

Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: patient-reported outcomes from the 24-month Phase 3 ORAL Scan study

V. Strand¹, D. van der Heijde², Y. Tanaka³, E. Keystone⁴, J. Kremer⁵, C.A.F. Zerbini⁶, M.H. Cardiel⁷, S. Cohen⁸, P. Nash⁹, Y.-W. Song¹⁰, D. Tegzová¹¹, D. Gruben¹², G. Wallenstein¹², C.A. Connell¹², R. Fleischmann⁸, for the ORAL Scan investigators.

¹Division of Immunology/Rheumatology, Stanford University, Palo Alto, CA, USA; ²Leiden University Medical Center, Leiden, The Netherlands; ³First Department of Internal Medicine, University of Occupational and Environmental Health Japan, Kitakyushu, Japan; ⁴Mount Sinai Hospital, University of Toronto, Toronto, Canada; ⁵Albany Medical College, Albany, NY, USA; ⁶Centro Paulista de Investigação Clínica, São Paulo, Brazil; ⁷Centro de Investigación Clínica de Morelia, Morelia, Mexico; ⁸Metroplex Clinical Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; ⁹University of Queensland, Queensland, Australia; ¹⁰Department of Internal Medicine, Medical Research Center, Seoul National University College of Medicine, Seoul, Korea; ¹¹Institute of Rheumatology, Prague, Czech Republic; ¹²Pfizer Inc, Groton, CT, USA.

Abstract Objective

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we present data from the completed Phase 3 randomised controlled trial (RCT) ORAL Scan (NCT00847613), which evaluated the impact of tofacitinib on patient-reported outcomes (PROs) through 24 months in patients with active RA and inadequate responses to methotrexate (MTX-IR).

Methods

Patients were randomised 4:4:1:1 to receive tofacitinib 5 or 10 mg twice daily (BID), or placebo advanced to tofacitinib 5 or 10 mg, plus background MTX. Patients receiving placebo advanced to tofacitinib at month 3 (non-responders) or month 6 (remaining patients). Mean changes from baseline in PROs, assessed at months 1-24, included Health Assessment Questionnaire-Disability Index, Patient Global Assessment of disease activity (visual analogue scale [VAS]), Patient Assessment of Arthritis Pain (VAS), health-related quality of life (Short Form-36 version 2), Functional Assessment of Chronic Illness Therapy-Fatigue and Medical Outcomes Study-Sleep.

Results

Overall, 539/797 (67.6%) patients completed 24 months' treatment. At month 3, tofacitinib-treated patients reported significant ($p < 0.05$) mean changes from baseline versus placebo across all PROs, and significantly more patients reported improvements \geq minimum clinically important differences versus placebo. Improvements in PROs with tofacitinib were sustained to month 24. Following advancement to tofacitinib, placebo-treated patients generally reported changes of similar magnitude to tofacitinib-treated patients.

Conclusion

Patients with RA and MTX-IR receiving tofacitinib 5 or 10 mg BID plus MTX reported significant and clinically meaningful improvements in PROs versus placebo at month 3, which were sustained through 24 months.

Key words

methotrexate, rheumatoid arthritis, patient-reported outcome measures, tofacitinib

Vibeke Strand, MD
 Désirée van der Heijde, MD, PhD
 Yoshiya Tanaka, MD, PhD
 Edward Keystone, MD, FRCPC
 Joel Kremer, MD
 Cristiano A.F. Zerbini, MD
 Mario H. Cardiel, MD, MSc
 Stanley Cohen, MD
 Peter Nash, MBBS (Hons), FRACP
 Yeong-Wook Song, MD, PhD
 Dana Tegzová, MD
 David Gruben, PhD
 Gene Wallenstein, PhD*
 Carol A. Connell, RN, PhD
 Roy Fleischmann, MD

*Affiliation at the time the work was conducted - Pfizer Inc, Groton, CT, USA.

Please address correspondence to:

Gene Wallenstein,
 East Greenwich,
 RI, 860-326-8783, USA.

E-mail: genewallenstein@yahoo.com

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Introduction

Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease characterised by systemic inflammation, persistent synovitis and joint destruction. RA causes a significant health and socioeconomic burden, and affects all aspects of health-related quality of life (HRQoL) (1, 2). As such, patients with RA can experience sleep disturbances and difficulty performing everyday activities, including engagement in family, social and leisure activities, as well as occupational roles (1-3). Assessment of patient-reported outcomes (PROs) in randomised controlled trials (RCTs) is recommended by the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and Outcome Measures in Rheumatology (OMERACT) (4-6) and represents an important means of evaluating treatment responses.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. In patients with moderately to severely active RA, the efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) as monotherapy or with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) have been demonstrated in Phase 3 RCTs (7-12) for up to 24 months, and in long-term extension studies with observations up to 114 months (13-15). Improvements across a broad range of PROs have been reported in tofacitinib Phase 3 RCTs (16-20). The 24-month, Phase 3 ORAL Scan (NCT00847613) RCT included patients with active RA and inadequate responses to methotrexate (MTX-IR) who received tofacitinib 5 or 10 mg BID plus MTX (10). Statistical significance for inhibition of structural damage was seen with tofacitinib 10 mg BID, but not 5 mg BID, *versus* placebo, and through 24 months, sustained clinical efficacy and continued safety and tolerability were demonstrated in patients receiving tofacitinib 5 and 10 mg BID (10, 21). A planned interim analysis of ORAL Scan at 12 months demonstrated that patients receiving tofacitinib reported clinically meaningful improvements in Patient Global Assessment of disease activity (PtGA), pain, physical function and fatigue (10). Here, we

report the 24-month PRO results from this Phase 3 RCT.

Patients and methods

Study design and patients

Full details of the ORAL Scan RCT were reported previously (10). In brief, eligible patients were randomised 4:4:1:1 to receive tofacitinib 5 or 10 mg BID, or placebo advanced to tofacitinib (placebo→tofacitinib) 5 or 10 mg BID. The randomisation schedule for the placebo sequences was pre-specified; at month 3, non-responders (defined as <20% improvement in swollen and tender joint counts) were blindly advanced to tofacitinib; at month 6, all remaining patients were blindly advanced to tofacitinib. All patients must have been receiving MTX continuously for ≥4 months with stable doses for ≥6 weeks, and continued stable doses (15–25 mg weekly) throughout the study. Weekly doses <15 mg were allowed only if there was documented intolerance to, or toxicity from higher doses, or where higher doses would violate the local label.

This RCT was approved by the Institutional Review Boards (IRB) and/or Independent Ethics Committees at each investigational centre, or a central IRB, and was conducted in accordance with Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent. Additional details of study investigators are provided in Supplementary Table S1.

Assessment of PROs

PROs assessed included: PtGA by visual analogue scale (VAS), Health Assessment Questionnaire-Disability Index (HAQ-DI) score, Patient Assessment of Arthritis Pain by VAS (Pain [VAS]), and HRQoL by Short Form-36 (SF-36; version 2, Acute) questionnaire, which assesses eight domains summarised into Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Fatigue was assessed using Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) total score, and quality of sleep using the Medical Outcomes Study (MOS)-Sleep

scale. PROs were measured at all visits: baseline and months 1, 3, 6, 9, 12, 15, 18, 21 and 24, except FACIT-F and MOS-Sleep which were measured at all visits except months 9, 15 and 21.

Mean changes from baseline in all PROs were pre-defined secondary endpoints, except HAQ-DI at month 3, which was a co-primary endpoint. Findings were analysed according to published minimum clinically important differences (MCIDs), defined as: a decrease ≥ 0.22 points from baseline in HAQ-DI, decreases ≥ 10 mm from baseline in PtGA and Pain (VAS), increases of ≥ 2.5 points from baseline in SF-36 PCS and MCS scores, increases of ≥ 5 points from baseline in SF-36 domain scores, and a 4-point increase from baseline in FACIT-F (22). No MCID is available for MOS-Sleep (23). The proportions of patients reporting HAQ-DI scores \leq normative values (defined as HAQ-DI ≤ 0.25) (24) or achieving functional remission (defined as HAQ-DI < 0.5) (25), as well as patients reporting FACIT-F scores \geq those of the general population (defined as FACIT-F ≥ 43.5) (26) and also defined as FACIT-F ≥ 40.1 (27)), were evaluated by treatment sequence through month 24.

Statistical analyses

All analyses were based on the full analysis set, defined as all patients who received ≥ 1 dose of study drug with ≥ 1 post-baseline assessment.

Least squares mean (LSM) changes from baseline in HAQ-DI at month 3 was a co-primary endpoint. To control for Type I error rate, it was tested using a step-down approach in the following order: $\geq 20\%$ improvement in ACR responses (ACR20), mean changes in total van der Heijde modified total Sharp scores, mean changes in HAQ-DI, and Disease Activity Score of 28 joints (erythrocyte sedimentation rate) remission < 2.6 (10). For the tofacitinib 5 mg BID dose, significance could only be declared if both the 10 mg BID dose at the same endpoint and 5 mg BID dose at the prior endpoint were significant. Additional details of the step-down method have been published previously (10). For the co-primary endpoint, and for each dose group, comparisons with

■ Age- and gender-matched US normative data specific to this protocol population
 ■ Composite weighted baseline data
 ■ Tofacitinib 5 mg BID ■ Tofacitinib 10 mg BID ■ Placebo

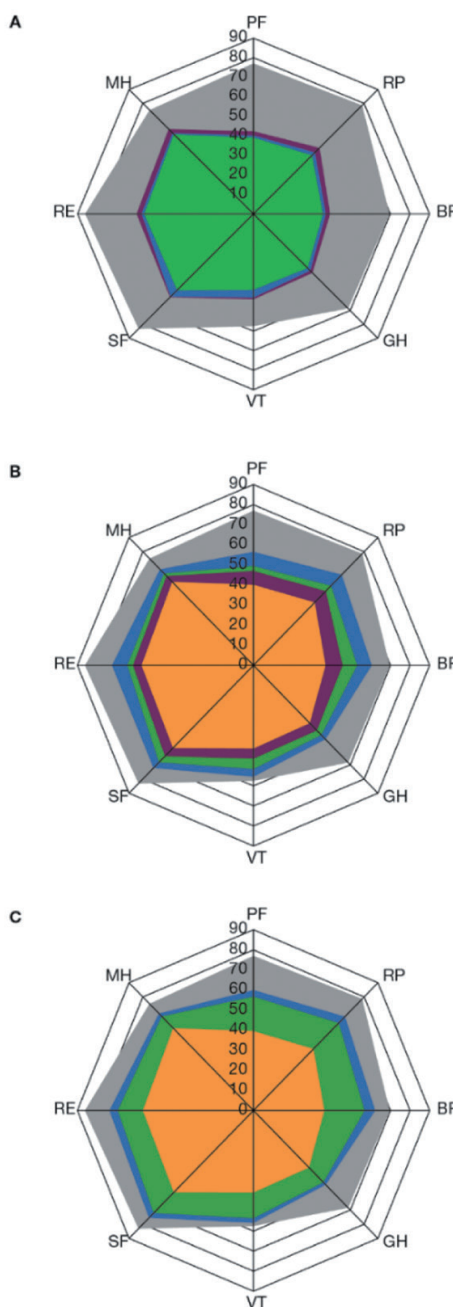


Fig. 1. Spidergram displaying 0-100 SF-36 domain scores for patients in ORAL Scan receiving tofacitinib or placebo at baseline (A), at month 3 (B) and for patients receiving tofacitinib at month 24 (C), for patients receiving tofacitinib compared with an age- and gender-matched US normative population.

All patients received background methotrexate, including those in the placebo groups. Patient numbers for tofacitinib 5 and 10 mg BID and placebo were: n=315, n=309, and n=156 at baseline and n=295, n=300, and n=146 at month 3; and n=211 and n=218 for tofacitinib 5 and 10 mg BID at month 24. BID: twice daily; BP: bodily pain; GH: general health; MH: mental health; PF: physical functioning; RE: role-emotional; RP: role-physical; SF: social functioning; VT: vitality.

placebo were conducted using a significance (alpha) level set at 0.05 (2-sided) or equivalently 0.025 (1-sided). For all other PROs, statistical significance was declared for p -values ≤ 0.05 , with no adjustments for multiple comparisons among these secondary endpoints.

All analyses were specified before the study blind was broken, except the following *post-hoc* analyses: percentages of patients reporting improvements \geq MCID in FACIT-F and their

corresponding numbers needed to treat (NNTs), and comparisons of SF-36 with age- and gender-matched normative scores.

Continuous endpoints HAQ-DI, PtGA, Pain, FACIT-F and MOS-Sleep were expressed as changes from baseline, and analysed using a longitudinal linear mixed-effects repeated-measures model. Missing data were not explicitly imputed, except for continuous variables where the longitudinal

Table I. Baseline demographics and patient-reported outcomes by randomised treatment.[‡]

Demographics	Tofacitinib 5 mg BID (n=321)	Tofacitinib 10 mg BID (n=316)	Placebo→ tofacitinib 5 mg BID (n=81)	Placebo→ tofacitinib 10 mg BID (n=79)
Female, n (%)	269 (83.8)	272* (86.1)	65 (80.2)	72 (91.1)
Race, n (%)				
White	152 (47.4)	144 (45.6)	36 (44.4)	36 (45.6)
Black	14 (4.4)	8 (2.5)	1 (1.2)	1 (1.3)
Asian	131 (40.8)	135 (42.7)	37 (45.7)	35 (44.3)
Other	24 (7.5)	29 (9.2)	7 (8.6)	7 (8.9)
Age (years), mean (SD)	53.7 (11.6)	52.0 (11.4)	53.2 (11.5)	52.1 (11.8)
Disease duration (years), mean (range)	8.9 (0.3–43.0)	9.0 (0.3–42.0)	8.8 (0.6–30.8)	9.5 (0.4–43.5)
Patient-reported outcomes, mean (SD)	Tofacitinib 5 mg BID (n=316)	Tofacitinib 10 mg BID (n=309)	Placebo→ tofacitinib 5 mg BID (n=79)	Placebo→ tofacitinib 10 mg BID (n=77)
HAQ-DI [†]	1.4 (0.7)	1.4 (0.7)	1.4 (0.6)	1.2 (0.7)
PtGA (VAS) [‡]	58.0 (23.6)	56.5 (23.0)	54.6 (20.1)	53.6 (25.5)
Pain (VAS)	58.4 (23.1)	57.6 (24.1)	57.9 (21.3)	51.9 (26.3)
MOS Overall Sleep Problems [§]	40.2 (20.1)	39.7 (19.5)	38.1 (17.9)	36.5 (18.8)
FACIT-F [§]	28.6 (10.6)	29.5 (10.6)	30.4 (11.6)	31.8 (10.5)
SF-36 component scores [‡]				
PCS [‡]	33.1 (7.9)	33.8 (7.8)	33.2 (7.6)	35.9 (8.3)
MCS [‡]	41.0 (11.5)	42.2 (11.5)	42.3 (11.5)	44.1 (12.4)
SF-36 domains [‡]				
PF [‡]	32.2 (10.0)	32.6 (9.9)	31.9 (10.1)	35.1 (11.1)
RP [‡]	34.6 (9.4)	35.4 (9.7)	35.3 (9.7)	38.1 (11.2)
SF [‡]	37.2 (11.1)	39.2 (11.4)	38.9 (11.0)	39.9 (12.1)
BP [‡]	34.0 (7.5)	34.6 (7.9)	34.7 (7.2)	36.5 (8.8)
MH [‡]	39.9 (11.3)	40.5 (11.2)	40.8 (10.4)	43.3 (12.1)
RE [‡]	35.6 (12.7)	36.3 (13.4)	36.3 (13.8)	38.6 (13.8)
VT [‡]	40.6 (9.9)	42.5 (9.7)	41.7 (9.5)	44.3 (10.2)
GH [‡]	35.2 (9.1)	36.0 (8.8)	35.4 (8.4)	38.3 (7.6)

[‡]Data for some outcomes were available for fewer patients than the total number of patients randomised to each treatment sequence.

*One patient was incorrectly coded as a female in the initial month 12 analyses and is correctly coded as a male here.

n: numbers for tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo→ tofacitinib 5 mg BID and placebo→ tofacitinib 10 mg BID groups were as follows:

[†]n=315, n=309, n=79 and n=77, respectively;

[‡]n=316, n=308, n=79 and n=77, respectively;

[§]n=314, n=309, n=79 and n=77, respectively;

[¶]n=315, n=307, n=79 and n=76, respectively.

All patients received background methotrexate, including those in the placebo groups. BID: twice daily; BP: bodily pain; FACIT-F: Functional Assessment of Chronic Illness Therapy- Fatigue; GH: general health; HAQ-DI: Health Assessment Questionnaire-Disability Index; MCS: Mental Component Summary; MH: mental health; MOS: Medical Outcomes Study; PCS: Physical Component Summary; PF: physical functioning; PtGA: Patient Global Assessment of disease activity; RE: role-emotional; RP: role-physical; SD: standard deviation; SF: social functioning; SF-36: Short Form-36 Health Survey (version 2, Acute); VAS: visual analogue scale; VT: vitality.

mixed-effect linear model accounted for missing data. Treatment visit, treatment-by-visit interaction and baseline were included as fixed effects, and patients were included as random effects. Estimates of mean changes from baseline for each treatment, as well as mean differences from placebo, were derived from the longitudinal model as LSMs,

with corresponding standard errors, *p*-values and 95% confidence intervals. Binary endpoints (*e.g.* improvements \geq MCID) were compared between tofacitinib and placebo treatment sequences (except for MOS-Sleep) in a *post-hoc* analysis, according to a Z-score using the normal approximation to the binomial.

NNTs were calculated as the reciprocal of the percentage-point differences in the rates (*i.e.* the value for the placebo group who failed in reporting improvement in scores \geq MCID minus the value for the tofacitinib group without improvement in scores \geq MCID). Patients with missing results were not included (not considered as failures or successes).

Results

Patient disposition and demographics

Of the 800 randomised patients, 797 received treatment (March 2009 to February 2012), as follows: tofacitinib 5 mg BID, n=321; tofacitinib 10 mg BID, n=316; placebo→ tofacitinib 5 mg BID, n=81; placebo→ tofacitinib 10 mg BID, n=79. Overall, 539 (67.6%) patients completed treatment through 24 months. The proportions of patients who discontinued were similar across treatment sequences: 34.0% (n=109), 30.1% (n=95), 32.1% (n=26), and 34.2% (n=27), respectively. Additional details through 24 months are provided in Supplementary Figure 1.

Patient demographics, baseline disease characteristics and PRO scores were similar across treatment sequences (Table I) (10). Large decrements were evident in baseline HRQoL scores compared with an age- and gender-matched US normative population (Fig. 1). PCS and MCS scores at baseline were approximately two and one standard deviations, respectively (normative standard deviations of 10), below normative scores of 50 (22) (Table I).

HAQ-DI

Patients receiving tofacitinib 10 mg BID reported significant improvements in LSM changes from baseline in HAQ-DI ($p<0.0001$) versus placebo at month 3 (Fig. 2A and 3A). LSM changes from baseline were numerically improved with tofacitinib 5 mg BID, but were not statistically significant due to the pre-defined step-down approach (10). Improvements in HAQ-DI were sustained to month 24 in both tofacitinib groups (Fig. 3A). Patients receiving placebo→ tofacitinib at months 3 or 6 reported changes from baseline at months 9 to 24 of similar magnitude to those treated with tofacitinib throughout.

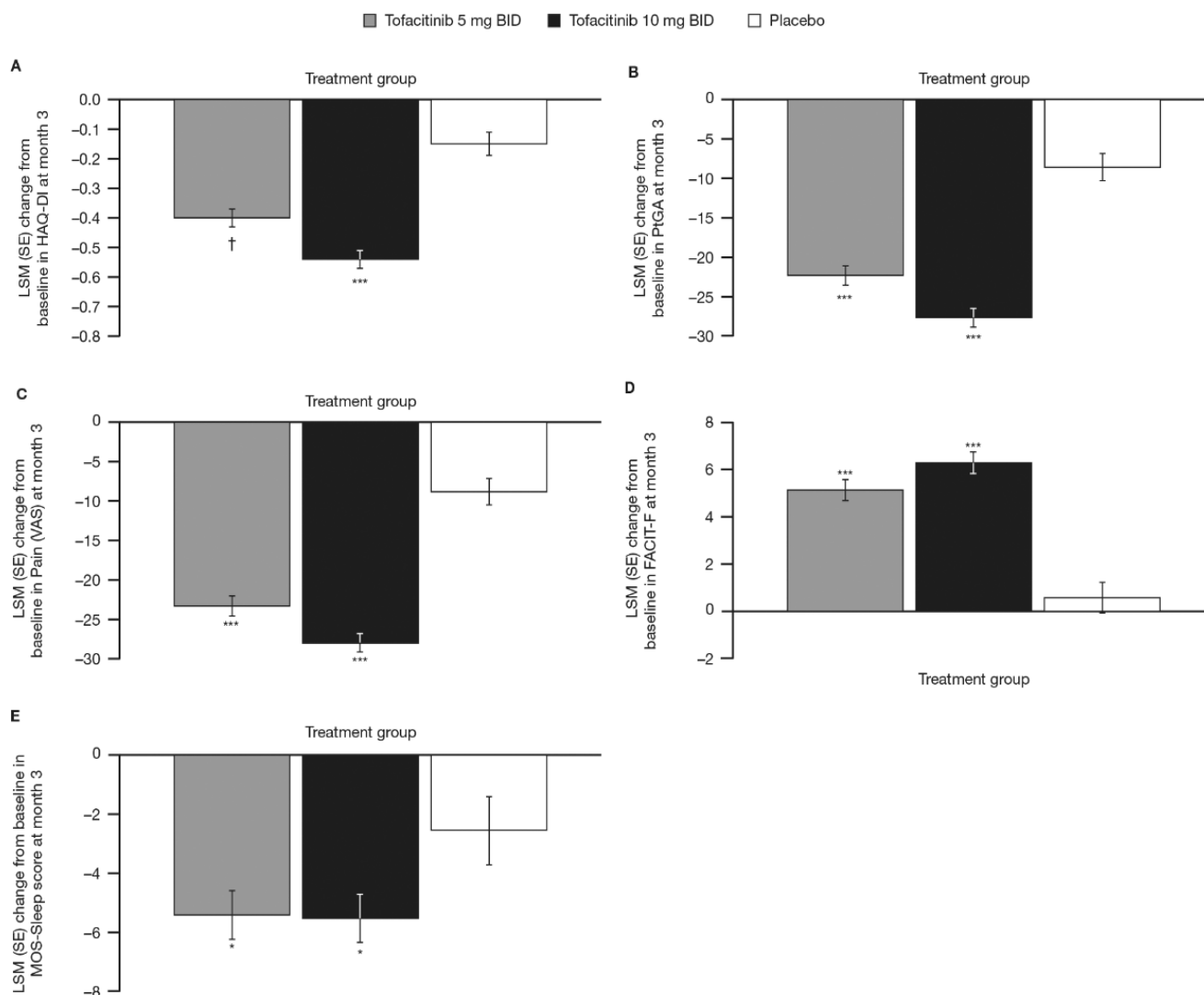


Fig. 2. PRO endpoints at month 3 (FAS, longitudinal model) by treatment group: (A) HAQ-DI, (B) PtGA (VAS), (C) Pain (VAS), (D) FACIT-F, and (E) MOS-Sleep.

* $p < 0.05$; *** $p < 0.0001$ vs. placebo. †Significance was not declared for tofacitinib 5 mg BID due to the step-down method.

All patients received background methotrexate, including those in the placebo groups.

Patient numbers at month 3 for tofacitinib 5 and 10 mg BID and placebo were: HAQ-DI, $n=294$, $n=300$ and $n=146$; PtGA, $n=295$, $n=299$ and $n=146$; Pain (VAS), $n=295$, $n=300$ and $n=146$; FACIT-F, $n=294$, $n=298$ and $n=145$; MOS-Sleep, $n=293$, $n=300$ and $n=146$.

BID: twice daily; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; LSM: least squares mean; MOS: Medical Outcomes Study; PRO, patient-reported outcome; PtGA: Patient Global Assessment of disease activity; SE: standard error; VAS: visual analogue scale.

At month 3, significantly greater proportions of patients reported clinically meaningful improvements from baseline in HAQ-DI (\geq MCID; ≥ 0.22 -point improvement from baseline) in both tofacitinib groups versus placebo ($p < 0.0001$; Table II). These proportions were sustained through months 12 and 24 in both tofacitinib 5 and 10 mg BID groups; in addition, the proportion of patients reporting clinically meaningful improvements increased in both placebo groups following advancement to tofacitinib (Table II).

Treatment with tofacitinib 10 mg BID resulted in numerically greater LSM changes in HAQ-DI (Fig. 3A), higher proportions of patients reporting clinically meaningful improvements at month 3, and lower NNTs (3.2 vs. 5.1), than tofacitinib 5 mg BID (Table II). By month 24, normative HAQ-DI scores (≤ 0.25 ; Suppl. Fig. 2A) were reported by 28.9% of patients receiving tofacitinib 5 mg BID and 39.0% of patients receiving 10 mg BID, while functional remission (HAQ-DI < 0.5 ; Suppl. Fig. 2B) was reported by 33.6%

and 46.8% of patients receiving tofacitinib 5 and 10 mg BID, respectively. In comparison, at month 24, \geq -normative values were reported by 31.5% of placebo→tofacitinib 5 mg BID patients and 50.0% of placebo→tofacitinib 10 mg BID patients, while functional remission was reported by 38.9% and 53.8% of patients, respectively. Full details are shown in Supplementary Figure 2.

Patient Global Assessment of disease activity

At month 3, patients receiving tofacitinib

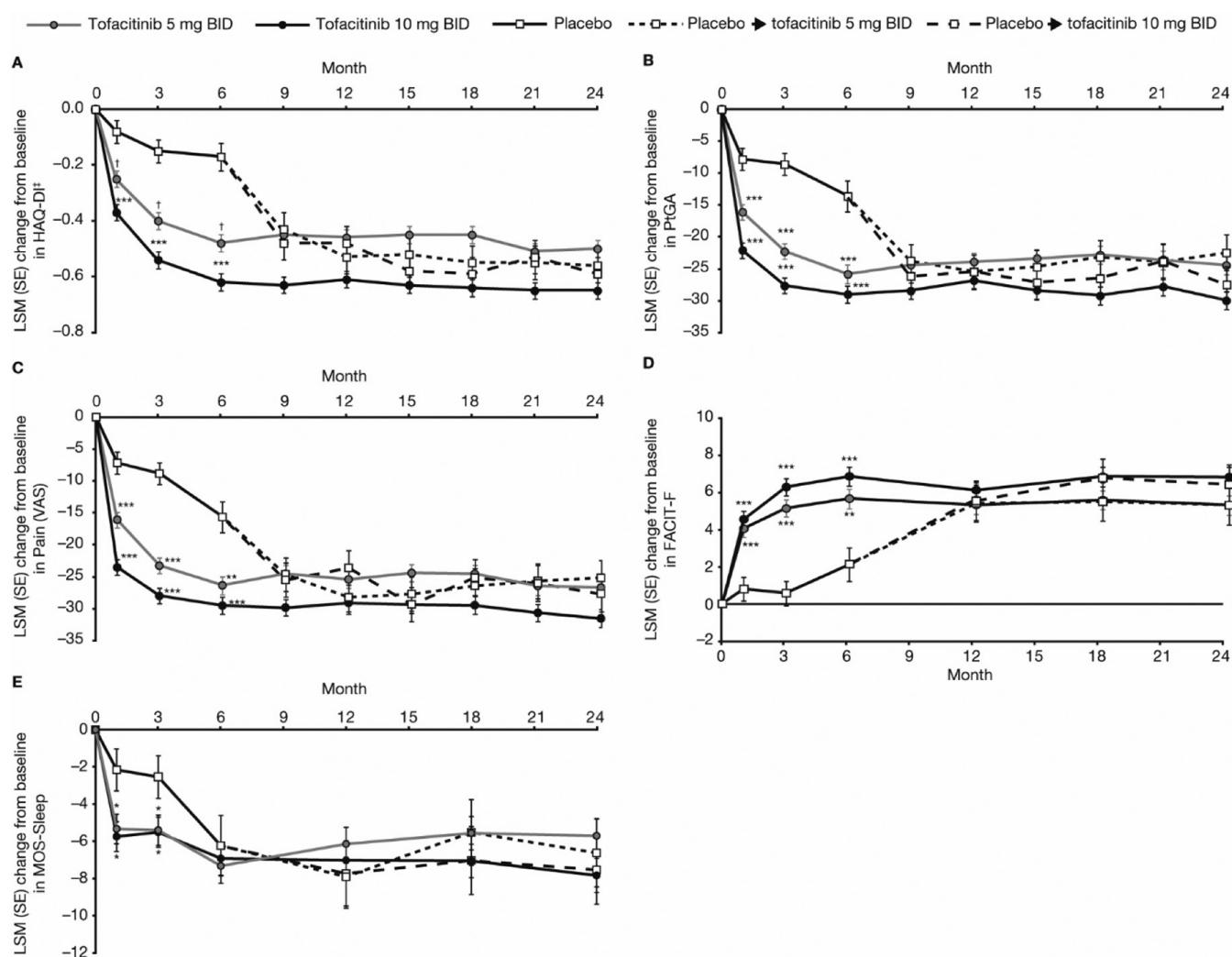


Fig. 3. LSM change from baseline in (A) HAQ-DI, (B) PtGA (VAS), (C) Pain (VAS), (D) FACIT-F and (E) MOS-Sleep, through month 24 (FAS, longitudinal model).

* $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$ vs. placebo. †Significance was not declared for tofacitinib 5 mg BID due to the step-down method. ‡LSM change from baseline in HAQ-DI at months 0–12, and significance versus placebo, were reported previously (10) and are presented here for comparison. All patients received background methotrexate, including those in the placebo groups.

BID: twice daily; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; LSM: least squares mean; MOS: Medical Outcomes Study; PtGA: Patient Global Assessment of disease activity; SE: standard error; VAS: visual analogue scale.

5 or 10 mg BID reported statistically significant ($p < 0.0001$) improvements from baseline in PtGA compared with placebo (Fig. 2B), sustained through 24 months; similar changes were reported in the placebo groups following advancement to tofacitinib (Fig. 3B). A significantly ($p < 0.0001$) higher proportion of patients reported improvements (\geq MCID; ≥ 10 mm improvement from baseline) in PtGA with both tofacitinib doses compared with placebo at month 3, again, sustained at months 12 and 24 and increased in the placebo groups following tofacitinib advancement (Table II). Through month 24, LSM

changes from baseline in PtGA were numerically greater in patients receiving tofacitinib 10 mg BID than tofacitinib 5 mg BID (Fig. 3B), with lower NNTs (3.1 vs. 4.2; Table II).

Pain

Patients receiving both tofacitinib doses reported significant ($p < 0.0001$) decreases in Pain versus placebo at month 3 (Fig. 2C), sustained through month 24, and similar in placebo-treated patients after advancement (Fig. 3C). The proportions of patients reporting clinically meaningful improvements (\geq MCID; ≥ 10 mm improvement from baseline)

were significantly ($p < 0.0001$) greater in both tofacitinib groups versus placebo at month 3 (Table II) and sustained at months 12 and 24, and increased in placebo \rightarrow tofacitinib patients after advancement (Table II). LSM changes from baseline (Fig. 3C) and percentages of patients reporting changes \geq MCID at month 3 were numerically greater with tofacitinib 10 mg BID than 5 mg BID, with lower NNTs (3.1 vs. 3.7; Table II).

Health-related quality of life (SF-36)

Through month 3, significantly ($p < 0.05$) greater proportions of patients receiv-

Table II. Months 3, 12 and 24 \geq MCID outcomes and NNTs[‡] for month 3 comparison *versus* placebo (FAS, no imputation).

PRO measure [MCID value] % patients reporting \geq MCID	Month 3			Month 12				Month 24			
	Tofacitinib 5 mg BID (n=294)	Tofacitinib 10 mg BID (n=300)	Placebo (n=146)	Tofacitinib 5 mg BID (n=251)	Tofacitinib 10 mg BID (n=265)	Placebo→ tofacitinib 5 mg BID (n=67)	Placebo→ tofacitinib 10 mg BID (n=63)	Tofacitinib 5 mg BID (n=210)	Tofacitinib 10 mg BID (n=218)	Placebo→ tofacitinib 5 mg BID (n=54)	Placebo→ tofacitinib 10 mg BID (n=52)
HAQ-DI \geq MCID [-0.22]	62.6***	74.0***	43.2	70.1	77.4	71.6	66.7	69.1	80.3	79.6	69.2
NNT	5.1	3.2									
PtGA (VAS) \geq MCID [-10]	67.1****	75.9**** ¹	43.2	69.4 [§]	74.2 [§]	74.6	66.7	70.0	78.3 [§]	70.4	73.1
NNT	4.2	3.1									
Pain (VAS) \geq MCID [-10]	69.2****	73.7****	41.8	73.0 [§]	72.8	77.6	69.8	74.8	78.9	81.5	69.2
NNT	3.7	3.1									
SF-36 domains											
PF \geq MCID [5.0]	44.9*	55.0***	30.8	49.0	55.1	58.2	49.2	53.3	57.3	59.3	59.6
NNT	7.1	4.1									
RP \geq MCID [5.0]	47.6**	54.7***	30.8	51.4	56.1 [§]	55.2	47.6	52.6 ^{‡‡}	59.2	50.0	48.1
NNT	6.0	4.2									
BP \geq MCID [5.0]	53.1***	62.0***	28.8	60.2	59.6	61.2	61.9	56.7	67.4	57.4	61.5
NNT	4.1	3.0									
GH \geq MCID [5.0]	45.7****	48.0***	25.3	44.6	49.4	52.2	46.0	41.2 ^{‡‡}	45.9	53.7	36.5
NNT	4.9	4.4									
VT \geq MCID [5.0]	55.8***	52.7***	32.9	55.4	50.6	59.7	52.4	56.7	56.0	57.4	51.9
NNT	4.4	5.1									
SF \geq MCID [5.0]	55.8*	56.7*	40.4	57.4	60.0	68.7	49.2	59.1	58.7	63.0	53.9
NNT	6.5	6.2									
RE \geq MCID [5.0]	42.9*	48.7***	29.5	45.0	51.1 [§]	49.3	44.4	48.3 ^{‡‡}	54.1	42.6	44.2
NNT	7.5	5.2									
MH \geq MCID [5.0]	47.6**	50.3***	30.1	49.4	48.3	44.8	46.0	46.7	50.9	50.0	44.2
NNT	5.7	5.0									
SF-36 component scores											
PCS \geq MCID [2.5],	67.6****	71.7***	43.8	71.3	74.6 [§]	83.6	68.3	69.7 ^{‡‡}	76.2	75.9	67.3
NNT	4.2	3.6									
MCS \geq MCID [2.5],	51.9**	56.7**	39.0	55.8	54.9 [§]	59.7	57.1	53.9 ^{‡‡}	56.0	57.4	50.0
NNT	7.8	5.7									
Fatigue (FACIT-F) \geq MCID [4],	56.8***	59.1**** ^{§§}	33.8 ^{§§}	59.2 ^{§§}	58.7 [§]	55.2	60.7 ^{‡‡‡}	54.8 ^{‡‡}	60.0 ^{***}	48.2	58.8 ^{‡‡‡}
NNT	4.3	4.0									

* $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$ vs. placebo. [‡]NNT values are *versus* placebo only and are therefore not presented post-month 3. [•]n=295. ¹n=299. [§]n=252. [§]n=264. [§]n=217. ^{‡‡}n=209. ^{‡‡‡}n=293. ^{‡‡‡‡}n=208. ^{‡‡‡‡‡}n=298. ^{‡‡‡‡‡‡}n=145. ^{‡‡‡‡‡‡‡}n=250. ^{‡‡‡‡‡‡‡‡}n=61. ^{‡‡‡‡‡‡‡‡‡}n=215. ^{‡‡‡‡‡‡‡‡‡‡}n=51.

All patients received background methotrexate, including those in the placebo groups.

BID: twice daily; BP: bodily pain; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FAS: full analysis set; GH: general health; HAQ-DI: Health Assessment Questionnaire-Disability Index; MCID: minimum clinically important difference; MCS: Mental Component Summary; MH: mental health; NNT: number needed to treat; Pain: Patient Assessment of Arthritis Pain; PCS: Physical Component Summary; PF: physical functioning; PRO: patient-reported outcome; PtGA: Patient Global Assessment of disease activity; RE: role-emotional; RP: role-physical; SF: social functioning; SF-36: Short Form-36 Health Survey (version 2, Acute); VAS: visual analogue scale; VT: vitality.

ing tofacitinib reported improvements (\geq MCID; ≥ 2.5 -point improvement) in PCS and MCS scores *versus* placebo (Table II). NNTs were lower for tofacitinib 10 mg BID *versus* tofacitinib 5 mg BID for both PCS and MCS scores: 3.6 *versus* 4.2, and 5.7 *versus* 7.8, respectively. The proportion of patients with clinically meaningful improvements in

PCS and MCS scores were generally maintained from month 12 to month 24, in all four sequences, with the exception of modest decreases in PCS score at month 24 with placebo→tofacitinib 5 mg BID, and in MCS score with placebo→tofacitinib 10 mg BID. Across all SF-36 domains, treatment with tofacitinib 5 and 10 mg BID result-

ed in significant improvements ($p < 0.05$) *versus* placebo at month 3 (Table II), with scores across all domains approaching US age- and gender-matched normative scores by month 24 (Fig. 1). Significantly more ($p < 0.05$) tofacitinib-treated patients reported clinically meaningful improvements (\geq MCID; ≥ 5 -point improvement) *versus* placebo

at month 3 across all SF-36 domain scores (Table II), sustained in both tofacitinib groups at months 12 and 24, and increased in placebo→tofacitinib patients after advancement (Table II). At month 3, a higher percentage of patients receiving tofacitinib 10 mg BID than 5 mg BID reported clinically meaningful changes across all SF-36 domains except vitality, with lower NNTs (Table II).

FACIT-F and MOS-Sleep

Through month 3, patients receiving tofacitinib 5 and 10 mg BID reported significant LSM changes from baseline *versus* placebo in FACIT-F (both $p < 0.0001$) and MOS-Sleep scores (both $p < 0.05$; Fig. 2D-E), which were generally sustained through month 24 (Fig. 3D-E). Once placebo→tofacitinib patients were advanced, they reported generally similar improvements in FACIT-F and MOS-Sleep scores at month 24 to patients who had received tofacitinib throughout the study. A significantly ($p < 0.0001$) greater proportion of tofacitinib- *versus* placebo-treated patients reported clinically meaningful improvements (\geq MCID; 4-point improvement) in FACIT-F at month 3, maintained at months 12 and 24, and increased in placebo→tofacitinib patients, once receiving tofacitinib (Table II). Patients receiving tofacitinib 10 mg BID reported numerically greater LSM changes in FACIT-F (Fig. 2D), with higher proportions of patients with clinically meaningful improvements \geq MCID than tofacitinib 5 mg BID, and lower NNTs (4.0 *vs.* 4.3; Table II).

At baseline, the proportion of patients reporting scores \geq -normative FACIT-F values (≥ 43.5 [≥ 40.1]) were higher for placebo→tofacitinib 5 mg BID (17.7% [20.3%]) and placebo→tofacitinib 10 mg BID patients (15.8% [23.7%]) compared with patients receiving tofacitinib 5 and 10 mg BID (9.5% [13.7%] and 9.4% [15.3%], respectively). However, at month 3, tofacitinib 5 and 10 mg BID groups demonstrated larger increases in proportions of patients reporting scores \geq normative values (19.3% [31.2%] and 27.3% [38.7%], respectively) than placebo→tofacitinib 5 and 10 mg BID (9.3% [14.7%] and

18.3% [26.8%]). After month 6, all patients were receiving tofacitinib, and at month 12 the proportion of patients with scores \geq -normative FACIT-F values in the placebo→tofacitinib 5 and 10 mg BID sequences (29.9% [34.3%] and 32.3% [40.3%], respectively) met or exceeded tofacitinib 5 or 10 mg BID patients (21.5% [33.5%] and 25.7% [36.6%]). Similar data were reported at month 24, proportions of patients in placebo→tofacitinib 5 and 10 mg BID sequences were generally higher (33.3% [38.9%] and 42.3% [50.0%], respectively) compared with tofacitinib 5 and 10 mg BID (24.9% [36.8%] and 32.4% [44.0%]).

Discussion

In the 24-month, Phase 3 ORAL Scan study, MTX-IR patients with RA receiving tofacitinib 5 or 10 mg BID (plus MTX) reported statistically significant and clinically meaningful improvements in PROs at month 3 compared with placebo, maintained through 24 months of treatment. After advancing to tofacitinib at months 3 or 6, patients initially treated with placebo generally reported improvements of a similar magnitude at month 24 to patients' initially assigned tofacitinib. LSM changes from baseline in PROs were generally numerically greater with tofacitinib 10 mg BID than 5 mg BID, with correspondingly lower NNTs.

Results presented here reflect the early onset of efficacy and sustained benefits observed with tofacitinib treatment across Phase 3 trials in DMARD-IR and MTX-naïve populations (7-12). Similar to previous RCTs investigating the effect of tofacitinib on PROs, this patient population reported a significant burden of disease in HRQoL at baseline, compared with a US age- and gender-matched normative population as a benchmark. HRQoL was significantly improved with tofacitinib *versus* placebo at months 3 and 24, with scores approaching those of an age- and gender-matched US normative population. Previous tofacitinib trials have evaluated the effect of tofacitinib on PROs through 6, 12 and 24 months in patients with inadequate responses to DMARDs (16, 20), MTX (17), tumour necrosis factor inhibitors (19),

and those naïve to MTX (18), all of whom reported similar improvements in HRQoL to values presented here. Although PROs for different patient populations receiving tofacitinib have previously been evaluated (16-20), the key findings of the ORAL Scan study demonstrate a maintenance of clinical efficacy with tofacitinib 5 and 10 mg BID, in addition to improvements in physical markers of disease, including inhibition of structural damage with tofacitinib 10 mg BID. Furthermore, the data reported here show that improvements in non-clinical outcomes that are important to patients, including physical function, fatigue and pain, are also maintained. Taken together these findings support a holistic improvement with tofacitinib plus background MTX, through 2 years.

Findings of ORAL Scan also bolster our increasingly comprehensive understanding of the benefits and risks of RA treatments (28). For context, generally similar ameliorations of impaired HRQoL were reported in RCTs with certolizumab and sarilumab in MTX-IR RA patients (29-31), adalimumab in MTX-naïve RA patients (32) and tocilizumab and sarilumab in RA patients with IR to tumour necrosis factor inhibitors (33, 34). However, differences between study designs preclude direct comparisons between PROs in different trials.

Aside from the clinical, physical and functional effects of RA on patients' lives, RA is also associated with fatigue, depressed mood, and sleep disturbances (2, 3). Following treatment with tofacitinib, statistically significant and clinically meaningful improvements *versus* placebo were reported across all SF-36 domains at month 3, including MCS and PCS scores, indicating that tofacitinib treatment positively impacts patients' social, emotional and mental wellbeing. Furthermore, tofacitinib treatment resulted in significant improvements from baseline *versus* placebo in fatigue and sleep scores, and 48–61% of patients reported clinically meaningful improvements in FACIT-F through month 24. These data indicate that tofacitinib treatment not only results in clinical efficacy and improved physical function in RA, but also positively impacts

overall HRQoL and social, emotional and mental wellbeing, which are of high importance to patients.

The safety profile and tolerability of tofacitinib 5 and 10 mg BID through 24 months in ORAL Scan have been reported elsewhere (21) and were consistent with the month 12 analysis (10). Although improvements in PROs were reported to month 24, direct comparison with all placebo-treated patients beyond month 3 was not possible due to the short duration of placebo treatment. Limited exposure to placebo at early time points, or termination of the control arm, present a challenge when comparing longer- and shorter-term data, and are a limitation of this type of analysis. Additionally, there is the potential for bias with longer-term data, as there is a tendency for responders to have a higher likelihood of remaining in the trial. Therefore, this may impact upon the generalisability of these data as only treatment responders are likely to continue through to the study end.

In summary, in MTX-IR patients with RA who were receiving tofacitinib plus background MTX, all evaluated PRO endpoints were improved at month 3, compared with placebo and generally sustained through the 24-month study period; both in patients initially randomised to tofacitinib, and those who advanced to tofacitinib following placebo. Tofacitinib treatment decreased the broad burden of RA, reflected in improvements in physical functioning, pain, fatigue and all aspects of HRQoL.

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Data sharing

Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programmes that have been terminated (*i.e.* development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Disclosure of previous presentation of data and other relevant publications

Twelve-month data from this study have been published in a peer-reviewed journal, and 24-month data were reported at the 2012 American College of Rheumatology Annual Meeting:

VAN DER HEIJDE D, TANAKA Y, FLEISCHMANN R, KEYSTONE E, KREMER J, ZERBINI CAF *et al.*: ORAL Scan Investigators. Tofacitinib (CP-690, 550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomised radiographic study. *Arthritis Rheum* 2013; 65: 559-70.

A manuscript presenting 24-month analysis of efficacy and safety data from this study (endpoints which are not contained within this submission) has been published:

VAN DER HEIJDE D, STRAND V, TANAKA Y, KEYSTONE E, KREMER J, ZERBINI CAF *et al.*: Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic and safety outcomes from the 24-month Phase 3 ORAL Scan study. *Arthritis Rheum* 2019; 71: 878-89.

Competing interests

V. Strand has received consultancy fees, speaking fees and/or honoraria from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Corrona, Crescendo, Eli Lilly, EMD Serono, Genentech, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer Inc, Regeneron, Roche, Samsung, Sandoz, Sanofi and UCB.

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J. Kremer has received consultancy fees and/or honoraria from AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly, Genentech, Novartis and Pfizer Inc; and is an employee and shareholder at Corrona.

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D. Gruben, and C.A. Connell are employees and shareholders of Pfizer Inc. G. Wallenstein is a shareholder of Pfizer Inc, and was an employee of Pfizer Inc at the time of the analysis.

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