

ORIGINAL RESEARCH

The effect of tofacitinib on residual pain in patients with rheumatoid arthritis and psoriatic arthritis

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To cite: Dougados M, Taylor PC, Bingham III CO, *et al.* The effect of tofacitinib on residual pain in patients with rheumatoid arthritis and psoriatic arthritis. *RMD Open* 2022;**8**:e002478. doi:10.1136/rmdopen-2022-002478

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2022-002478>).

This manuscript is based on work previously presented at the EULAR 2022 Annual Congress.²⁹

Received 19 May 2022
Accepted 1 August 2022



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ABSTRACT

Objective Post hoc analysis of pooled data from nine randomised controlled trials to assess the effect of tofacitinib (oral Janus kinase inhibitor for treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA)) on residual pain in patients with RA or PsA with abrogated inflammation.

Methods Patients who received ≥ 1 dose of tofacitinib 5 mg twice daily, adalimumab or placebo with/without background conventional synthetic disease-modifying antirheumatic drugs and had abrogated inflammation (swollen joint count (SJC)=0 and C reactive protein (CRP)<6 mg/L) after 3 months' therapy were included. Assessments included Patient's Assessment of Arthritis Pain at month 3 (Visual Analogue Scale [VAS] 0–100 mm). Scores were summarised descriptively; treatment comparisons assessed by Bayesian network meta-analyses (BNMA).

Results From the total population with RA/PsA, 14.9% (382 of 2568), 17.1% (118 of 691) and 5.5% (50 of 909) of patients receiving tofacitinib, adalimumab and placebo, respectively, had abrogated inflammation after 3 months' therapy. Patients with RA/PsA with abrogated inflammation receiving tofacitinib/adalimumab had higher baseline CRP versus placebo; patients with RA receiving tofacitinib/adalimumab had lower SJC and longer disease duration versus placebo. Median residual pain (VAS) at month 3 was 17.0, 19.0 and 33.5 in patients with RA treated with tofacitinib, adalimumab or placebo, and 24.0, 21.0 and 27.0 in patients with PsA, respectively. Residual pain reductions with tofacitinib/adalimumab versus placebo were less prominent in patients with PsA versus patients with RA, with no significant differences between tofacitinib/adalimumab, per BNMA.

Conclusion Patients with RA/PsA with abrogated inflammation receiving tofacitinib/adalimumab had greater residual pain reduction versus placebo at month 3. Results were similar between tofacitinib and adalimumab.

Trial registration number ClinicalTrials.gov registry (NCT00960440; NCT00847613; NCT00814307; NCT00856544; NCT00853385; NCT01039688; NCT02187055; NCT01877668; NCT01882439).

INTRODUCTION

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are chronic, immune-mediated

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Phase 3 randomised controlled trials have shown that patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA) treated with tofacitinib report improvements in pain, compared with placebo.
- ⇒ Many patients who have achieved low disease activity or remission continue to report 'residual pain'.

WHAT THIS STUDY ADDS

- ⇒ This post hoc analysis of patients with RA or PsA showed that in patients with abrogated inflammation, treatment with tofacitinib or adalimumab reduced the level of residual pain at 3 months, compared with placebo.
- ⇒ Network meta-analyses showed no differences in the level of residual pain reduction between tofacitinib and adalimumab.
- ⇒ These results suggest that tofacitinib and adalimumab may have analgesic effects beyond those associated with a reduction in inflammation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The analgesic effects of tofacitinib and adalimumab may be of use for the treatment of residual pain symptoms in patients with RA/PsA who have achieved an abrogation of inflammation.

inflammatory diseases of the musculoskeletal system.^{1–3} RA is typically characterised by systemic inflammation, persistent synovitis and potential articular destruction.¹ Key manifestations of PsA are peripheral arthritis, psoriasis (including nail lesions), axial disease, enthesitis and dactylitis.^{2,3}

Pain is one of the most common symptoms in patients with RA or PsA and is considered by patients to be the most important and highest priority domain.^{4–6} It is one of the main pillars of inflammation (along with redness, swelling, warmth and loss of function),⁷ and, consequently, the presence of pain during inflammatory phases of chronic immune-mediated diseases is well characterised. With

disease progression, pain can also arise as a result of structural damage within the joint,⁸ potentially due to the development of secondary osteoarthritis.⁹ However, a substantial percentage of patients who have achieved low disease activity or remission continue to report 'residual pain', even in the absence of structural damage.^{10–12}

The presence of residual pain despite abrogation of inflammation suggests that additional non-inflammatory processes might contribute,¹⁰ but the underlying mechanisms of pain are not well understood. It has been hypothesised that microglial-derived central sensitisation (investigated in a rodent model)¹³ and concomitant fibromyalgia¹⁴ may have roles in arthritis pain. In addition, a potential deleterious structural impact of local inflammation on peripheral nerve endings may promote hyperalgesia at affected joints.¹⁵ Tumour necrosis factor (TNF) and interleukin-6 have been shown to affect pain thresholds in animal models of arthritis,^{16 17} and vitamin D deficiency has been linked to increased neuropathic pain in patients with RA.¹⁸ These findings suggest that, in the absence of inflammation, other mechanisms could contribute to residual pain.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA and PsA. The efficacy and safety of tofacitinib have been demonstrated in phase 3 and phase 3/4b randomised controlled trials (RCTs) in patients with RA who either showed inadequate responses to a prior disease-modifying antirheumatic drug (DMARD) or TNF inhibitor (TNFi), or were naïve/inadequate responders to methotrexate.^{19–25} Two phase 3 RCTs of patients with active PsA with inadequate responses to a conventional synthetic (cs)DMARD or TNFi have also shown the efficacy and safety of tofacitinib.^{26 27} Previous analyses have shown that patients with RA or PsA with either an inadequate response to csDMARDs or TNFi receiving tofacitinib report similar improvements in pain, compared with placebo.²⁸ This post hoc analysis assessed the effect of tofacitinib, administered at a dose of 5 mg twice daily, on residual pain in patients with RA and PsA who had an abrogation of inflammation (defined as swollen joint count (SJC)=0 and C reactive protein (CRP) <6 mg/L).²⁹

METHODS

Study design and patients

This post hoc analysis used pooled data from six phase 3 RCTs and one phase 3/4b RCT of patients with RA: ORAL Step (NCT00960440),¹⁹ ORAL Scan (NCT00847613),²⁰ ORAL Solo (NCT00814307),²¹ ORAL Sync (NCT00856544),²² ORAL Standard (NCT00853385),²³ ORAL Start (NCT01039688)²⁴ and ORAL Strategy (NCT02187055).²⁵ In addition, pooled data from two phase 3 RCTs of patients with PsA, OPAL Broaden (NCT01877668)²⁶ and OPAL Beyond (NCT01882439),²⁷ were included. Patients with RA or PsA were randomised to receive either tofacitinib 5 or 10 mg twice daily, or placebo, either as a monotherapy or with concomitant csDMARD therapy. In RCTs in patients with PsA, patients

received therapy with a single csDMARD. Adalimumab (40 mg subcutaneously every 2 weeks) was included as a treatment arm in two RCTs in patients with RA (ORAL Standard and ORAL Strategy) and in one RCT of patients with PsA (OPAL Broaden). Only ORAL Strategy was designed to perform non-inferiority and superiority comparisons between tofacitinib and adalimumab.

In this analysis, data were included from patients who received at least one dose of the study drug and who achieved an abrogation of inflammation after 3 months of therapy, defined as SJC=0 (66-joint count) and CRP <6 mg/L. As a substantial number of patients included were from ORAL Strategy, which studied tofacitinib 5 mg twice daily only, patients who received tofacitinib 10 mg twice daily in the RCTs were excluded. Patients who received analgesic (non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, opioids or paracetamol) and/or corticosteroid (≤ 10 mg/day of prednisone or equivalents) treatment prior to enrolment were required to remain on the stable baseline dose; however, dose adjustments for safety reasons were permitted at the discretion of the investigator.

Assessments

The primary endpoint of this analysis was the Patient's Assessment of Arthritis Pain at month 3. Patients assessed the severity of their arthritis pain in response to the statement 'My pain at this time is' using a Visual Analogue Scale (VAS), ranging from 0 ('no pain') to 100 mm ('most severe pain'). Key secondary endpoints were: the proportion of patients with at least a 50% decrease in Patient's Assessment of Arthritis Pain at month 3 compared with baseline; the proportion of patients with Patient's Assessment of Arthritis Pain <20 at month 3; and the proportion of patients with Patient's Assessment of Arthritis Pain <30 at month 3.

Statistical analysis

Demographics and disease characteristics were described by treatment group overall and separately for RA and PsA study populations. Treatment effects were summarised for all outcomes, and inferential methods were used to analyse primary and secondary endpoints at month 3.

Traditional meta-analyses focus on pairwise direct comparisons of treatments which do not permit inferences about the comparative effectiveness of more than two interventions, unless all have been compared directly in head-to-head trials. A network meta-analysis can be used to estimate the relative efficacy of many competing interventions by analysing the evidence from direct and indirect comparisons simultaneously. A Bayesian network meta-analysis (BNMA) was chosen, as it uses direct interpretation and probabilistic estimates for modelling and decision-making. BNMA, based on individual patient-level data, was used to perform mixed-treatment comparisons (combining direct and indirect comparisons) and to estimate comparative efficacy between tofacitinib 5 mg twice daily, adalimumab and placebo. The analyses

were adjusted for the following covariates: disease (RA/PsA); sex; age; disease duration; baseline measurements (Patient's Assessment of Arthritis Pain, Psoriasis Area and Severity Index (PASI) (not performed and defaulted to 0 for all patients with RA and for those patients with PsA if <3% of their body surface area was affected at baseline)) and concomitant treatments at month 3 (corticosteroid, analgesic and methotrexate).

In fixed-effects BNMA, one assumes that there is one common effect. However, random-effects BNMA assumes that each study has a different underlying true effect, and these effects are related. In this analysis, fixed-effects BNMA is reasonable as the studies are homogeneous clinically and methodologically, justifying the assumption of common effect, and the number of studies for each comparison is small to estimate between trial heterogeneity. Therefore, fixed-effects BNMA was used for the analysis of primary and secondary endpoints. Unlike with traditional BNMA, the primary endpoint did not follow a normal distribution; therefore, several candidate parametric distributions were investigated to find the appropriate model for BNMA. Based on the deviance information criterion and clinical interpretability of the model estimates, a truncated Laplace distribution showed an optimal fit (online supplemental table 1). A logistic regression model was used for the secondary endpoints with binary outcomes. Populations with RA and PsA were individually investigated using the same methodology but excluding disease from the list of covariates. Posterior means and 95% credible intervals (CrIs) for comparative efficacy measures (eg, mean difference, risk difference)

between tofacitinib 5 mg twice daily, adalimumab and placebo were reported, along with the posterior probability of a larger pain reduction (ie, the updated probability for each efficacy measure of interest, given the collected data). Non-informative priors for model parameters were used for the BNMA. Further details of the model and prior specifications are provided in the online supplemental materials.

RESULTS

Patients

Pooled data from nine RCTs (4168 patients) were included in this analysis: 3588 patients with RA and 580 patients with PsA. Adalimumab was an active treatment in two RCTs of patients with RA (ORAL Standard and ORAL Strategy) and in one RCT of patients with PsA (OPAL Broaden) (online supplemental table 2). Only ORAL Strategy was designed to perform non-inferiority and superiority comparisons between tofacitinib and adalimumab.

An abrogation of inflammation (SJC=0 and CRP <6 mg/L) after 3 months of therapy was achieved in 14.1% (328 of 2330), 14.9% (87 of 585) and 3.0% (20 of 673) of patients with RA who received tofacitinib 5 mg twice daily, adalimumab and placebo, respectively (figure 1 and online supplemental table 2). In patients with PsA, an abrogation of inflammation after 3 months of therapy occurred in 22.7% (54 of 238), 29.2% (31 of 106) and 12.7% (30 of 236) of patients who received tofacitinib

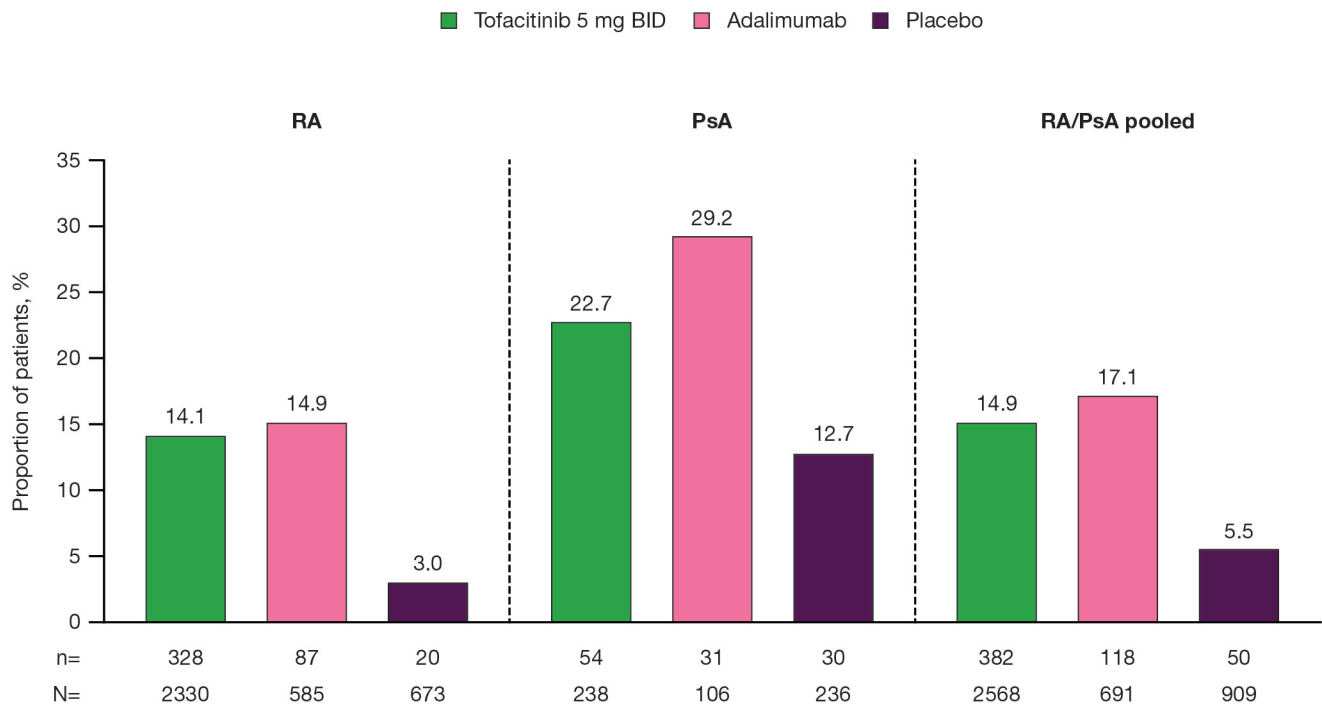


Figure 1 Proportion of patients with an abrogation of inflammation^a after 3 months of therapy by indication. ^aAn abrogation of inflammation was defined as SJC=0 and CRP <6 mg/L. BID, twice daily; CRP, C-reactive protein; N, number of patients evaluated; n, number of patients with an abrogation of inflammation after 3 months of therapy; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SJC, swollen joint count.

5mg twice daily, adalimumab and placebo, respectively (figure 1 and online supplemental table 2).

Patient demographics and baseline disease characteristics of patients who achieved an abrogation of inflammation after 3 months of therapy were generally similar across treatment groups (table 1). In the RA and PsA groups, a lower percentage of women received tofacitinib and adalimumab versus placebo (table 1). Patients with RA in the tofacitinib and adalimumab groups had longer disease duration than those in the placebo group. In patients with PsA, those receiving tofacitinib had longer disease duration than those receiving adalimumab and placebo (table 1). In patients with RA and PsA, median levels of baseline CRP were higher in the tofacitinib and adalimumab groups than in the placebo group. Patients with RA receiving tofacitinib and adalimumab had lower SJC compared with patients in the placebo group. In patients with RA, the median pain score (VAS) was lower in the tofacitinib and adalimumab groups than in the placebo group; patients with PsA in the tofacitinib group had a higher pain score compared with the adalimumab and placebo groups (table 1).

A lower proportion of patients with RA in the tofacitinib 5mg twice daily group were receiving concomitant corticosteroids, compared with the adalimumab and placebo groups. In patients with RA/PsA, a higher proportion of patients in the tofacitinib 5mg twice daily group were receiving concomitant analgesics, compared with the adalimumab and placebo groups (table 1).

Assessment of arthritis pain

At month 3, in patients with RA, Patient's Assessment of Arthritis Pain (VAS; median score (Q1, Q3)) was 17.0 (6.0, 31.0) with tofacitinib, 19.0 (7.0, 31.0) with adalimumab and 33.5 (7.0, 48.0) with placebo (figure 2A). Similar observations were observed in the pooled RA/PsA cohort (figure 2A). In patients with RA, the posterior mean (95% CrI) and probability showed strong evidence of a pain reduction for tofacitinib versus placebo (−9.85 (−19.65 to 0.98) and 0.965, respectively). Similar results were obtained with adalimumab versus placebo. The posterior mean (95% CrI) and probability of a larger pain reduction with tofacitinib over adalimumab were −0.42 (−4.91 to 4.18) and 0.571, respectively (figure 2B). Overall, results were similar in the pooled RA/PsA cohort. In patients with PsA, Patient's Assessment of Arthritis Pain (VAS; median score (Q1, Q3)) was 24.0 (8.0, 44.0) with tofacitinib, 21.0 (9.0, 49.0) with adalimumab and 27.0 (8.0, 52.0) with placebo (figure 2A). The posterior mean (95% CrI) and probability showed weak evidence of a larger pain reduction for tofacitinib versus placebo (−2.26 (−14.06 to 9.66) and 0.650, respectively) (figure 2B). Similar results were obtained with adalimumab versus placebo. The posterior mean (95% CrI) and probability of a larger pain reduction between tofacitinib and adalimumab were −0.22 (−12.12 to 12.05) and 0.520, respectively (figure 2B).

At month 3, the proportion of patients with RA with at least a 50% decrease in arthritis pain at month 3 compared with baseline was higher with tofacitinib (67.4%) and adalimumab (65.1%) treatment versus placebo (40.0%); results for the pooled RA/PsA cohort were similar (figure 3A). In patients with PsA, 57.4% and 50.0% treated with tofacitinib and adalimumab, respectively, experienced at least a 50% decrease in arthritis pain, compared with 40.0% treated with placebo (figure 3A). The posterior mean (95% CrI) and probability of larger proportion of patients with a decrease of at least 50% in arthritis pain at month 3 in patients with RA were 24.0% (4.6% to 48.5%) and 0.993, respectively, for tofacitinib versus placebo. Similar results were observed for adalimumab versus placebo. The posterior mean (95% CrI) and probability values were −5.1% (−19.8% to 8.7%) and 0.235, respectively, for tofacitinib versus adalimumab. In patients with PsA, the posterior mean (95% CrI) and probability were −4.1% (−31.4% to 21.4%) and 0.366 for tofacitinib versus placebo; 10.0% (−20.3% to 43.9%) and 0.762 for adalimumab versus placebo; and −14.1% (−48.1% to 13.1%) and 0.155 for tofacitinib versus adalimumab (figure 3B).

The proportion of patients with Patient's Assessment of Arthritis Pain <20 was higher in patients with RA receiving tofacitinib (55.7%) or adalimumab (51.7%) versus placebo (40.0%); results were similar in the pooled RA/PsA cohort (figure 3C). In patients with PsA, 46.3% and 48.4% treated with tofacitinib and adalimumab, respectively, reported Patient's Assessment of Arthritis Pain <20, compared with 33.3% treated with placebo (figure 3C). The posterior mean (95% CrI) and probability of a larger proportion of patients achieving Patient's Assessment of Arthritis Pain <20 at month 3 in patients with RA were 17.9% (−2.7% to 49.7%) and 0.941, respectively, for tofacitinib versus placebo. Similar results were observed for adalimumab versus placebo. The posterior mean (95% CrI) and probability values were 0.2% (−8.6% to 8.9%) and 0.526, respectively, for tofacitinib versus adalimumab. In patients with PsA, the posterior mean (95% CrI) and probability were 9.1% (−10.1% to 37.5%) and 0.834 for tofacitinib versus placebo; 16.6% (−1.8% to 53.0%) and 0.958 for adalimumab versus placebo; and −7.5% (−36.1% to 8.8%) and 0.158 for tofacitinib versus adalimumab (figure 3D).

The percentage of patients with Patient's Assessment of Arthritis Pain <30 was higher in patients with RA receiving tofacitinib (73.2%) or adalimumab (72.4%) versus placebo (45.0%). Similar observations were reported in the pooled RA/PsA cohort (figure 3E). In patients with PsA, 61.1% and 58.1% treated with tofacitinib and adalimumab, respectively, and 53.3% treated with placebo reported Patient's Assessment of Arthritis Pain <30 (figure 3E). The posterior mean (95% CrI) and probability of a larger proportion of patients achieving pain <30 at month 3 in patients with RA were 18.1% (1.4% to 54.1%) and 0.997, respectively, for tofacitinib versus placebo. Similar results were observed for

Table 1 Baseline demographics and disease characteristics of patients who achieved an abrogation of inflammation* after 3 months of therapy

	RA (N=435)		PsA (N=115)		RA/PsA pooled data (N=550)	
	Tofacitinib 5 mg twice daily (N=328)	Adalimumab (N=87)	Placebo (N=20)	Tofacitinib 5 mg twice daily (N=54)	Adalimumab (N=31)	Placebo (N=30)
Patient demographics						
Age, years, mean±SD	50.7±12.8	49.2±13.9	44.6±9.9	51.1±11.7	47.4±11.6	49.7±11.6
Female, n (%)	259 (79.0)	67 (77.0)	18 (90.0)	24 (44.4)	11 (35.5)	21 (70.0)
Weight, kg, mean±SD	68.9±16.9	72.5±21.8	71.4±25.0	89.1±22.7	83.2±19.0	76.7±15.7
Disease duration, years, median	4.8	5.8	2.6	7.8	2.7	4.3
(Q1, Q3)	(1.4, 9.5)	(2.4, 11.1)	(1.7, 8.5)	(4.0, 14.3)	(1.0, 6.0)	(2.7, 10.0)
Disease characteristics						
CRP, mg/L, median	8.0	8.6	3.9	3.7	3.6	2.2
(Q1, Q3)	(3.6, 20.0)	(3.6, 15.7)	(1.4, 6.4)	(1.1, 9.2)	(1.2, 12.5)	(1.2, 4.5)
SJC, n, median	9.0	8.0	10.5	6.0	5.0	5.0
(Q1, Q3)	(7.0, 14.0)	(6.0, 12.0)	(9.0, 19.5)	(4.0, 10.0)	(4.0, 8.0)	(4.0, 7.0)
TJC, n, median	18.0	15.0	27.5	13.0	10.0	10.0
(Q1, Q3)	(11.0, 27.0)	(9.0, 20.0)	(16.0, 47.0)	(8.0, 20.0)	(8.0, 16.0)	(7.0, 16.0)
HAQ-DI, median	1.4	1.5	1.4	1.3	0.8	0.9
(Q1, Q3)	(1.0, 1.9)	(1.0, 1.9)	(0.7, 1.8)	(1.0, 1.8)	(0.5, 1.1)	(0.5, 1.1)
PtGA, median	57.5	56.0	66.0	60.5	49.0	46.5
(Q1, Q3)	(40.0, 75.0)	(37.0, 76.0)	(36.5, 70.5)	(50.0, 69.0)	(30.0, 62.0)	(24.0, 57.0)
Pain, VAS, median	57.0	52.5	62.0	58.0	48.0	48.5
(Q1, Q3)	(39.0, 72.7)	(35.0, 69.0)	(38.5, 67.0)	(51.0, 75.0)	(36.0, 65.0)	(21.0, 61.0)
FACIT-F, median	32.0	29.0	33.0	26.0	34.0	31.0
(Q1, Q3)	(21.0, 38.0)	(23.0, 35.0)	(23.0, 37.0)	(18.0, 33.0)	(22.0, 38.0)	(20.0, 36.0)
SF-36 PCS, median	33.7	34.4	38.0	35.3	39.4	41.3
(Q1, Q3)	(28.2, 39.1)	(29.0, 39.2)	(30.1, 41.7)	(29.5, 39.4)	(34.9, 42.6)	(34.8, 46.1)
SF-36 MCS, median	40.1	39.4	34.3	38.0	43.4	38.0
(Q1, Q3)	(32.2, 48.3)	(33.9, 47.1)	(30.2, 39.7)	(30.2, 46.3)	(38.3, 50.7)	(32.6, 48.1)
EQ-5D-3L pain/discomfort, median	2.0	2.0	2.0	2.0	2.0	2.0
(Q1, Q3)	(2.0, 2.0)	(2.0, 2.0)	(2.0, 2.0)	(2.0, 2.0)	(2.0, 2.0)	(2.0, 2.0)

Continued

Table 1 Continued

	RA (N=435)		PsA (N=115)		RA/PsA pooled data (N=550)				
	Tofacitinib 5 mg twice daily (N=328)	Adalimumab (N=87)	Placebo (N=20)	Tofacitinib 5 mg twice daily (N=54)	Adalimumab (N=31)	Placebo (N=30)	Tofacitinib 5 mg twice daily (N=382)	Adalimumab (N=118)	Placebo (N=50)
CDAI, median	33.0	32.0	37.3	-	-	-	-	-	-
(Q1, Q3)	(26.2, 43.4)	(24.3, 42.1)	(28.0, 49.0)	-	-	-	-	-	-
ESR, mm/hour, median	40.0	37.0	39.0	-	-	-	-	-	-
(Q1, Q3)	(30.0, 58.0)	(29.0, 58.0)	(27.0, 65.0)	-	-	-	-	-	-
DAS28-ESR, median	6.2	6.3	6.5	-	-	-	-	-	-
(Q1, Q3)	(5.6, 6.8)	(5.4, 6.9)	(5.6, 7.3)	-	-	-	-	-	-
PASDAS, median	-	-	-	6.0	5.5	5.1	-	-	-
(Q1, Q3)	-	-	-	(5.3, 6.6)	(4.7, 6.1)	(4.3, 6.1)	-	-	-
PASI, median	-	-	-	7.6	6.5	6.3	-	-	-
(Q1, Q3)	-	-	-	(3.2, 16.1)	(4.5, 13.1)	(3.9, 18.7)	-	-	-
Prior and concomitant treatment									
Prior TNFi, n (%)	40 (12.2)	6 (6.9)	3 (15.0)	31 (57.4)	0 (0.0)	17 (56.7)	71 (18.6)	6 (5.1)	20 (40.0)
Prior bDMARD, n (%)	48 (14.6)	9 (10.3)	3 (15.0)	31 (57.4)	0 (0.0)	17 (56.7)	79 (20.7)	9 (7.6)	20 (40.0)
Prior csDMARD, n (%)	286 (87.2)	87 (100.0)	19 (95.0)	54 (100.0)	31 (100.0)	30 (100.0)	340 (89.0)	118 (100)	49 (98.0)
Concomitant corticosteroid, n (%)	174 (53.0)	56 (64.4)	14 (70.0)	9 (16.7)	8 (25.8)	3 (10.0)	183 (47.9)	64 (54.2)	17 (34.0)
Concomitant analgesic, n (%)	247 (75.3)	62 (71.3)	14 (70.0)	40 (74.1)	19 (61.3)	19 (63.3)	287 (75.1)	81 (68.6)	33 (66.0)
*An abrogation of inflammation was defined as SJC=0 and CRP <6 mg/L. bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR, Disease Activity Score in 28 joints, erythrocyte sedimentation rate; EQ-5D-3L, EuroQol-Five Dimensions-Three Level Health Questionnaire; ESR, erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCS, Mental Component Summary; n, number of patients with characteristic; N, total number of patients; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PCS, Physical Component Summary; PsA, psoriatic arthritis; PtGA, Patient Global Assessment of Arthritis; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); RA, rheumatoid arthritis; SD, standard deviation; SF-36, Short Form-36 Health Survey; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor; VAS, Visual Analogue Scale.									

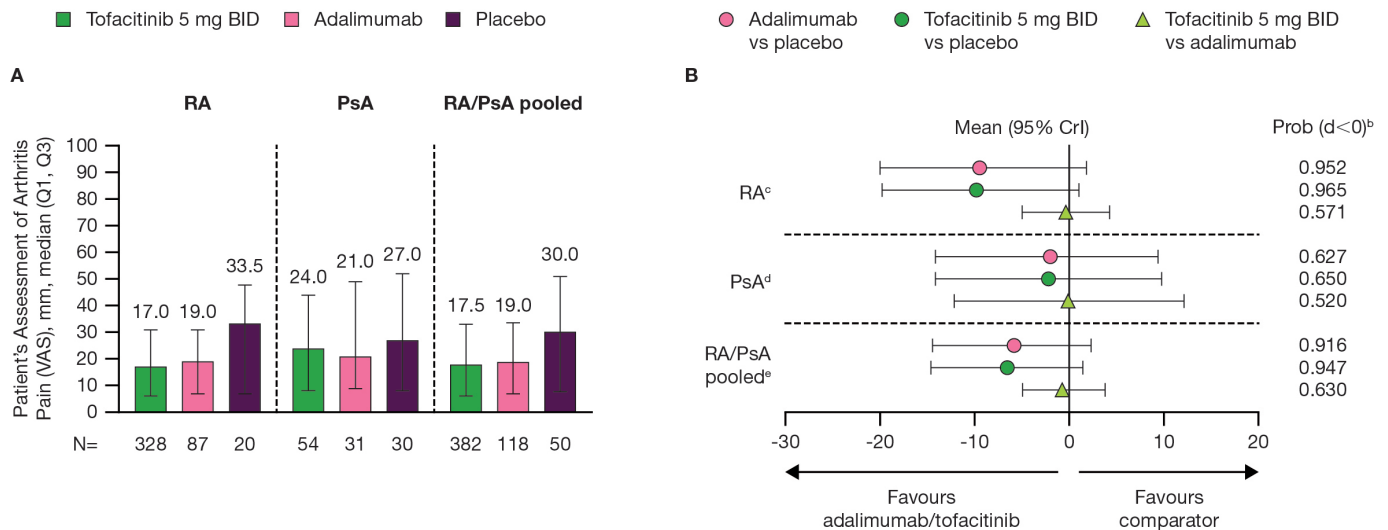


Figure 2 Patient's Assessment of Arthritis Pain in patients with an abrogation of inflammation^a after 3 months of therapy: (A) pain (VAS) scores and (B) Bayesian network meta-analysis. ^aAn abrogation of inflammation defined as SJC=0 and CRP <6 mg/L. ^bProb(d<0): posterior probability of a larger pain reduction. ^cAnalysis adjusted for age, sex, disease duration, month 0 pain, month 3 corticosteroid treatment, month 3 analgesic treatment and month 3 methotrexate treatment. ^dAnalysis adjusted for age, sex, disease duration, month 0 PASI, month 0 pain, month 3 corticosteroid treatment, month 3 analgesic treatment and month 3 methotrexate treatment. ^eAnalysis adjusted for disease, age, sex, disease duration, month 0 PASI, month 0 pain, month 3 corticosteroid treatment, month 3 analgesic treatment and month 3 methotrexate treatment. BID, twice daily; CrI, credible interval; CRP, C-reactive protein; d, difference; N, number of patients evaluated; PASI, Psoriasis Area Severity Index; Prob, probability; PsA, psoriatic arthritis; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); RA, rheumatoid arthritis; SJC, swollen joint count; VAS, Visual Analogue Scale.

adalimumab versus placebo. The posterior mean (95% CrI) and probability values were -0.7% (-5.0% to 2.0%) and 0.285, respectively, for tofacitinib versus adalimumab. In patients with PsA, the posterior mean (95% CrI) and probability were -0.7% (-15.3% to 10.9%) and 0.446 for tofacitinib versus placebo; -2.0% (-23.0% to 11.9%) and 0.368 for adalimumab versus placebo; and 1.3% (-13.2% to 20.1%) and 0.599 for tofacitinib versus adalimumab (figure 3F).

DISCUSSION

A prior post hoc analysis of RA and PsA RCTs has shown that patients receiving tofacitinib report pain improvements.²⁸ However, residual pain is frequently observed in patients with RA and PsA, despite achieving remission or low disease activity.^{10–12} This post hoc analysis assessed the effect of tofacitinib on residual pain in patients with RA and PsA who had an abrogation of inflammation (SJC=0 and CRP <6 mg/L) after 3 months of therapy. A strict definition of abrogation of inflammation was used, which assessed both a physical manifestation of inflammation (ie, joint swelling) and an acute phase marker of inflammation (ie, CRP). This analysis showed that a substantial number of patients with an abrogation of inflammation after 3 months of therapy continue to report residual pain. However, in patients with an abrogation of inflammation, a reduction in residual pain was observed in those receiving tofacitinib and adalimumab versus placebo. No differences in the magnitude of

residual pain reduction were observed between tofacitinib and adalimumab.

The presence of concomitant fibromyalgia,¹⁴ effects of vitamin D deficiency on neuropathic pain,¹⁸ central sensitisation³⁰ and the impact of inflammation on peripheral sensitisation¹⁵ have all been suggested to play a role in mediating pain in rheumatic diseases. However, the relationships between these pain mechanisms in rheumatic diseases and treatments are not well understood. Tofacitinib has been shown to reduce pain in patients with RA or PsA by week 2 (first post-baseline assessment),²⁸ and faster times to improvement have been observed in those with higher baseline pain.³¹ The results of our study suggest that treatment with a JAK inhibitor (tofacitinib) or a TNFi (adalimumab) can decrease residual pain in patients with RA or PsA whose inflammation is controlled, compared with placebo. This may be attributable to analgesic effects of these treatments independent of their anti-inflammatory properties³²; no specific differences regarding their pain-reducing abilities were observed between tofacitinib versus adalimumab. Collectively, these data suggest that the JAK and TNF signalling pathway may be potential mediators of residual pain in individuals with rheumatic diseases, yet the underlying mechanisms are yet to be elucidated. Interleukin-6 is thought to induce JAK/signal transducer and activator of transcription 3 signalling in spinal microglia, which in turn can contribute to neuropathic pain development, and it has been shown that a JAK2 inhibitor can reduce both mechanical allodynia and thermal hyperplasia

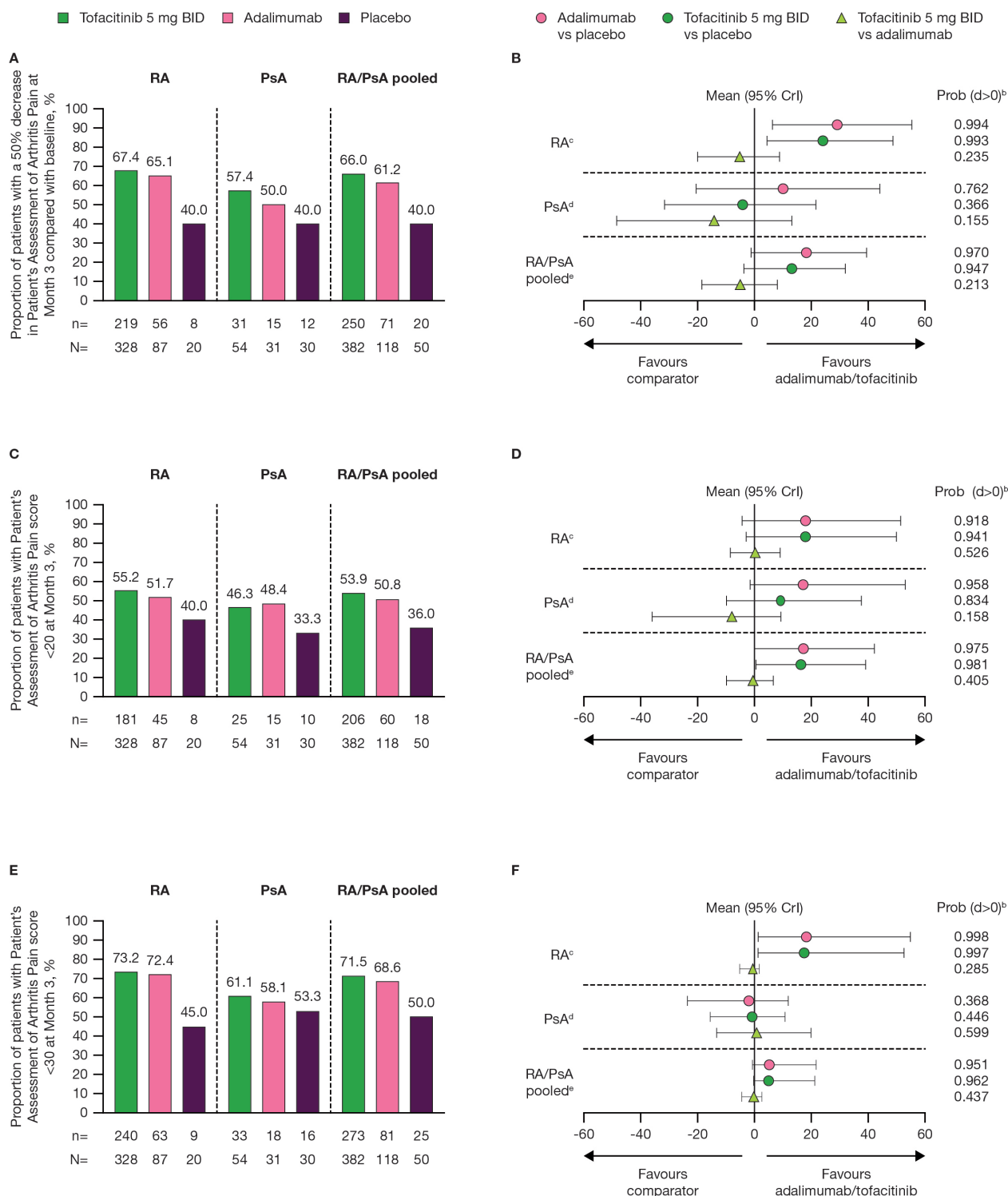


Figure 3 (A) Proportion of patients with a 50% decrease in Patient's Assessment of Arthritis Pain at month 3 compared with baseline with (B) Bayesian network meta-analysis; (C) Proportion of patients with Patient's Assessment of Arthritis Pain score <20 with (D) Bayesian network meta-analysis; and (E) Proportion of patients with Patient's Assessment of Arthritis Pain score <30 with (F) Bayesian network meta-analysis in patients with an abrogation of inflammation^a after 3 months of therapy. ^aAn abrogation of inflammation was defined as SJC=0 and CRP <6 mg/L. ^bProb(d>0): posterior probability of a larger proportion of patients with a pain improvement. ^cAnalysis adjusted for age, sex, disease duration, month 0 pain, month 3 corticosteroid treatment, month 3 analgesic treatment and month 3 methotrexate treatment. ^dAnalysis adjusted for age, sex, disease duration, month 0 PASI, month 0 pain, month 3 corticosteroid treatment, month 3 analgesic treatment and month 3 methotrexate treatment. ^eAnalysis adjusted for disease, age, sex, disease duration, month 0 PASI, month 0 pain, month 3 corticosteroid treatment, month 3 analgesic treatment and month 3 methotrexate treatment. BID, twice daily; CrI, credible interval; CRP, C-reactive protein; d, difference; N, number of patients evaluated; n, number of patients achieving respective outcome; PASI, Psoriasis Area Severity Index; Prob, probability; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SJC, swollen joint count.

in rodent models of neuropathic pain.³³ In addition, blockade of granulocyte-macrophage colony-stimulating factor significantly reduced arthritis pain in a rodent model of osteoarthritis.³⁴ TNF has also been implicated in nociceptive pain in patients with RA and in animal models.³⁵ Therefore, these potential mechanisms mediated through JAK and TNF signalling may mediate the residual pain reduction observed with tofacitinib and adalimumab treatment, respectively.

In this analysis, tofacitinib did not have as pronounced an effect on residual pain in patients with PsA compared with RA. Differences in baseline characteristics between patients with RA and PsA with abrogated inflammation after 3 months of therapy were observed; for example, patients with PsA had lower baseline CRP (all treatment groups) and pain (adalimumab and placebo groups) than those with RA. It might be speculated that pain mechanisms, such as the impact of inflammation on peripheral sensitisation,¹⁵ may have less impact in patients with PsA than those with RA. Additionally, while SJC and CRP might be adequate surrogate criteria to define abrogation of inflammation for RA, they might not be sufficient for PsA. Specific manifestations of PsA, such as skin inflammation, itch, dactylitis and enthesitis, could lead to differences in the experience of pain in these patients compared with RA.^{28, 36} Indeed, patients with PsA have reported higher levels of neuropathic pain compared with RA.³⁷ Patients with RA and PsA have also been shown to have distinct cytokine profiles, which may account for the varying effects of tofacitinib and adalimumab on pain in these diseases.³⁸ Overall, it is likely that differences in pain mechanisms in RA and PsA may contribute to the observed differences in outcomes for the respective indications in this study.

In the present analysis, treatment with tofacitinib and adalimumab resulted in greater magnitude of residual pain reduction, compared with placebo, and both treatments reduced pain by a similar extent. This raises questions as to whether the inflammation suppression mediated by inhibition of different pro-inflammatory cytokines has a differential effect on pain experience, presumed to be driven by other mechanisms. A recent mediation analysis of data from patients with RA revealed that baricitinib had a greater overall ability to alleviate pain than adalimumab.³⁹ Changes in inflammation accounted for a higher proportion of pain improvement for adalimumab versus baricitinib, and factors not associated with markers of inflammation (ie, not attributable to changes in erythrocyte sedimentation rate, CRP or SJC) may be responsible for a higher level of pain relief with baricitinib versus adalimumab.³⁹ However, a recent matching-adjusted indirect comparison analysis (based on treatment arm matching) in biological DMARD/csDMARD-naïve patients with RA showed no statistical differences in pain reduction magnitude between baricitinib and tofacitinib.⁴⁰ A mediation modelling analysis in PsA demonstrated that the majority of the effect of tofacitinib on pain is mediated through itch, as well as via enthesitis and CRP,³⁶

supporting the hypothesis that other manifestations, such as enthesitis, may contribute to the experience of pain in patients with PsA, compared with RA.

Our study has limitations that should be considered. The study was post hoc in nature and used pooled data from several clinical trials from two distinct diseases, which cannot easily be compared directly. Adalimumab was included in only two RCTs of patients with RA (ORAL Standard and ORAL Strategy), and one RCT of patients with PsA (OPAL Broaden). Only ORAL Strategy performed non-inferiority and superiority comparisons between tofacitinib and adalimumab. Also, the cohort of patients with RA was substantially larger than that for PsA. While the SJC component of the criteria for an abrogation of inflammation was based on a 66-joint count, pain reductions may be due to a reduction in inflammation at joints not included in this count, and independent from systemic measures (CRP). Although the analyses presented here accounted for disease duration, there was no assessment of concomitant osteoarthritis or joint structural damage due to RA or PsA. In addition, the proportion of patients with a baseline diagnosis of fibromyalgia and/or osteoarthritis was not evaluated. Finally, assessments were conducted only at the end of the placebo-controlled period at month 3, and so it is likely that the proportion of patients achieving an abrogation of inflammation was lower than would be expected if the assessment was made at a later time point.

SUMMARY

Many patients with rheumatic diseases continue to report residual pain, despite abrogation of inflammation. Our post hoc analysis revealed that, in patients with RA and PsA with abrogated inflammation after 3 months of therapy, treatment with tofacitinib and adalimumab resulted in a reduction in residual pain, compared with placebo. This suggests that tofacitinib and adalimumab have analgesic effects beyond those associated with a reduction in inflammation. There were no observable differences between tofacitinib and adalimumab treatment in their ability to reduce residual pain in these patients. Further analyses are required to determine the underlying mechanisms of residual pain in patients with rheumatic diseases who have an abrogation of inflammation.

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Acknowledgements Medical writing support, under the guidance of the authors, was provided by Lewis C Rodgers, CMC Connect, a division of IPG Health Medical

Communications, funded by Pfizer in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015;163:461–4).

Contributors Conceptualisation of study and design—MD, COB and LW. Acquisition of data—YB and LW. Analysis and interpretation of data—MD, PCT, COB, YB, SR and LW. Guarantor of study—MD. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

Funding This study was sponsored by Pfizer.

Competing interests MD has served as a consultant for AbbVie, Eli Lilly, Gilead Sciences, Janssen, Merck, Novartis, Pfizer Inc and UCB, and has received grant and/or research support from AbbVie, Eli Lilly, Gilead Sciences, Janssen, Merck, Novartis, Pfizer Inc and UCB. PT has served as a consultant for AbbVie, Biogen, Celltrion, Eli Lilly, Fresenius, Galapagos, Gilead Sciences, GlaxoSmithKline, Janssen, Nordic Pharma, Pfizer Inc, Roche, Sanofi and UCB, and has received grant and/or research support from Celgene and Galapagos. COB has served as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Eli Lilly, Janssen, Pfizer Inc and Sanofi/Genzyme, and has received grant and/or research support from Bristol-Myers Squibb. LF, YB, SR, LW and MK are employees and shareholders of Pfizer Inc.

Patient consent for publication Not required.

Ethics approval All studies were conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Guidelines for Good Clinical Practice. The study protocols were approved by the Institutional Review Board and/or Independent Ethics Committee for each study centre. All patients provided written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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