMS, Chugai, Genzyme, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sanofi, and UCB Pharma.AJ Kivitz has received research grants, consultancy fees, or speaker fees from AbbVie, Amgen, BMS, Genentech, and Pfizer Inc. Z Luo, R DeMasi, K Soma, R Zhang, L Takiya, S Tatulych, C Mojcik, S Krishnaswami, and S Menon are all employees and shareholders of Pfizer Inc. JS Smolen has received consultancies, speaking fees, and honoraria from AbbVie, Amgen, AstraZeneca, Astro, Celgene, Celtrion, Glaxo, ILTOO, Janssen, Lilly, MedImmune, MSD, Novartis-Sandoz, Pfizer Inc, Roche, Samsung, Sanofi, and UCB; and has received institutional grants from AbbVie, Janssen, Lilly, MSD, Pfizer Inc, and Roche.

Acknowledgements

This study was sponsored by Pfizer Inc. Medical writing support, under direction from the authors, was provided by Martin Bell, PhD, of Complete Medical Communications, and was funded by Pfizer Inc.

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# **Figure 1: Patient disposition**



AE=adverse event. BID=twice daily. MTX=methotrexate. Q2W=every 2 weeks.

\*Urosepsis (n=1); atypical pneumonia and respiratory distress syndrome associated with influenza A (n=1).

# Table 1: Patient demographics and baseline disease characteristics (FAS)

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Tofacitinib monotherapy (N=384)** | **Tofacitinib + MTX (N=376)** | **Adalimumab + MTX (N=386)** |
| Gender, female, n (%)  | 319 (83·1) | 311 (82·7) | 320 (82·9) |
| Age (years), mean (SD)  | 49·7 (12·2) | 50·0 (13·4) | 50·7 (13·4) |
| Race, n (%)  |  |  |  |
| White  | 296 (77·1) | 286 (76·1) | 293 (75·9) |
| Black  | 11 (2·9) | 19 (5·1) | 18 (4·7) |
| Asian  | 41 (10·7) | 38 (10·1) | 40 (10·4) |
| Other  | 36 (9·4) | 33 (8·8) | 35 (9·1) |
| Geographic region, n (%) |  |  |  |
| North AmericaCanada, United States | 62 (16·1%) | 71 (18·9%) | 73 (18·9%) |
| Central and South AmericaArgentina, Chile, Mexico, Peru | 93 (24·2%) | 91 (24·2%) | 92 (23·8%) |
| Eastern Europe, Middle East and AfricaBosnia and Herzegovina, Bulgaria, Czech Republic, Estonia, Israel, Latvia, Lithuania, Poland, Romania, Russia, South Africa | 170 (44·3%) | 159 (42·3%) | 164 (42·5%) |
| Western Europe and TurkeySpain, Turkey, United Kingdom | 13 (3·4%) | 15 (4·0%) | 14 (3·6%) |
| Asia and Pacific regionAustralia, Korea, Philippines, Taiwan, Thailand | 46 (12·0%) | 40 (10·6%) | 43 (11·1%) |
| Duration of disease (years), median (range)  | 6·1 (0·2–41·6) | 5·4 (0·0–43·5) | 6·0 (0·3–42·8) |
| Prior medication use, n (%) |  |  |  |
| csDMARD (excluding MTX) | 122 (31·8) | 115 (30·6) | 142 (36·8) |
| bDMARD (excluding TNFi) | 17 (4·4) | 14 (3·7) | 20 (5·2) |
| TNFi  | 28 (7·3) | 16 (4·3) | 19 (4·9) |
| Background weekly MTX dose (mg), mean (SD) | 0 | 16·7 (3·7) | 16·4 (3·7) |
| Corticosteroid use at baseline, n (%) | 223 (58·1) | 214 (56·9) | 218 (56·5) |
| Daily corticosteroid dose at baseline (mg), mean (SD) | 7·3 (13·3) | 6·5 (2·5) | 6·5 (2·6) |
| Tender joint count (28), mean (SD)  | 15·4 (6·5) | 15·6 (6·5) | 15·2 (6·7) |
| Swollen joint count (28), mean (SD)  | 11·2 (5·6) | 11·8 (5·7) | 11·0 (5·4) |
| Patient Global Assessment, mean (SD)  | 60·1 (21·4) | 61·7 (22·0) | 60·2 (23·5) |
| Physician Global Assessment, mean (SD)  | 59·7 (17·7) | 60·7 (18·0) | 60·3 (19·6) |
| Pain, mean (SD)  | 61·2 (21·7) | 60·7 (22·4) | 60·6 (22·6) |
| DAS28-4(ESR), mean (SD) | 6·5 (0·9) | 6·6 (0·9) | 6·5 (1·0) |
| DAS28-4(CRP), mean (SD) | 5·7 (0·9) | 5·8 (0·9) | 5·7 (1·0) |
| SDAI, mean (SD) | 40·2 (13·0) | 41·6 (13·2) | 39·8 (13·3) |
| CDAI, mean (SD) | 38·6 (12·6) | 39·7 (12·7) | 38·2 (12·9) |
| HAQ-DI, mean (SD)  | 1·6 (0·6) | 1·6 (0·6) | 1·6 (0·6) |
| hsCRP (mg/L), mean (SD)  | 16·6 (19·3) | 18·7 (21·9) | 16·7 (21·3) |
| Patients assessed for rheumatoid factor at screening, n (%) | 275 (71·6%) | 267 (71·0%) | 277 (71·8%) |
| Rheumatoid factor in patients assessed (IU/mL), mean (SD)  | 412·9 (601·0) | 439·3 (896·5) | 359·3 (565·9) |
| Anti-CCP-positive, n (%) | 291 (75·8%) | 282 (75·0%) | 299 (77·5%) |
| Received live herpes zoster vaccination at screening/baseline, n (%) | 69 (18·0%) | 75 (19·9%) | 72 (18·7%) |

bDMARD=biological disease-modifying antirheumatic drug. CCP=cyclic citrullinated peptide. CDAI=Clinical Disease Activity Index. csDMARD=conventional synthetic disease-modifying antirheumatic drug. DAS28-4(CRP)=Disease Activity Score in 28 joints, C-reactive protein. DAS28-4(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate. FAS=full analysis set. HAQ-DI=Health Assessment Questionnaire-Disability Index. hsCRP=high-sensitivity C-reactive protein. MTX=methotrexate. SD=standard deviation. SDAI=Simplified Disease Activity Index. TNFi=tumour necrosis factor inhibitor.

# **Figure 2**: Results from FAS for (A) ACR50 response rates over 12 months; (B) differences between treatment arms for ACR50 at 6 months; (C) ACR20 response rates over 12 months; (D) ACR70 response rates over 12 months



ACR=American College of Rheumatology. BID=twice daily. CI=confidence intervals. FAS=full analysis set. MTX=methotrexate.

\*Criteria for non-inferiority met.

# Table 2: Proportion of patients in FAS achieving ACR response, LDA, and remission as assessed by SDAI, CDAI, and DAS28-4(ESR)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Tofacitinib monotherapy (N=384)** | **Tofacitinib + MTX (N=376)** | **Adalimumab** **+ MTX (N=386)** |
| **Proportion of patients achieving ACR criteria, n (%)** |
| **ACR20** |  |  |  |
| 6 months | 249 (64·8%) | 275 (73·1%) | 274 (71·0%) |
| 12 months | 237 (61·7%) | 264 (70·2%) | 261 (67·6%) |
| **ACR50** |  |  |  |
| 6 months | 147 (38·3%) | 173 (46·0%) | 169 (43·8%) |
| 12 months | 151 (39·3%) | 179 (47·6%) | 177 (45·9%) |
| **ACR70** |  |  |  |
| 6 months | 70 (18·2%)  | 94 (25·0%) | 80 (20·7%) |
| 12 months | 81 (21·1%) | 109 (29·0%) | 100 (25·9%) |
| **Proportion of patients achieving LDA, n (%)** |
| **SDAI (≤11)** |  |  |  |
| 6 months | 167 (43·5%) | 187 (49·7%) | 182 (47·2%) |
| 12 months | 169 (44·0%) | 187 (49·7%) | 204 (52·9%) |
| **CDAI (≤10)** |  |  |  |
| 6 months | 163 (42·5%) | 183 (48·7%) | 179 (46·4%) |
| 12 months | 173 (45·1%) | 188 (50·0%) | 202 (52·3%) |
| **DAS28-4(ESR) (<3·2)** |  |  |  |
| 6 months | 79 (20·6%) | 100 (26·6%) | 106 (27·5%) |
| 12 months | 87 (22·7%) | 102 (27·1%) | 128 (33·2%) |
| **DAS28-4(CRP) (<3·2)\*** |  |  |  |
| 6 months | 159 (41·4%) | 174 (46·3%) | 181 (46·9%) |
| 12 months | 157 (40·9%) | 175 (46·5%) | 201 (52·1%) |
| **Proportion of patients achieving remission, n (%)**  |
| **SDAI (≤3·3)** |  |  |  |
| 6 months | 38 (9·9%) | 50 (13·3%) | 50 (13·0%) |
| 12 months | 53 (13·8%) | 61 (16·2%) | 62 (16·1%) |
| **CDAI (≤2·8)** |  |  |  |
| 6 months | 39 (10·2%) | 52 (13·8%) | 51 (13·2%) |
| 12 months | 54 (14·1%) | 70 (18·6%) | 65 (16·8%) |
| **DAS28-4(ESR) (<2·6)** |  |  |  |
| 6 months | 40 (10·4%) | 45 (12·0%) | 48 (12·4%) |
| 12 months | 43 (11·2%) | 55 (14·6%) | 66 (17·1%) |
| **DAS28-4(CRP) (<2·6)\*** |  |  |  |
| 6 months | 81 (21·1%) | 115 (30·6%) | 108 (28·0%) |
| 12 months | 92 (24·0) | 114 (30·3) | 136 (35·2%) |
| **ACR-EULAR Boolean criteria** |  |  |  |
| 6 months | 27 (7·0%) | 31 (8·2%) | 34 (8·8%) |
| 12 months | 37 (9·6%) | 49 (13·0%) | 47 (12·2%) |

CDAI=Clinical Disease Activity Index. DAS28-4(CRP)=Disease Activity Score in 28 joints, C-reactive protein. DAS28-4(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate. FAS=full analysis set. LDA=low disease activity. MTX=methotrexate. SDAI=Simplified Disease Activity Index. \*Remission and LDA values for DAS28-4(CRP) (<2.6 and < 3.2, respectively) have not been validated, but are commonly used in rheumatology.

# **Figure 3:** LSM change from baseline in FAS at various timepoints in: (A) SDAI; (B) CDAI; (C) DAS28-4(ESR); (D) DAS28-4(CRP); (E) HAQ-DI



CDAI=Clinical Disease Activity Index. DAS28-4(CRP)=Disease Activity Score in 28 joints, C-reactive protein. DAS28-4(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate. FAS=full analysis set. HAQ-DI=Health Assessment Questionnaire-Disability Index. LSM=least squares mean. MTX=methotrexate. SDAI=Simplified Disease Activity Index.

# **Table 3:** Summary of AEs, SAEs and discontinuations (SAS)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Tofacitinib monotherapy (N=384)** | **Tofacitinib + MTX(N=376)** | **Adalimumab + MTX(N=386)** |
| Total number of AEs, n\* | 598 | 652 | 620 |
| Patients with AEs, n (%) | 226 (58·9%) | 231 (61·4%) | 253 (65·5%) |
| Patients with treatment-related AEs, n (%) | 101 (26·3%) | 111 (29·5%) | 133 (34·5%) |
| Patients with SAEs, n (%) | 35 (9·1%) | 27 (7·2%) | 24 (6·2%) |
| Patients discontinuing due to AEs, n (%) | 23 (6·0%) | 26 (6·9%) | 36 (9·3%) |
| Patients with severe AEs, n (%) (defined by the investigator) | 24 (6·3%) | 17 (4·5%) | 23 (6·0%) |
| Deaths† | 2 (0·5%) | 0 | 0 |
| **AEs of special interest** |
| Serious infections, n (%) | 6 (1·6%) | 10 (2·7%) | 6 (1·6%) |
| Herpes zoster (serious and non-serious), n (%) | 4 (1·0%) | 8 (2·1%) | 6 (1·6%) |
| Herpes zoster (serious and non-serious) in patients who were vaccinated, n/N (%) | 1/69 (1·4%) | 2/75 (2·6%) | 0/72 (0·0%) |
| Opportunistic infections (excluding tuberculosis), n (%) | 2 (0·5%) | 1 (0·3%) | 2 (0·5%) |
| Tuberculosis, n (%) | 0 | 2 (0·5%) | 0 |
| Major adverse cardiovascular events (non-fatal), n (%) | 0 | 0 | 2 (0·5%) |
| Malignancy (excluding NMSC), n (%) | 1 (0·3%) | 0 | 0 |
| NMSC, n (%) | 2 (0·5%) | 0 | 1 (0·3%) |

AE=adverse event. MTX=methotrexate. NMSC=non-melanoma skin cancer. SAE=serious AE. SAS=safety analysis set.

MACE: non-fatal myocardial infarction, fatal cardiovascular event, non-fatal cerebrovascular accident.

SAE: any medical event that results in death, is life-threatening, requires hospitalisation, causes substantial disability/incapacity, or results in a congenital anomaly/birth defect.

Severe AE: any AE that interferes with the patient’s usual function, as deemed by the investigator on the case report form.

\*Patients could have experienced more than one AE.

†Urosepsis (n=1); atypical pneumonia and respiratory distress syndrome associated with influenza A (n=1).

# Table 4. Liver function tests as multiples of upper limit of normal

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Tofacitinib monotherapy (N=384)** | **Tofacitinib + MTX(N=376)** | **Adalimumab+ MTX(N=386)** |
| **Alanine aminotransferase, n (%)** |
| ≥1 x ULN  | 110 (28·9%) | 164 (43·6%) | 182 (47·3%) |
| ≥2 x ULN  | 17 (4·5%) | 53 (14·1%) | 62 (16·1%) |
| ≥3 x ULN  | 7 (1·8%) | 29 (7·7%) | 27 (7·0%) |
| **Aspartate aminotransferase, n (%)** |
| ≥1 x ULN  | 85 (22·4%) | 129 (34·3%) | 143 (37·1%) |
| ≥2 x ULN  | 11 (2·9%) | 33 (8·8%) | 38 (9·9%) |
| ≥3 x ULN  | 3 (<1·0%) | 16 (4·3%) | 15 (3·9%) |
| **Total bilirubin, n (%)** |
| ≥1 x ULN  | 6 (1·6%) | 15 (4·0%) | 15 (3·9%) |
| ≥2 x ULN  | 1 (<1·0%) | 0 | 0 |
| ≥3 x ULN  | 1 (<1·0%) | 0 | 0 |

MTX=methotrexate. ULN=upper limit of normal.

# Supplementary Materials

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The Principal Investigators at each of the participating study sites in ORAL Strategy are listed below.

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**Section 2. Complete patient selection criteria**

Patients who were enrolled into ORAL Strategy had to meet the following inclusion criteria:

* Evidence of personally signed and dated informed consent form from the patient or legally acceptable representative
* Aged ≥18 years old
* For administration of the zoster vaccine:
	+ The zoster vaccine should be administered in eligible patients, in eligible sites/countries if deemed appropriate by the investigator
	+ Only patients aged ≥50 years old will be administered the zoster vaccine.
* ≥4 tender/painful joints on motion and ≥4 swollen joints (28 joint count) at Screening and Baseline visits
* Screening C-reactive protein (CRP) >3 mg/L in the central laboratory
* Moderate to severe rheumatoid arthritis inadequate controlled with methotrexate
* A score of 6 or greater on the 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis
* Met Class I, II, or III of the ACR 1991 Revised Criteria for Global Functional Status in RA where usual self-care activities including dressing, feeding, bathing, grooming, and toileting; avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific:
	+ Class I – Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
	+ Class II – Able to perform usual self-care and vocational activities, but limited in avocational activities
	+ Class III – Able to perform usual self-care activities, but limited in vocational and avocational activities.
* Had been receiving a methotrexate treatment regimen continuously for ≥4 months prior to the Screening visit and had been taking a stable weekly dose of oral methotrexate with supplemental folic or folinic acid for ≥6 weeks prior to the Baseline visit. Conversion from parenteral to oral also required ‘stabilisation’ over this period of time:
	+ Methotrexate doses less than 15 mg/week were allowed only if there was documented intolerance or toxicity from higher doses
	+ Methotrexate doses higher than 25 mg/week were not permitted under any circumstances
	+ Folic acid doses had to be at least 5 mg/week; folinic acid doses had to be at least 2·5 mg/week
	+ The patient must have had an inadequate clinical response to methotrexate, defined as the presence of sufficient residual disease activity to meet the entry criteria.
* Female patients of childbearing potential had to test negative for pregnancy
* Male and female patients of childbearing potential and at risk for pregnancy had to agree to use two highly effective methods of contraception throughout the study and for ≥3 months after the last dose of assigned treatment. A patient was of childbearing potential if, in the opinion of the investigator, he/she was biologically capable of having children and was sexually active
* Female patients who were not of childbearing potential (ie, met at least one of the following criteria:
	+ Had undergone a documented hysterectomy and/or bilateral oophorectomy
	+ Had medically confirmed ovarian failure or
	+ Achieved post-menopausal status, defined as: cessation of regular menses for ≥12 consecutive months with no alternative pathological or physiological cause; and had a serum follicle-stimulating hormone (FSH) level within the laboratory’s reference range for postmenopausal females.
* Patients had to screen negative for active tuberculosis or inadequately treated tuberculosis infection (active or latent) as evidenced by the following:
	+ Negative QuantiFERON Gold®TM In-Tube test performed at screening:
		- This was required unless the patient had been adequately treated for active or latent tuberculosis or a negative QuantiFERON Gold®TM In-Tube test was previously performed and documented within the 3 months prior to screening
		- A negative tuberculin skin test (TST) was one that was <5 mm induration and could be substituted for the QuantiFERON Gold®TM In-Tube test only if the central laboratory was unable to perform the test or the test was reported as indeterminate after at least 2 successive attempts
		- QuantiFERON Gold®TM In-Tube test was strongly recommended for patients with a history of Bacille Calmette Guérin (BCG) vaccination.
	+ Chest radiograph (or chest computed tomography (CT) scan, if available) taken at screening without changes suggestive of active tuberculosis infection, unless previously performed and documented with 3 months prior to screening
	+ No history of tuberculosis infection unless one of the following was documented:
		- Patient with prior or current latent tuberculosis had no evidence of active tuberculosis and had to be taking or have completed an adequate course of therapy for latent tuberculosis in a locale where rates of primary multi-drug resistant TB infection were <5%, and a chest radiograph was negative for active disease; the chest radiograph had to be obtained at screening or, if previously performed and documented, within 3 months prior to screening
		- Patient with prior active tuberculosis had no current evidence of active disease and had completed an adequate course of therapy for active tuberculosis (a multi-drug regimen recognised by the World Health Organization) and a chest radiograph was negative for active disease; the chest radiograph had to be obtained at screening or, if previously performed and documented, within 3 months prior to screening.
* Patients had to be willing and able to comply with schedule visits, treatment plan, laboratory tests, and other study procedures.

The following exclusion criteria applied:

* Patients who were investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or patients who were Pfizer employees directly involved in the conduct of the study
* Patients who had an allergy or hypersensitivity to methotrexate, patients who had experienced a serious toxicity when administered methotrexate, or had any contraindication to treatment with methotrexate according to the local label for treatment of RA with methotrexate
* Patients who had Class III or Class IV heart failure according to the New York Heart Association (NYHA) functional classification system or any other contraindication to treatment with adalimumab
* Pregnant female patients; breastfeeding female patients; males and females of childbearing potential who were unwilling or unable to use two methods of highly effective contraception for the duration of the study and for at least 3 months after last dose of investigational product
* Patients who had infections or history of infections:
	+ Any infection requiring treatment within 2 weeks prior to the Baseline visit
	+ Any infection requiring hospitalisation, parenteral antimicrobial therapy, or as otherwise judged to be an opportunistic infection or clinically significant by the Investigator, within the past 6 months
	+ Infected joint prosthesis at any time with the prosthesis still in situ
	+ Recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex
	+ Patients were screened for human immunodeficiency virus (HIV). Patients who tested positive for HIV were excluded from the study
	+ Patients were screened for hepatitis B virus infection. Patients who had hepatitis B surface antigen (HBsAg) negative testing but who tested positive for hepatitis B core antibody (HBcAb) had to have further testing for hepatitis B surface antibody (HBsAb). If HBsAb was negative, the patient was excluded from the study
	+ Patients were screened for hepatitis C virus antibodies (HCV Ab). Patients with positive HCV Ab tests were reflex tested for hepatitis C virus ribonucleic acid (HCV RNA). Only patients with negative HCV Ab or HCV RNA were allowed to enrol in the study
	+ Patients were excluded for current active tuberculosis infection or prior active or latent tuberculosis that was inadequately treated or could not be documented.
* Patients with any current malignancy or a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ
* Patients with any uncontrolled clinically significant laboratory abnormality or any of the following laboratory abnormalities:
	+ Evidence of haematopoietic disorder or haemoglobin <9 g/dL
	+ Absolute lymphocyte count <0·75 x 109/L (<750/mm3)
	+ Absolute neutrophil count <1·2 x 109/L (<1200/mm3)
	+ Platelet count <100 x 109/L (<100,000/mm3)
	+ Alanine aminotransferase (ALT), or aspartate aminotransferase (AST) >1·5 times the upper limit of normal (× ULN)
	+ Estimated glomerular filtration rate (GFR) <40 mL/min using the Cockcroft‑Gault formula.
* Participation in other (Phase 1–4) studies involving investigational drugs within 4 weeks or 5 half-lives (whichever was longer) after discontinuation of the investigational compound before the current study began and/or during study participation
* Patients who required or had received any prohibited concomitant medication or dietary supplement including:
	+ Patients who had received live or live attenuated vaccines within 6 weeks prior to the first dose of study drug (or the zoster vaccine) or were planning to receive live or live attenuated vaccines at any time during treatment or within 6 weeks following discontinuation of study drug, except for the zoster vaccine which was administered as per the protocol
	+ Patients who had previously been treated with tofacitinib
	+ Patients who had failed any TNFi for either lack of efficacy or a TNF mechanism-related AE
	+ Patients who had previously received adalimumab therapy for any reason
	+ Patients who were being treated with biologic or non-biologic DMARDs (including antimalarials) other than methotrexate within their specified washout window at study entry
	+ Patients who were being treated with corticosteroids, other than low dose oral corticosteroids in doses equivalent to ≤10 mg prednisone per day or equivalent, for 4 weeks prior to first dose of study drug
	+ Patients who had received intraarticular, intramuscular, or intravenous corticosteroids within 4 weeks prior to first dose of study drug
	+ Patients who required concomitant treatment with medications that are potent inhibitors of cytochrome P450 3A4 (CYP3A4), both moderate inhibitors of CYP3A4 and potent inhibitors of CYP2C19, and potent CYP inducers.
* Patients with a screening 12-lead electrocardiogram that demonstrated clinically significant abnormalities requiring urgent treatment (eg, acute myocardial infarction, serious tachy- or bradyarrhythmias) or that was indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads)
* Patients who had significant trauma or surgical procedure within 1 month prior to the Baseline visit
* Patients with any rheumatic autoimmune disease, other than RA and Sjogren’s syndrome
* Patients who were classified Class IV of the ACR 1991 Revised Criteria for Global Functional Status in RA (ie, were limited in their ability to perform usual self-care, vocational, and avocational activities)
* Patients with lymphoproliferative disorders (eg, Epstein Barr Virus (EBV)-related lymphoproliferative disorder), a history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease
* Alcohol or substance abuse unless in full remission for greater than 6 months prior to first dose of study drug
* Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the Investigator, would have made the patient inappropriate for entry into this study
* Specific exclusion criteria for administration of the zoster vaccine in eligible patients:
	+ History of receiving any zoster-containing vaccine
	+ History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine
	+ Patients who were <140 lbs or <63 kg, receiving more than 20 mg/week of methotrexate were not eligible for the administration of the zoster vaccine
	+ Patients with clinical or laboratory evidence of an unspecified cellular immunodeficiency
	+ History of any severe adverse reaction associated with a vaccine
	+ History of Guillain-Barre Syndrome.

**Section 3. Summary of discontinuations due to AEs**

|  |
| --- |
| **Tofacitinib monotherapy: n=23** |
| Cellulitis (n=2) |
| Rheumatoid arthritis (n=2) |
| Abdominal distension, Abdominal pain, Nausea, Malaise (n=1) |
| Asthma (n=1) |
| Blood creatine phosphokinase increased (n=1) |
| Breast cancer (n=1) |
| Condition aggravated (n=1) |
| Drug-induced liver injury (n=1) |
| Human chorionic gonadotropin positive (n=1) |
| Lung neoplasm (n=1) |
| Osteoarthritis (n=1) |
| Osteonecrosis (n=1) |
| Pericarditis (n=1) |
| Polyneuropathy (n=1) |
| Pregnancy (n=1) |
| Retinal haemorrhage (n=1) |
| Sexual dysfunction (n=1) |
| Skin ulcer (n=1) |
| Tonsillitis (n=1) |
| Unintended pregnancy (n=1) |
| Varicella zoster virus infection (n=1) |
| **Tofacitinib + MTX: n=26** |
| Liver function test abnormal (n=2) |
| Abdominal wall haematoma (n=1) |
| Abortion spontaneous, Pregnancy (n=1) |
| Anaemia (n=1) |
| Anogenital warts (n=1) |
| Bronchitis (n=1) |
| Cellulitis with abscess (n=1) |
| Depression (n=1) |
| Headache (n=1) |
| Hepatic enzyme increased (n=1) |
| Herpes zoster (n=1) |
| Hypoxia (n=1) |
| Lobular breast carcinoma in situ (n=1) |
| Meningioma (n=1) |
| Meningitis bacterial (n=1) |
| Meningitis tuberculosis (n=1) |
| Pancytopenia (n=1) |
| Platelet count decreased (n=1) |
| Pneumonia (n=1) |
| Pulmonary tuberculosis (n=1) |
| Pyelonephritis (n=1) |
| Skin reaction (n=1) |
| Tracheobronchitis (n=1) |
| Urinary tract infection (n=1) |
| Urticaria (n=1) |
| **Adalimumab + MTX: n=36** |
| Herpes zoster (n=3) |
| Alanine aminotransferase increased (n=2) |
| Hepatic enzyme increased (n=2) |
| Neutropenia (n=2) |
| Pyrexia (n=2) |
| Arthralgia (n=1) |
| Arthritis (n=1) |
| Bipolar disorder (n=1) |
| Bronchitis (n=1) |
| Cholecystitis chronic (n=1) |
| Clostridial sepsis (n=1) |
| Depression (n=1) |
| Dyspepsia (n=1) |
| Dyspnoea (n=1) |
| Folliculitis (n=1) |
| Hepatitis (n=1) |
| Herpes simplex (n=1) |
| Human chorionic gonadotropin increased (n=1) |
| Injection site pruritus, Injection site rash (n=1) |
| Limb injury (n=1) |
| Liver injury (n=1) |
| Lupus-like syndrome (n=1) |
| Paraesthesia (n=1) |
| Peritonitis (n=1) |
| Pneumonia (n=1) |
| Pneumonitis (n=1) |
| Rash pruritic (n=1) |
| Rheumatoid arthritis (n=1) |
| Sinusitis (n=1) |
| Tendon rupture (n=1) |

**Section 4. Summary of all protocol-specified endpoints**

|  |  |
| --- | --- |
| **ENDPOINT DESCRIPTION** | **STATUS**  |
| **Primary efficacy endpoint** |  |
| * ACR50 response rates at Month 6
 | Reported |
| **Secondary efficacy endpoint** |  |
| * Change from Baseline in DAS28-4 (CRP) and DAS28-4 (ESR) at Month 6
 | Reported |
| * Rate of remission at Month 6, as assessed by: ACR-EULAR Boolean remission criteria;4 SDAI ≤3.3; CDAI ≤2.8; DAS28-4 (ESR) <2.6 and DAS28-4 (CRP) <2.6
 | Reported |
| * Rate of LDA at Month 6, as assessed by: SDAI ≤11; CDAI ≤10; DAS28-4 (ESR) <3.2 and DAS28-4 (CRP) <3.2.
 | Reported |
| * ACR20 and ACR70 response rates at Month 6
 | Reported |
| * Change from Baseline in HAQ-DI at Month 6
 | Reported |
| * Percentage HAQ-DI responders (decrease of at least 0.22) at Month 6
 | Reported |
| * Change from Baseline in the SF-36 8 domain scores and 2 component scores at Month 6
 | Not reported due to space limitations |
| * Change from Baseline in WPAI at Month 6.
 | Not reported due to space limitations |
| * Change from Baseline in the EuroQol EQ-5D at Month 6
 | Not reported due to space limitations |
| * Change from Baseline in the FACIT-Fatigue scale at Month 6
 | Not reported due to space limitations |
| **Other efficacy endpoints** |  |
| * Primary and secondary efficacy endpoints at all other post-Baseline scheduled visits.
 | Reported |
| **Safety endpoints** |  |
| * All adverse events (AEs), including serious AEs (SAEs)
 | Reported |
| * Clinically significant abnormal laboratory parameters
 | Reported |
| * Assessment of the rate of adverse reactions, injection site reactions and development of zoster-like lesions after vaccination
 | Reported |
| * Assessment of the rate of clinical herpes zoster events by study treatment group after initiation of study treatments
 | Reported |