Effects of the oral Janus kinase inhibitor tofacitinib on patient-reported outcomes in patients with active rheumatoid arthritis: results of two Phase 2 randomised controlled trials

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Abstract

Objective

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we investigated the effects of tofacitinib on patient-reported outcomes (PRO) in patients with active RA.

Methods

Two, 6-month, double-blind, placebo-controlled Phase 2b studies were performed. The combination study evaluated patients with inadequate response to methotrexate who received tofacitinib 1–15 mg twice daily (BID), 20 mg once daily or placebo, on background methotrexate. In the monotherapy study, patients with inadequate response to disease-modifying anti-rheumatic drugs received tofacitinib 1–15 mg BID, adalimumab 40 mg once every other week or placebo. PROs measured were: Patient's Assessment of Arthritis Pain (PAAP), Patient's Assessment of Disease Activity, HAQ-DI, FACIT-F and SF-36.

Results

In the combination study (n=507), significant improvements ($p<0.05$) versus placebo were observed at Week 12 in PAAP (visual analogue scale) and HAQ-DI for all tofacitinib groups. In the monotherapy study (n=384), significant improvements in PAAP were observed at Week 12 for tofacitinib 5, 10 and 15 mg BID, and in HAQ-DI for tofacitinib 3, 5, 10 and 15 mg BID. Significant improvements versus placebo were seen at Week 2 in PAAP (both studies) and HAQ-DI (monotherapy study) with tofacitinib, and were maintained throughout each study. In both studies, improvements in several domains of the SF-36 in the tofacitinib groups were observed at Weeks 12 and 24.

Conclusion

In patients with active RA, tofacitinib, either in combination with methotrexate or as monotherapy, demonstrated rapid and sustained improvement in pain, physical functioning and health-related quality of life.

Key words

tofacitinib, Janus kinases, rheumatoid arthritis, pain, quality of life

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Competing interests:
R. Fleischmann and M. Genovese have received Pfizer study grants and have been paid as consultants to Pfizer Inc.;
J. Gomez-Reino, J. Kremer, E.B. Lee and V. Strand have been paid as consultants to Pfizer Inc.;
M. Cutolo has received a Pfizer study grant;
S. Cohen is a shareholder of Pfizer Inc.
D. Gruben, K. Kanik, S. Krishnaswami, G. Wallenstein, B. Wilkinson and S.H. Zwillich are employees and shareholders of Pfizer Inc.

Introduction

Pain, fatigue and poor physical functioning associated with rheumatoid arthritis (RA) have a substantial negative impact on patients' health-related quality of life (HRQoL). Fatigue is a widespread problem for RA patients which is associated with a high comorbidity burden, disease activity and disability (1). Physical functioning is also particularly affected in RA, with a disease burden that is well above that of age- and gender-matched norms for the US general population (2, 3). In addition, patients with RA frequently experience sleep disturbance and difficulty performing activities of daily living, including social and occupational roles (4, 5).

Patient-reported outcomes (PROs), in conjunction with other clinical data such as American College of Rheumatology (ACR) 20 ACR50, ACR70 responses and radiographic responses, can provide valuable information on treatment efficacy (6). PRO measures can also detect improvements and changes that are functionally important and meaningful to patients.

Disease-modifying anti-rheumatic drugs (DMARDs) are the cornerstone of modern therapy for RA and biologic agents can provide significant additional improvement in physical functioning and HRQoL (7-9), especially if administered early (3, 10). Although a combination of DMARDs with biologic agents is more effective than either DMARDs or biologics alone, approximately 30% of patients treated in combination do not respond to initial treatment as measured by ACR20 responses (11-13). In addition, biologics are unsuitable for some patients (14-17). Therefore, there is a clinical need for RA treatments that have a positive impact on PROs, either as monotherapy or in combination therapy.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. Intracellular pathways that include JAKs are critical to immune cell activation, pro-inflammatory cytokine production and cytokine signalling (18). Tofacitinib exhibits functional selectivity for JAK1/3 and JAK1/2 signalling over JAK2/2 signalling in a cellular setting (19). Tofacitinib subsequently modulates adaptive and innate immunity with limited effects on haematopoiesis (19, 20).

In a Phase 2a study, tofacitinib monotherapy at doses of 5, 15 and 30 mg twice daily (BID) significantly improved the clinical signs and symptoms of RA over six weeks *versus* placebo (21). Clinically meaningful improvements in pain, physical functioning, global assessment of disease activity and HRQoL were observed (22). Based on the Phase 2a data, two Phase 2b dose-ranging studies were initiated; one to assess tofacitinib combined with stable background methotrexate (MTX; the combination study), and the other to assess tofacitinib as monotherapy (the monotherapy study) (23, 24). In both of these Phase 2b studies, tofacitinib demonstrated sustained efficacy with a manageable safety profile at doses ≥3 mg BID over 24 weeks. More recently, the efficacy and safety of tofacitinib 5 and 10 mg BID has been demonstrated in randomised Phase 3 studies (25-30).

Here we report from the two Phase 2b studies the effects of tofacitinib *versus* placebo on PRO measures of pain, physical functioning, fatigue and HRQoL in patients with active RA. The primary efficacy and safety data from these studies have been presented elsewhere (23, 24).

Materials and methods

The combination study (Clinicaltrials.gov registration: NCT00413660) was conducted in 72 centres in Europe, North and South America and the United States. The monotherapy study (Clinicaltrials.gov registration: NCT00550446) was conducted in 59 centres in Asia, Europe, South America and the United States. Both studies were performed in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines, and were approved by the Institutional Review Boards/Independent Ethics Committees for each study centre. All patients provided written, informed consent.

Patients, study design and treatment

Full details of the trial design, eligibility, exclusion criteria, patient population and treatment for both studies have been

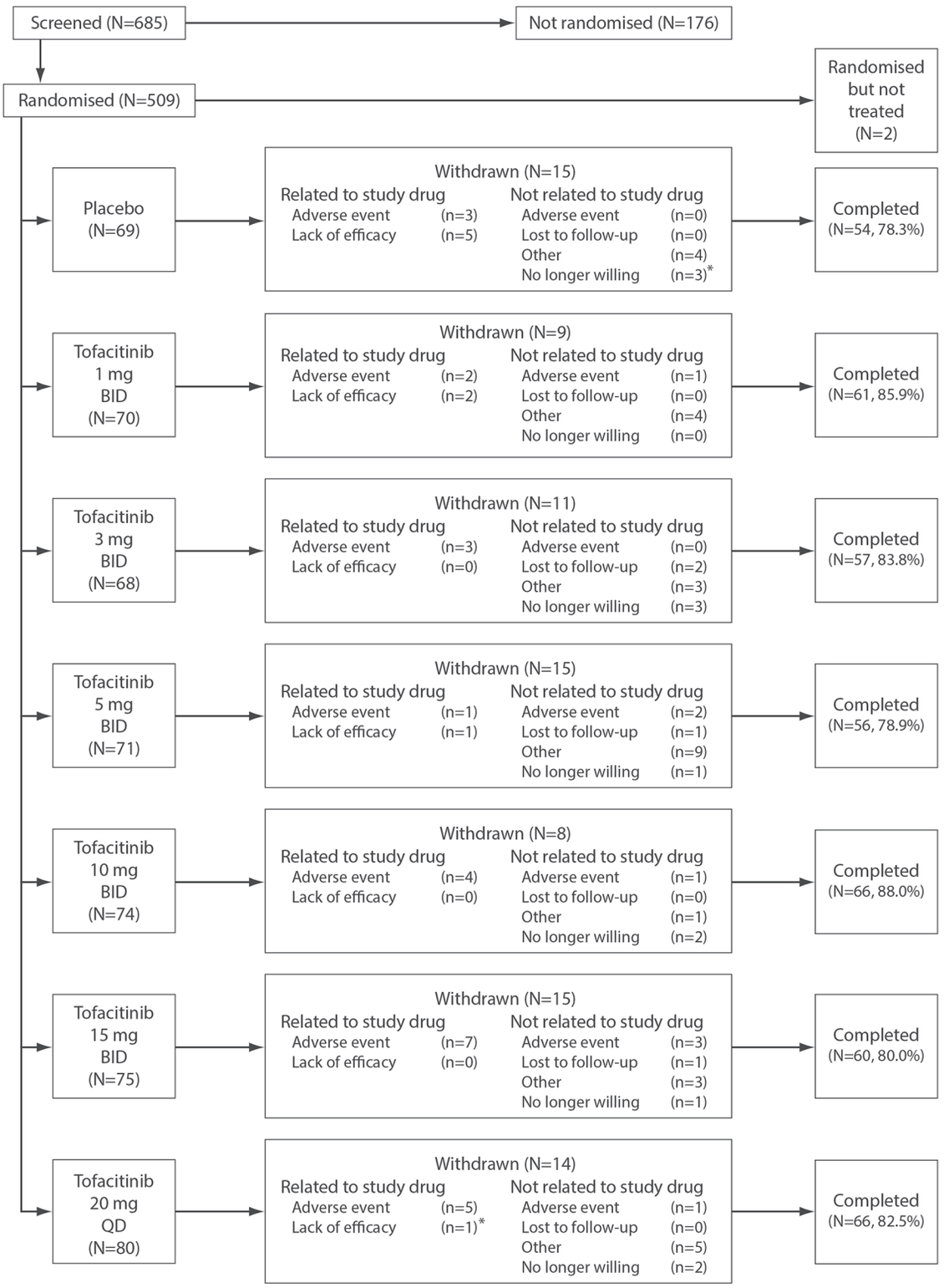

Fig. 1A. CONSORT flow diagram (combination study).
*Including 1 patient who was withdrawn after being reassigned to 5 mg BID tofacitinib. BID: twice daily; QD; once daily

described previously (23, 24). Briefly, patients had a diagnosis of RA based on the ACR 1987 revised criteria (31) and active disease defined by six or more tender or painful joints (out of 68) and six or more swollen joints (out of 66) at both screening and baseline visits, plus either C-reactive protein >7 mg/L or erythrocyte sedimentation rate above the upper limit of normal.

The combination study was a 24-week dose-ranging investigation of tofacitinib in patients with an inadequate response to MTX. Patients on stable background oral or parenteral MTX continuously

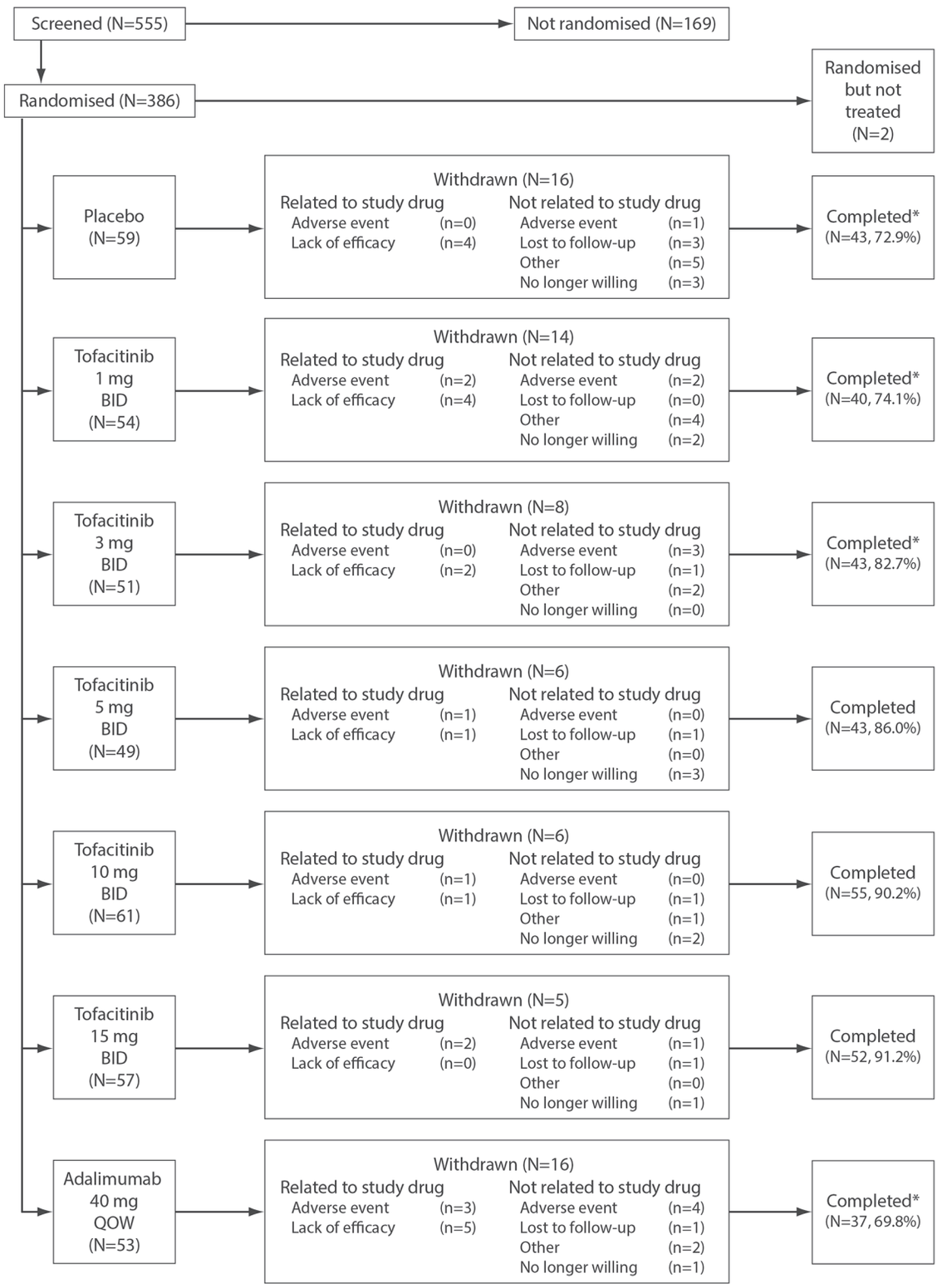

Fig. 1B. CONSORT flow diagram (monotherapy study).
*Patients completing treatment through Week 24, including reassigned patients. BID: twice daily; QOW: every other week

for ≥4 months (7.5–25 mg weekly for ≥6 weeks prior to first dose of study drug) were randomly assigned to tofacitinib 1, 3, 5, 10 or 15 mg BID, or 20 mg once daily (QD), or placebo (24).

The monotherapy study was a 24-week dose-ranging investigation of tofacitinib as monotherapy in patients who had an inadequate response to DMARDs. Patients were randomly assigned to placebo, tofacitinib 1, 3, 5, 10 or 15 mg BID, or adalimumab 40 mg once every other week (QOW) for 10 weeks (a total of six injections per patient).

In both studies, patients receiving to-

Table IA. Baseline demographics and characteristics; combination study.

	Tofacitinib dose						
	PBO (n=69)	1 mg BID (n=70)	3 mg BID (n=68)	5 mg BID (n=71)	10 mg BID (n=74)	15 mg BID (n=75)	20 mg QD (n=80)
Sex, % Female	81.2	81.4	76.5	80.3	74.3	88.0	78.8
Age in years, mean (SD)	52.9 (13.4)	52.1 (11.6)	50.8 (14.9)	51.7 (12.8)	56.0 (10.4)	54.1 (11.1)	54.2 (10.8)
Race, %							
White	84.1	87.1	79.4	88.7	86.5	86.7	90.0
Black	4.3	1.4	1.5	2.8	1.4	1.3	2.5
Asian	0	0	1.5	0	0	0	0
Other	11.6	11.4	17.6	8.5	12.2	12.0	7.5
Duration since diagnosis, years, mean (SD)	9.2 (8.7)	11.8 (9.8)	9.4 (9.7)	9.0 (8.2)	7.5 (7.5)	10.8 (10.5)	9.8 (9.3)
MTX dose, mg/week, mean (SD)	16.9 (3.7)	16.6 (3.8)	16.9 (3.0)	16.0 (3.3)	16.7 (3.8)	16.6 (3.3)	16.4 (3.7)
Number of prior failed DMARDs, mean (SD)	1.7 (1.0)	1.9 (1.2)	1.9 (1.4)	1.7 (1.1)	1.7 (1.1)	1.9 (1.3)	1.7 (1.2)
Prior failed ≥1 TNFi, %	7.2	5.7	11.8	8.5	6.8	13.3	8.8
Prior NSAID use, %	78.3	77.1	82.4	77.5	78.4	80.0	68.8
Concomitant glucocorticoids, %	44.9	61.4	60.3	57.7	56.8	64.0	61.3
Concomitant anti-malarial use, %	20.3	32.9	23.5	29.6	25.7	28.0	26.3
Rheumatoid factor positive, %	83.0	79.3	89.8	82.8	67.7	87.1	75.0
Tender joints, 68 count, mean (SD)	21.6 (13.2)	23.6 (11.6)	22.8 (10.6)	21.5 (13.0)	24.8 (12.5)	23.7 (12.7)	23.1 (12.7)
Swollen joints, 66 count, mean (SD)	15.7 (8.8)	16.5 (8.2)	15.7 (8.6)	14.1 (7.4)	14.7 (7.5)	15.3 (7.0)	15.2 (8.0)
HAQ-DI, 0–3 scale, mean (SD)	1.2 (0.7)	1.6 (0.6)	1.4 (0.8)	1.4 (0.6)	1.3 (0.6)	1.4 (0.6)	1.5 (0.6)
ESR, mm/hr, mean (SD)	37.5 (19.3)	37.7 (17.8)	38.8 (26.1)	36.7 (15.6)	42.4 (21.1)	39.0 (19.4)	41.0 (22.3)
CRP, mg/L, mean (SD)	18.9 (19.5)	16.3 (18.1)	15.8 (19.3)	18.0 (25.0)	14.4 (17.8)	17.2 (16.9)	14.7 (17.2)
DAS28-4 (ESR), mean (SD)	6.0 (0.9)	6.4 (0.8)	6.1 (1.0)	6.1 (0.8)	6.3 (0.8)	6.2 (0.9)	6.3 (1.0)
DAS28-3 (CRP), mean (SD)	5.3 (1.0)	5.5 (0.8)	5.3 (1.0)	5.1 (0.8)	5.3 (0.9)	5.4 (0.9)	5.3 (0.9)

BID: twice daily; CRP: C-reactive protein; DAS: disease activity score; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; PBO: placebo; QD: once daily; SD: standard deviation; TNFi: tumour necrosis factor inhibitor

facitinib 1 or 3 mg BID, 20 mg QD (combination study only), or placebo with <20% reduction from baseline in at least one of tender or swollen joint counts at Week 12 were classified as non-responders and reassigned to tofacitinib 5 mg BID for the remainder of the study (23, 24). In the monotherapy study all patients initially randomised to adalimumab received tofacitinib 5 mg BID after Week 12.

Study assessments

• *Patient-reported outcomes*

PROs were assessed at baseline, Weeks 2, 4, 6, 8, 10 (monotherapy study only), 12, 16, 20 and 24, except for Short-Form 36 (SF-36), which was assessed at baseline, Weeks 12 and 24 and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), which was assessed at baseline, Weeks 2, 12 and 24. The PRO study endpoints at Week 12 were: Patient's Assessment of Arthritis Pain (PAAP; visual analogue scale [VAS]); Patient's Global Assessment of Arthritis (PtGA; VAS); HAQ-DI (32); FACIT-F (33); and HRQoL as assessed by the SF-36 health survey (34).

Changes from baseline in PAAP, PtGA, HAQ-DI, FACIT-F and SF-36 were compared with published values for minimum clinically important differences (MCID). Changes considered to reflect MCID were: ≥10 points in PAAP and in PtGA; ≥0.22 points in HAQ-DI (35); and >5 points and >2.5 points in SF-36 (34) domain and component scores (0–100 scale), respectively.

Statistical analyses

Analyses are based on the full analysis set (FAS) of data, which included all patients randomised to the study who received at least one dose of study medication (tofacitinib, adalimumab or placebo) and, for endpoints expressed as change from baseline, had at least one post-baseline value. Results presented are based on observed data (no imputation) and last observation carried forward (LOCF). For LOCF, post-Week-12 data from tender and swollen joint count non-responders were treated as missing and the last observational value before Week 12 was carried forward. For analyses of observed data, post-Week-12 values of non-responders in all treatment groups were treated as missing and were not included in any further analyses.

A longitudinal, mixed-effect, repeated-measures model was employed to calculate change from baseline using LOCF imputed data. Treatment, week and treatment-by-week interaction were included as fixed effects, along with patients as a random effect. Estimates of mean and mean difference from placebo were derived from the model and contrasts with placebo were formed, along with 95% confidence intervals. Rates of patients achieving MCID for endpoints were calculated using observed data; a normal approximation to the binomial was used to assess differences from placebo, and 95% confidence intervals were calculated. Differences in rates were used to calculate number needed to treat (NNT) in instances where there was a statistical improvement from placebo in the rates of achieving MCID for a given meas-

Table 1B. Baseline demographics and characteristics; monotherapy study.

	Tofacitinib dose						
	PBO (n=59)	1 mg BID (n=54)	3 mg BID (n=51)	5 mg BID (n=49)	10 mg BID (n=61)	15 mg BID (n=57)	ADA 40 mg QOW/5 mg BID (n=53)
Sex, % female	88.1	85.2	86.3	87.8	86.9	87.7	84.9
Age in years, mean (SD)	52.5 (13.7)	55.1 (13.3)	53.4 (12.2)	53.7 (13.5)	52.4 (10.9)	53.2 (13.0)	53.5 (11.9)
Race, %							
White	72.9	81.5	74.5	73.5	72.1	80.7	81.1
Black	5.1	0	3.9	0	4.9	0	1.9
Asian	10.2	9.3	9.8	12.2	8.2	7.0	7.5
Other	11.9	9.3	11.8	14.3	14.8	12.3	9.4
Duration since diagnosis, years, mean (SD)	10.8 (9.6)	9.4 (9.5)	9.9 (8.3)	8.1 (7.9)	8.6 (8.3)	8.7 (8.2)	7.7 (8.0)
Number of prior failed DMARDs, mean (SD)	1.9 (1.4)	1.5 (1.0)	1.9 (1.4)	1.9 (1.2)	1.8 1.2)	1.9 (1.3)	1.9 (1.2)
Prior failed ≥1 TNFi, %	8.5	1.9	7.8	6.1	9.8	8.8	7.5
Prior NSAID use, %	67.8	75.9	72.5	71.4	77.0	68.4	75.5
Prior MTX use*, %	78.0	85.2	86.3	83.7	82.0	77.2	81.1
MTX dose among prior MTX use patients[¥], mg/week, mean (SD)	12.7 (4.5)	13.5 (3.1)	13.7 (4.7)	13.8 (9.2)	11.9 (4.8)	14.6 (4.3)	14.7 (4.3)
Concomitant glucocorticoids, %	57.6	61.1	51.0	55.1	54.1	56.1	54.7
Concomitant anti-malarial use, %	30.5	24.1	27.5	38.8	23.0	36.8	30.2
Rheumatoid factor positive, %	74.6	85.2	88.2	77.6	80.3	80.7	73.6
Tender joints, 68 count, mean (SD)	25.9 (12.9)	27.0 (15.4)	24.6 (11.3)	27.1 (14.6)	25.7 (13.9)	25.9 (13.4)	24.1 (13.9)
Swollen joints, 66 count, mean (SD)	16.9 (9.8)	16.7 (8.9)	15.9 (8.5)	17.4 (10.3)	16.3 (8.3)	16.9 (9.0)	14.9 (8.1)
HAQ-DI, 0–3 scale, mean (SD)	1.5 (0.7)	1.6 (0.7)	1.5 (0.6)	1.4 (0.7)	1.5 (0.7)	1.6 (0.7)	1.4 (0.6)
ESR, mm/hr, mean (SD)	46.2 (22.4)	46.5 (20.3)	41.9 (22.9)	47.4 (25.3)	43.8 (20.0)	43.1 (22.6)	44.8 (24.0)
CRP, mg/L, mean (SD)	23.5 (27.1)	21.4 (22.2)	16.2 (19.5)	24.5 (30.4)	16.7 (16.8)	21.7 (33.0)	20.1 (23.5)
DAS28-4 (ESR), mean (SD)	6.6 (1.0)	6.5 (0.9)	6.4 (1.0)	6.6 (0.9)	6.5 (0.9)	6.5 (1.0)	6.3 (1.0)
DAS28-3 (CRP), mean (SD)	5.6 (0.9)	5.5 (0.9)	5.4 (0.9)	5.6 (0.9)	5.5 (0.8)	5.5 (1.0)	5.4 (1.0)

*Three patients were receiving MTX concomitantly as of baseline: one at 15 mg/week (tofacitinib 10 mg BID); one at 15 mg/week (tofacitinib 15 mg BID); one at 20 mg/week (tofacitinib 15 mg BID). [¥]Three subjects are excluded from these summaries as associated doses were not available ADA: adalimumab; BID: twice daily; CRP: C-reactive protein; DAS: Disease Activity Score; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PBO: placebo; QOW: once every other week; SD: standard deviation; TNFi: tumour necrosis factor inhibitor.

ure (36). NNT=1/(Cr-Er), where Cr is the rate of placebo-treated patients failing to achieve MCID, and Er is the rate of patients in active treatment groups failing to achieve MCID, with NNT rounded up to the nearest integer. Mean values based on observed data are displayed for the domain and component scores of the SF-36. *P*-values reported here are not corrected for multiple comparisons. Statistical significance was determined by $p \leq 0.05$.

Results

Patient disposition has been described previously (23, 24). Briefly, 509 patients were randomised to treatment and 507 received study drug in the combination study, and 386 patients were randomised and 384 received study drug in the monotherapy study (Fig. 1A-B). In both studies the majority of patients were white, female, with a mean age across treatment groups of 51–56 years. At baseline, the mean duration of RA was 7.5–11.8 years (combination study) and 7.7–10.8 years (monotherapy study). Patients had failed a mean of 1.7–1.9 and 1.5–1.9 prior DMARDs in the combination study and monotherapy study, respectively. Mean stable MTX dose in the combination study ranged from 16.0 to 16.9 mg/week. Baseline demographic characteristics were comparable between treatment groups for both studies. Details of the patient population at baseline and patient disposition are shown in Tables 1A-B.

Patient-reported outcomes

• *Patient's Assessment of Arthritis Pain*

Mean changes from baseline in PAAP scores are shown in Figure 2A (combination study) and Figure 3A (monotherapy study). At Week 2, decreases from baseline were statistically significant compared with placebo for tofacitinib 10 and 15 mg BID and 20 mg QD in the combination study, and tofacitinib 3, 5, 10 and 15 mg BID and adalimumab in the monotherapy study. At Week 12, statistically significant improvements were achieved for all tofacitinib dose groups in the combination study and for tofacitinib 5, 10 and 15 mg BID in the monotherapy study; these improvements were sustained to Week 24 in both studies. In the monotherapy study, no statistically significant improvements were recorded in patients receiving adalimumab at Week 12 or at Week 24 (after per-protocol reassignment to tofacitinib 5 mg BID at Week 12).

In the combination study there was a statistically significant difference compared with placebo in patients achieving MCID ≥10 points for the majority (four out of six) of tofacitinib dose groups at Week 12 (Table II). In the monotherapy study, a statistically significant difference was recorded for the 10 mg BID dose group at Week 12

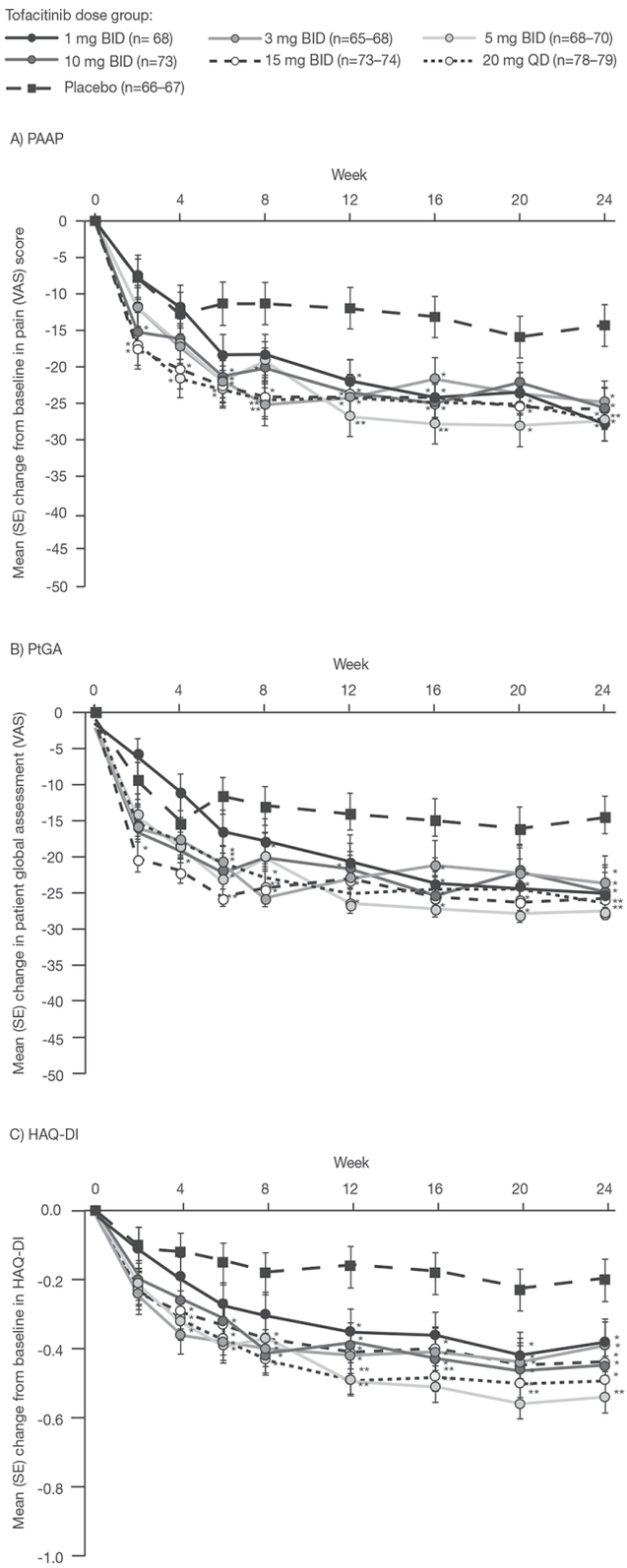

Fig. 2. Combination study: change from baseline in PAAP, PtGA and HAQ-DI. Mean change from baseline in (**A**) PAAP (VAS), (**B**) PtGA (VAS) and (**C**) HAQ-DI from baseline to Week 24 in the combination study (FAS, LOCF). *$p \leq 0.05$, **$p < 0.001$, ***$p < 0.0001$ *vs*. placebo. BID: twice daily; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; LOCF: last observation carried forward; PAAP: Patient Assessment of Arthritic Pain; PtGA: Patient's Global Assessment of Arthritis; QD: once daily; SE: standard error; VAS: visual analogue scale.

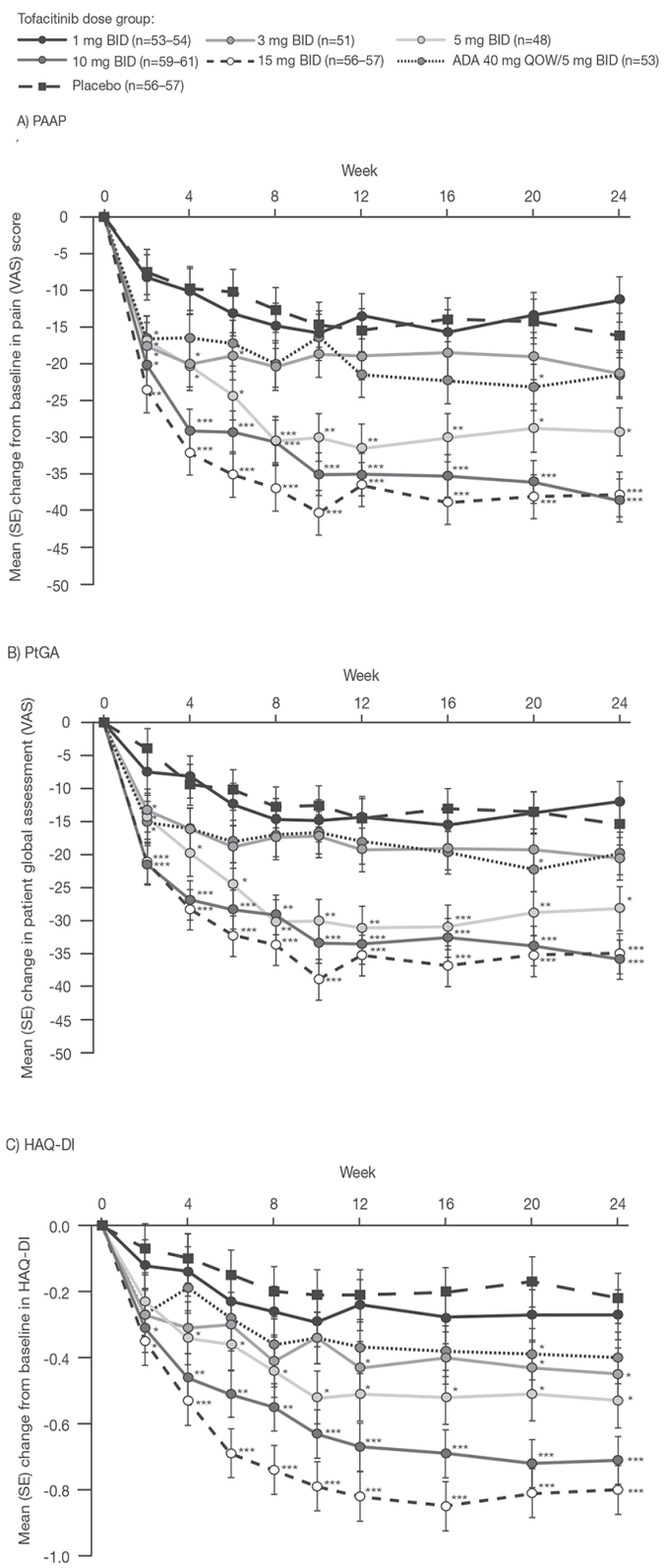

Fig. 3. Monotherapy study: change from baseline in PAAP, PtGA and HAQ-DI. Mean change from baseline in (**A**) PAAP (VAS), (**B**) PtGA (VAS) and (**C**) HAQ-DI from baseline to Week 24 in the monotherapy study (FAS, LOCF). *$p \leq 0.05$, **$p < 0.001$, ***$p < 0.0001$ *vs*. placebo. ADA: adalimumab; BID: twice daily; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; LOCF: last observation carried forward; PAAP: Patient Assessment of Arthritic Pain; PtGA: Patient's Global Assessment of Arthritis; QOW: once every other week; SE: standard error; VAS: visual analogue scale.

Table II. Percentage of patients achieving MCID compared with placebo; combination study and monotherapy study (FAS, no imputation).

Domain	Tofacitinib dose													
	Week 12							Week 24						
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	PBO	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	PBO
Combination study														
PAAP	64.1	70.2*	68.8*	66.2	71.2*	72.9*	50.8	70.0	81.0	79.5	76.0	78.0	79.2	63.9
PtGA	57.8	67.8	67.2	78.5*	69.7	73.9*	53.3	70.0	77.3	89.7*	80.4	74.0	75.5	63.9
HAQ-DI (reduction)	62.5*	62.1*	67.2*	67.7*	63.6*	69.1*	42.6	72.5	66.7	71.1	74.0	70.0	69.8	72.2
HAQ-DI (normative)	20.3	40.7	31.3	36.9	30.3	36.8	27.9	20.0¥	41.1	44.4	34.9	35.6	38.5	39.6
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	ADA 40 mg QOW/ 5 mg BID	PBO	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	ADA 40 mg QOW/ 5 mg BID	PBO
Monotherapy study														
PAAP	52.3	56.5	73.9	84.2*	75.9	71.7	60.9	50.0	69.0	77.4	90.9	80.0	81.0	70.0
PtGA	63.6	54.3	76.1	78.9*	77.8*	63.0	58.7	54.2	65.5	74.2	95.5*	80.0	66.7	75.0
HAQ-DI (reduction)	61.4	65.2	67.4*	76.8*	83.3***	58.7	46.7	75.0	69.0	61.3	83.7	88.9*	71.4	60.0
HAQ-DI (normative)	18.2	28.3	41.3*	40.4*	40.7*	26.1	19.6	15.0#	40.9	39.5	41.8	44.2	32.5	40.9

Difference from placebo: *p<0.05, **p<0.001, ***p<0.0001; ¥p<0.05 favouring placebo. PAAP: MCID ≥10 points; PtGA: MCID ≥10 points; HAQ-DI (reduction): MCID ≥0.22 points; HAQ-DI (normative): HAQ-DI <0.5; ADA: adalimumab; BID: twice daily; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; MCID: minimum clinically important difference; PAAP: Patient Assessment of Arthritic Pain; PBO: placebo; PtGA: Patient's Global Assessment of Arthritis; QD: once daily; QOW: once every other week.

Table III. NNT values based on patients achieving MCID and statistically significant improvement compared with placebo; combination study and monotherapy study (FAS, no imputation).

Domain	Tofacitinib dose											
	Week 12						Week 24					
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD
Combination study												
PAAP	n/c	6	6	n/c	5	5	n/c	n/c	n/c	n/c	n/c	n/c
PtGA	n/c	n/c	n/c	4	n/c	5	n/c	n/c	4	n/c	n/c	n/c
HAQ-DI	6	6	5	4	5	4	n/c	n/c	n/c	n/c	n/c	n/c
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	ADA 40 mg QOW/ 5 mg BID	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	ADA 40 mg QOW/ 5 mg BID
Monotherapy study												
PAAP	n/c	n/c	n/c	5	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c
PtGA	n/c	n/c	n/c	5	6	n/c	n/c	n/c	n/c	5	n/c	n/c
HAQ-DI	n/c	n/c	5	4	3	n/c	n/c	n/c	n/c	n/c	4	n/c

PAAP MCID ≥10 points; PtGA MCID ≥10 points; HAQ-DI MCID ≥0.22 points. n/c, not calculated: patients did not achieve both MCID ≥10 points and statistically significant improvement compared with placebo (p<0.05). ADA: adalimumab; BID: twice daily; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; MCID: minimum clinically important difference; NNT: number needed to treat; PAAP: Patient's Assessment of Arthritis Pain; PtGA: Patient's Global Assessment of Arthritis; QD: once daily; QOW: once every other week.

(Table II). No clinically meaningful improvements were recorded in patients treated with adalimumab/tofacitinib 5 mg BID at Week 12 or at Week 24. NNT values (FAS, no imputation), based on patients achieving MCID ≥10 points and statistically significant difference from placebo, are shown in Table III for both studies.

• *Patient's Global Assessment of Arthritis*

Statistically significant improvements in PtGA compared with placebo were recorded as early as Week 2 in the combination study (15 mg BID; Fig. 2B) and the monotherapy study (3, 5, 10 and 15 mg BID, and adalimumab; Fig. 3B). At Week 12, statistically significant improvements in PtGA were observed with all tofacitinib doses ≥3 mg BID in the combination study and with all tofacitinib doses ≥5 mg BID in the monotherapy study; these improvements were sustained to Week 24 in both studies. In the monotherapy study, no significant improvements were recorded in patients receiving adalimum-

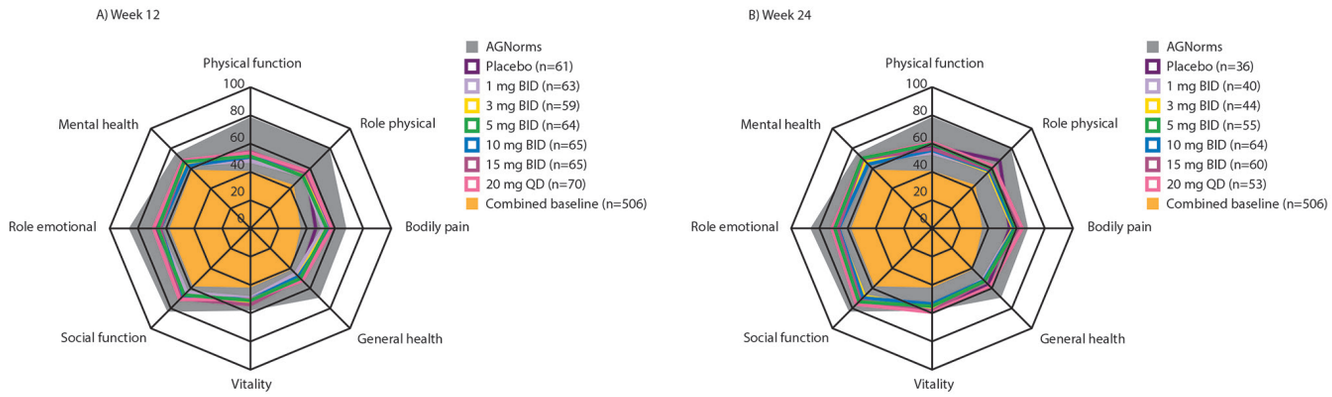

Fig. 4. Combination study: overall SF-36 domain scores. 'Spydergrams©' representing mean overall SF-36 domain scores in the combination study at (**A**) Week 12 and (**B**) Week 24 (FAS, no imputation).
Baseline: mean baseline for all tofacitinib dose groups and placebo. AGNorm: age- and gender-matched US normative data specific to this study; BID: twice daily; FAS: full analysis set; QD: once daily; SF-36: Short-Form 36.

Table IV. Mean change from baseline in SF-36 domain scores per tofacitinib dose group; combination study and monotherapy study (FAS, LOCF).

Domain	Tofacitinib dose													
	Week 12							Week 24						
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	PBO	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	PBO
Combination study														
Physical function	3.9	3.8	4.8	4.2	6.1	7.0*	3.1	4.7	4.3	6.6*	6.4*	6.4*	7.5*	2.7
Role physical	3.8	4.5	3.2	4.6	5.0	6.2	3.5	4.1	4.1	4.8	6.3	5.5	5.5	4.1
Bodily pain	7.3	8.5*	7.9*	8.9*	9.6**	10.1**	4.1	7.7*	7.3*	9.1**	9.4**	9.9**	10.3***	3.6
General health	3.0	3.8	5.0	3.1	4.6	5.3	3.4	4.2	3.9	5.6	4.8	4.9	5.8	3.9
Vitality	4.6	4.4	4.7	2.9	6.6*	4.9	2.6	5.6*	4.1	5.6*	4.4	7.9**	6.2*	2.3
Social function	3.3	5.0	4.1	4.0	5.1	5.7*	1.9	3.6	3.5	5.7	5.3	4.7	5.6	2.6
Role emotional	3.9	3.2	3.1	2.9	3.4	5.1	1.8	3.4	3.5	3.8	3.9	4.4	4.0	1.6
Mental health	4.4*	4.2*	4.0*	0.9	4.7*	5.5*	0.5	4.4*	3.9**	5.4**	1.4	5.8**	4.4*	-0.2
Physical component summary	4.4	5.4	5.5	6.3	7.0*	7.7*	4.2	5.4	5.1	6.9	8.1*	7.1	8.4*	4.4
Mental component summary	3.9*	3.5	3.2	1.0	3.8*	4.3*	0.3	3.7*	3.1	4.1*	1.6	4.7*	3.4*	-0.1
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	ADA 40 mg QOW/ 5 mg BID	PBO	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	ADA 40 mg QOW/ 5 mg BID	PBO
Monotherapy study														
Physical function	2.9	5.0	6.5*	9.1**	8.3*	5.3	2.3	2.4	4.1	6.2*	9.8***	9.5**	5.5	2.2
Role physical	4.7	5.0	6.5	8.6*	9.5*	3.9	4.8	3.3	5.7	7.4	9.2*	8.7*	4.3	4.1
Bodily pain	6.4	6.3	8.9	12.5***	13.8***	5.6	5.4	5.1	6.0	8.0*	13.4***	13.4***	7.1	4.4
General health	4.2	4.5	6.4	6.4	7.3*	4.7	4.0	4.5	5.6	5.9	7.5*	5.9	5.1	3.9
Vitality	5.7	4.8	5.8	9.4*	10.3**	6.8	3.7	4.4	5.5	5.8	8.8*	8.2*	7.3	4.4
Social function	4.9	4.2	7.1	7.5	8.0	2.9	5.6	3.9	3.4	6.0	8.0	7.1	2.6	4.6
Role emotional	5.1	3.6	6.3	6.5	6.0	7.0	6.3	1.3*	6.0	6.4	7.1	7.1	6.5	6.2
Mental health	5.4	3.4	6.3	6.0	5.6	6.5	6.1	3.8	3.9	6.2	7.0	4.9	6.8	5.2
Physical component summary	3.8	5.5	7.0*	10.0***	10.9***	3.9	2.8	3.8	5.0	6.7*	10.8***	10.7***	4.7	2.4
Mental component summary	5.7	3.0	5.8	5.5	6.2	6.5	6.5	3.1	4.4	5.7	5.9	4.6	6.2	6.1

Difference from placebo: *p<0.05, **p<0.001, ***p<0.0001. ADA: adalimumab; BID: twice daily; FAS: full analysis set; LOCF: last observation carried forward; PBO: placebo; QD: once daily; QOW: once every other week; SF-36: Short-Form 36.

ab at Week 12, or adalimumab/tofacitinib at Week 24.

At Week 12 in the combination study, the proportions of patients reporting improvements ≥MCID (≥10 points) were statistically significant for the tofacitinib 10 mg BID and 20 mg QD dose groups (Table II). In the monotherapy study, a statistically significant proportion of patients in the 10 mg and 15 mg tofacitinib BID groups reported improvements ≥MCID *versus* placebo

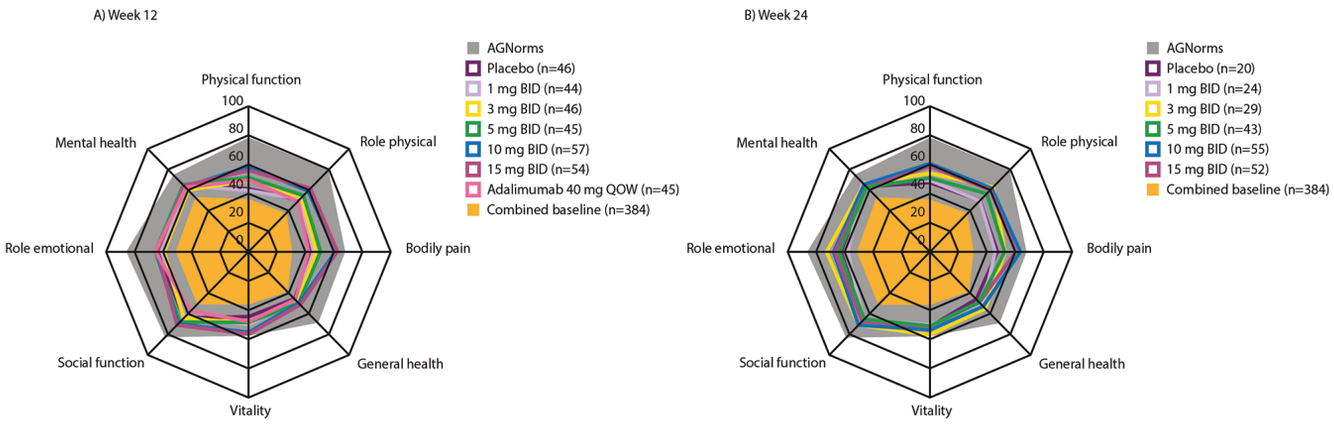

Fig. 5. Monotherapy study: overall SF-36 domain scores. 'Spydergrams©' representing mean overall SF-36 domain scores in the combination study at (**A**) Week 12 and (**B**) Week 24 (FAS, no imputation).
Baseline: mean baseline for all tofacitinib dose groups and placebo. AGNorm: age- and gender-matched US normative data specific to this study; BID: twice daily; FAS: full analysis set; QOW: once every other week; SF-36: Short-Form 36.

Table V. Percentage of patients achieving MCID in SF-36 domain (improvement >5 points) and component (improvement >2.5 points) scores compared with placebo; combination study and monotherapy study (FAS, no imputation).

Domain and Component Scores	Tofacitinib dose													
	Week 12							Week 24						
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	PBO	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	PBO
Combination study														
Physical function	36.5	37.3	40.6	39.1	52.3*	52.9*	31.1	62.5	50.0	56.4	52.9	54.0	58.5	47.2
Role physical	33.3	39.0	29.7	45.3	46.2	47.1*	29.5	47.5	45.5	48.7	49.0	50.0	58.5	41.7
Bodily pain	50.8	61.0*	54.7	64.1*	61.5*	71.4***	37.7	67.5	70.5	74.4*	58.8	64.0	73.6*	50.0
General health	33.3	42.4	37.5	32.8	47.7	48.6	37.7	52.5	50.0	51.3	43.1	54.0	49.1	47.2
Vitality	49.2	40.7	45.3	32.8	61.5**	48.6	32.8	62.5*	45.5	51.3	37.3	72.0*	64.2*	38.9
Social function	49.2	49.2	54.7	46.9	44.6	58.6*	39.3	70.0	47.7	69.2	51.0	50.0	66.0	50.0
Role emotional	38.1*	39.0*	40.6*	40.6*	43.1*	44.3*	21.3	42.5*	36.4	46.2*	39.2*	46.0*	43.4*	19.4
Mental health	47.6*	47.5*	46.9*	32.8	43.1*	50.0*	26.2	60.0*	47.7	46.2	33.3	62.0*	50.9	36.1
Physical component	61.9	66.1	59.4	75.0*	73.8*	77.1*	52.5	77.5	72.7	82.1	74.5	70.0	79.2	63.9
Mental component	46.0	52.5	48.4	31.3	58.5*	54.3	37.7	57.5	52.3	56.4	43.1	58.0	56.6	44.4
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	ADA 40 mg QOW/ 5 mg BID	PBO	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	ADA 40 mg QOW/ 5 mg BID	PBO
Monotherapy study														
Physical function	34.1	47.8*	55.6*	57.9*	50.0*	48.9*	28.3	50.0	41.4	61.3	68.2	77.8	52.4	55.0
Role physical	40.9	41.3	48.9	59.6*	51.9	35.6	39.1	37.5	51.7	58.1	63.6	64.4	42.9	45.0
Bodily pain	52.3	47.8	64.4*	71.9*	77.8**	44.4	43.5	45.8	51.7	64.5	84.1*	82.2*	66.7	50.0
General health	34.1	34.8	44.4	45.6	50.9*	37.8	28.3	37.5	41.4	48.4	56.8	47.7	52.4	55.0
Vitality	52.3	39.1	57.8	56.1	61.1	60.0	45.7	41.7	48.3	61.3	65.9	73.3	71.4	60.0
Social function	50.0*	47.8*	66.7	70.2	64.8	53.3	71.7	54.2	41.4*	51.6*	70.5	60.0	61.9	80.0
Role emotional	45.5	41.3	48.9	47.4	47.2	46.7	50.0	50.0	58.6	51.6	50.0	60.0	61.9	40.0
Mental health	59.1	47.8	53.3	56.1	50.0	64.4	47.8	50.0	41.4	51.6	63.6	53.3	57.1	50.0
Physical component	56.8	54.3	75.6*	78.9**	78.8**	53.3	47.8	58.3	65.5	80.6	79.5	84.1	66.7	75.0
Mental component	59.1	47.8	57.8	63.2	57.7	68.9	65.2	45.8	48.3	51.6	70.5	63.6	61.9	65.0

Difference from placebo: *p<0.05, **p<0.001, ***p<0.0001. ADA: adalimumab; BID: twice daily; FAS: full analysis set; MCID: minimum clinically important difference; PBO: placebo; QD: once daily; QOW: once every other week; SF-36: Short-Form 36.

(Table II). No clinically meaningful improvements were recorded in patients treated with adalimumab/tofacitinib 5 mg BID at Week 12 or at Week 24. NNT values (FAS, no imputation) are shown in Table III for both studies.

• *HAQ-DI*

Improved physical functioning was demonstrated by a decrease in HAQ-DI scores (combination study [Fig. 2C]; monotherapy study [Fig. 3C]). In the combination study, improvements were statistically significant compared with placebo at Week 12 and were maintained to Week 24 for all tofacitinib dose groups. In the monotherapy study, similar significant improvements were recorded at Week 12 for tofacitin-

ib 3, 5, 10 and 15 mg BID, maintained to Week 24.

The percentage of patients in the combination study reporting improvement ≥MCID in HAQ-DI (≥0.22 points) was statistically significant compared with placebo at Week 12 for all tofacitinib doses (Table II). In the monotherapy study, statistically significant improvements in HAQ-DI were observed in three of the six doses at Week 12 (5, 10 and 15 mg BID). No clinically meaningful improvements were recorded in patients treated with adalimumab/tofacitinib 5 mg BID at Week 12 or at Week 24.

The proportion of patients achieving 'normative' HAQ-DI scores (≤0.5 points) in the combination study at Week 12 were not statistically significantly greater than placebo for any tofacitinib dose (Table II). At Week 12 in the monotherapy study, three of the six dose groups (5, 10 and 15 mg BID) had a statistically significantly greater proportion of patients achieving 'normative' HAQ-DI (Table II). NNT values (FAS, no imputation) are shown in Table III for both studies.

• *FACIT-F*

In the combination study there were no statistically significant improvements in fatigue from baseline for any tofacitinib dose group at any time point compared with placebo. In the monotherapy study, statistically significant improvements ($p<0.05$) from baseline *versus* placebo were observed at Week 2 for 10 and 15 mg BID (5.2 and 6.0, respectively, *vs*. 1.3 for placebo), at Week 12 for 5, 10 and 15 mg BID (7.5, 8.8 and 9.2, respectively, *vs*. 2.9 for placebo), and at Week 24 for 5, 10 and 15 mg BID (7.8, 8.3 and 8.1, respectively, *vs*. 3.3 for placebo). No statistically significant improvements were recorded in patients treated with adalimumab/tofacitinib 5 mg BID at Weeks 2, 12 or 24.

• ***SF-36***

In both studies improvements from baseline were observed in several domains of the SF-36 at Week 12 and Week 24. In the combination study, the greatest improvement compared with baseline at Week 12 and Week 24 was reported for the bodily pain domain (10.1 and 10.3, respectively), followed by the physical functioning domain (7.0 and 7.5, respectively) (Fig. 4 and Table IV). At Week 12 in the monotherapy study, the greatest improvements were reported for the bodily pain (13.8) and vitality (10.3) domains (Fig. 5A and Table IV), and at Week 24, for the bodily pain (13.4) and physical functioning (9.8) domains (Fig. 5B and Table IV).

In the combination study at Week 12, statistically significant differences from placebo occurred for at least one tofacitinib dose group in the physical functioning, bodily pain, vitality, social functioning and mental health domains (Table IV). Physical and mental component summary scores also recorded significant improvements for several tofacitinib dose groups at Week 12 and Week 24. In the monotherapy study at Week 12, statistically significant differences from placebo occurred for at least one tofacitinib dose group in the physical functioning, role physical, bodily pain, general health and vitality domains (Table IV). Physical component summary scores also recorded significant improvements for several tofacitinib dose groups at Week 12 and Week 24.

In the combination study, at least one tofacitinib dose group surpassed the MCID for all domains except general health (Table V). At Week 12 in the combination study, the greatest number of domains showing statistically significant clinically meaningful improvements, compared with placebo, were observed for 15 mg BID and 20 mg QD (significant in five and six domains, respectively). In the monotherapy study, at least one tofacitinib dose group surpassed the MCID for the physical functioning, role physical, bodily pain, general health and social functioning domains (Table V). At Week 12 and Week 24, 10 mg and 15 mg BID resulted in the greatest number of domains with statistically significant clinically meaningful improvements compared with placebo (Week 12, three domains; Week 24, one domain; Table V).

Discussion

Treatment with tofacitinib, either as monotherapy or with background MTX, resulted in improvements in PRO by Week 12 that were sustained to Week 24 (post-Week-12 efficacy data are for patients who continued on their original tofacitinib dose) and which were consistent with improvements reported in Phase 3 studies (37-42). These improvements were statistically significant *versus* placebo for several tofacitinib dose groups. Moreover, many of these effects were rapid; there were significant improvements in PAAP, PtGA and HAQ-DI at Week 2. By Week 12, mean changes from baseline exceeded the MCID for PAAP, PtGA and HAQ-DI for the majority of patients; these changes were frequently sustained to Week 24.

Patients' fatigue also improved in the monotherapy study in patients treated with tofacitinib 5, 10 or 15 mg BID; a significant difference from placebo was observed at Weeks 2 and 12, and these effects were sustained to Week 24. This finding was not reproduced in the combination study.

The SF-36 data indicate that at baseline there was substantial burden of disease in all domains. Relative to a mean (standard deviation [SD]) of 50 (10) in the general US population, patients from both the combination and monotherapy studies exhibited baseline values between 0.5 and 2 SDs below the mean in all domains. At Week 12 in the combination study, the largest differences from placebo were observed in the bodily pain, physical functioning and mental health domains, all of which showed some degree of dose dependence. Contrasting this pattern in some respects, the largest effects at Week 12 in the monotherapy study were observed in the bodily pain, physical functioning, role physical and vitality domains, also showing a dose-dependent response. It is interesting to note the apparent dissociation between improvements in mental health and vitality in both studies, given a recent report of an association between fatigue and depression measures in RA (43). The SF-36 mental health domain is composed of four questions: two that

focus on depression and two that focus on anxiety-related symptoms. Both studies showed statistically significant improvements in vitality for at least one tofacitinib dose at Week 12, but mental health only improved in the combination study (where four out of six dose groups were significantly different from placebo). Both domains exhibited comparable burden of disease at baseline and the two studies had comparable inclusion/exclusion criteria. Hence, it is difficult to attribute such dissociation to differences in experimental design or populations across the studies.

It has been suggested that PRO measures are as sensitive in detecting treatment-related changes in RA as other composite measures, and are equivalent to composite measures of clinical improvement such as the ACR, Disease Activity Score (DAS28), Clinical Disease Activity Index (CDAI) responses, objective measures of inflammation such as erythrocyte sedimentation rate and C-reactive protein, and clinician-reported outcomes such as tender and swollen joint counts (9, 44, 45). The improvements in PRO measures reported here generally correlate well with the clinical efficacy data from both studies (23, 24). Clinical efficacy as measured by ACR responses was statistically different from placebo in all doses of tofacitinib >3 mg BID at Week 12 and was sustained to Week 24 in both the combination and monotherapy studies. Tofacitinib therefore demonstrated clinical benefit for patients with RA when assessed by traditional measurements of disease activity, as well as by PROs.

In conclusion, administration of tofacitinib, either in combination with MTX or as monotherapy, led to rapid and sustained clinically and statistically significant improvements over 24 weeks in pain, physical functioning and HRQoL in patients with active RA.

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