

ORIGINAL RESEARCH

Median time to pain improvement and the impact of baseline pain severity on pain response in patients with psoriatic arthritis treated with tofacitinib

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ABSTRACT

Background Pain is a core domain of psoriatic arthritis (PsA). This post hoc analysis evaluated time to pain improvement and the impact of baseline pain severity on pain response in patients with PsA receiving tofacitinib.

Methods Data from two trials (NCT01877668; NCT01882439) in patients receiving tofacitinib 5 mg twice daily, placebo switching to tofacitinib 5 mg twice daily at month 3 (placebo-to-tofacitinib) or adalimumab (NCT01877668 only) were included. Improvement in pain ($\geq 30\%$ / $\geq 50\%$ decrease from baseline in Visual Analogue Scale pain score) was assessed; median time to initial (first post-baseline visit)/continued (first two consecutive post-baseline visits) pain improvement was estimated (Kaplan-Meier) for all treatment arms. A parametric model was used to determine the relationship between baseline pain severity and time to pain response in patients receiving tofacitinib.

Results At month 3, more patients experienced pain improvements with tofacitinib/adalimumab versus placebo. Median days (95% CI) to initial/continued pain improvements of $\geq 30\%$ and $\geq 50\%$, respectively, were 55 (29–57)/60 (57–85) and 85 (57–92)/171 (90–not estimable (NE)) for tofacitinib, versus 106 (64–115)/126 (113–173) and 169 (120–189)/NE (247–NE) for placebo-to-tofacitinib. Pain improvements were also experienced more quickly for adalimumab versus placebo. Predicted time to $\geq 30\%$ / $\geq 50\%$ pain improvement was shorter in patients with higher baseline pain versus lower baseline pain (tofacitinib arm only).

Conclusions In patients with PsA, pain improvements were experienced by more patients, and more rapidly, with tofacitinib and adalimumab versus placebo. In those receiving tofacitinib, higher baseline pain was associated with faster pain improvements.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, systemic, inflammatory arthritis that affects approximately 0.02%–0.25% of the global population (depending on disease classification)¹

Key messages

What is already known about this subject?

- Higher levels of pain have been reported in patients with psoriatic arthritis (PsA) compared with patients with other rheumatic diseases; reducing pain is a primary treatment concern for patients with PsA.

What does this study add?

- In this post hoc analysis of phase 3 data from patients with PsA, clinically important improvements in pain (defined as a decrease from baseline in patient-reported Visual Analogue Scale pain score of $\geq 30\%$ or $\geq 50\%$) were experienced by more patients, and more rapidly, with tofacitinib 5 mg twice daily and adalimumab 40 mg once every 2 weeks, compared with placebo.
- Predicted time to pain improvement with tofacitinib was more rapid in patients with higher baseline pain severity compared with those with lower baseline pain severity.

How might this impact on clinical practice or further developments?

- This analysis provides information on when clinically meaningful improvements in pain may be expected in patients with PsA receiving tofacitinib, and how baseline pain severity may impact response to tofacitinib, which is of value in clinical practice.

and up to 30% of patients with psoriasis.^{2–3} Characterised by peripheral arthritis, psoriasis (including nail psoriasis), axial disease, enthesitis and dactylitis,^{1–4} PsA is also associated with increased psychosocial difficulties and reduced quality of life.^{5–7}

In patients with rheumatic disease, pain has been reported to be a more important predictor of disability and poor quality of life than radiographic joint damage and disease activity,⁸ and pain is a core domain of PsA.⁹ Higher levels of pain—not necessarily only due

to joint inflammation—have been reported in patients with PsA compared with patients with other rheumatic diseases, including rheumatoid arthritis.^{10 11} Accordingly, reducing pain is a primary treatment concern for patients with PsA.¹² A cross-sectional survey of 782 patients with PsA revealed that most patients experienced moderate or severe pain despite receiving biologic disease-modifying antirheumatic drugs (DMARDs).¹³ Furthermore, in a prospective cohort study including 69 patients with PsA, those with widespread non-arthritic pain were less likely to achieve minimal disease activity after receiving conventional synthetic DMARD or biologic DMARD treatment compared with those without non-arthritic widespread pain.¹⁴ The mechanisms of pain in PsA, and the factors that impact the level of pain reduction in response to treatment, are not completely understood.¹⁵

Pain in PsA can be determined via several modalities. Patient assessment of pain is often measured on a Visual Analogue Scale (VAS) and is a core component of composite measures in PsA, such as the minimal disease activity criteria.^{16 17} Other instruments that have recently been used to measure pain in PsA include the painDETECT questionnaire for neuropathic pain,^{10 18 19} the Widespread Pain Index and the Symptom Severity Scale, the latter of which assesses the general spectrum of pain due to central sensitisation, including neuropathic pain and fibromyalgia.^{19–21} For evaluation of pain intensity with a VAS score, a reduction of ≥ 10 mm from baseline has been used in some studies as the minimum clinically important difference (MCID),^{22 23} while the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) suggests that improvements in VAS pain scores of $\geq 30\%$ and $\geq 50\%$ equate to pain being ‘much improved’ and ‘very much improved’, respectively.²⁴ However, these thresholds have not been specifically validated in PsA.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of PsA. The efficacy and safety of tofacitinib in PsA have been demonstrated in phase 3 trials of up to 12 months’ duration in patients with an inadequate response to conventional synthetic DMARDs (OPAL Broaden; NCT01877668²⁵) or tumour necrosis factor inhibitor (TNFi) therapy (OPAL Beyond; NCT01882439²⁶), and in a long-term extension study (OPAL Balance; NCT01976364²⁷). In post hoc analyses of OPAL Broaden and OPAL Beyond, greater improvements in VAS pain scores with tofacitinib 5 mg twice daily versus placebo at month 3 were observed, and improvements with tofacitinib 5 mg twice daily were maintained for the duration of the trials.^{22 23}

Using data from OPAL Broaden and OPAL Beyond, we aimed to estimate the time to clinically meaningful pain improvement (defined as a decrease from baseline in patient-reported VAS pain score of $\geq 30\%$ and $\geq 50\%$) in patients with PsA treated with tofacitinib 5 mg twice daily (approved dose), placebo switching to tofacitinib 5 mg twice daily at month 3 or adalimumab (OPAL Broaden only). We also sought to determine the impact of baseline pain severity as a predictor of time to pain improvement in patients with PsA receiving tofacitinib 5 mg twice daily.

METHODS

Study design

This post hoc analysis included data from two phase 3 randomised, double-blind, placebo-controlled trials of patients with active PsA (OPAL Broaden; OPAL Beyond); full study details have been published previously.^{25 26} OPAL Broaden was a 12-month trial that included patients who had an inadequate response to ≥ 1 conventional synthetic DMARD and were TNFi-naïve.²⁵ OPAL Beyond was a 6-month trial that included patients who had an inadequate response to ≥ 1 TNFi.²⁶ In both trials, patients were randomised to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily or placebo switching to tofacitinib 5 or 10 mg twice daily at month 3. OPAL Broaden included a subcutaneous adalimumab 40 mg once every 2 weeks treatment arm; however, OPAL Broaden was not designed to test non-inferiority or superiority between tofacitinib and adalimumab. All patients continued on a stable dose of a single conventional synthetic DMARD.

Exclusion criteria included, but were not limited to, history of autoimmune rheumatic disease other than PsA or known diagnosis of fibromyalgia, without sponsor approval.

Only patients treated with tofacitinib 5 mg twice daily, placebo switching to tofacitinib 5 mg twice daily at month 3 (subsequently referred to as ‘placebo-to-tofacitinib 5 mg twice daily’) and adalimumab 40 mg once every 2 weeks (OPAL Broaden only) were included in the current analysis.

Assessment of pain

For both trials, the American College of Rheumatology response criteria components, including patient-reported pain, were secondary efficacy endpoints. Patient-reported pain severity was determined using a 100 mm VAS, with higher scores indicating greater severity. For both OPAL Broaden and OPAL Beyond, patients were asked to place an ‘X’ mark between 0 and 100 mm on a scale that stated: ‘*my pain at this time is...*’. Pain was assessed at baseline, week 2 and months 1, 2, 3, 4, 6 (both trials), 9 and 12 (OPAL Broaden only).

In this post hoc analysis, the thresholds proposed by IMMPACT for determining clinically important improvement in pain relative to baseline were applied, that is, a decrease of $\geq 30\%$ (‘much improved’) and $\geq 50\%$ (‘very much improved’).²⁴ ‘Initial’ improvement was defined as the first post-baseline day with a pain improvement of $\geq 30\%$ or $\geq 50\%$ relative to baseline. ‘Continued’ improvement was defined as the first post-baseline visit where there was pain improvement of $\geq 30\%$ or $\geq 50\%$ relative to baseline that was maintained up to the next visit (ie, two consecutive observations).

The times at which an estimated 50% (median) and 25% (25th percentile) of patients, respectively, experienced pain improvement of $\geq 30\%$ or $\geq 50\%$ relative to baseline were determined for each treatment arm.

Heat maps were generated to evaluate whether initial pain improvements were maintained at subsequent

timepoints. Heat maps indicate the timepoints at which individual patients did and did not experience pain improvements of $\geq 30\%$ or $\geq 50\%$ relative to baseline. Separate heat maps were generated for patients who received tofacitinib 5 mg twice daily, placebo-to-tofacitinib 5 mg twice daily (pooled OPAL Broaden and OPAL Beyond, and OPAL Broaden only) and adalimumab 40 mg once every 2 weeks (OPAL Broaden only).

Statistical analyses

All analyses were based on evaluable patient data, that is, no missing data were imputed.

Analysis of time to pain improvement (tofacitinib, placebo-to-tofacitinib and adalimumab arms)

For all treatment arms, descriptive statistics were used to examine the proportion of patients experiencing $\geq 30\%$ and $\geq 50\%$ improvements in pain at each study visit. For this endpoint, patient populations from OPAL Broaden and OPAL Beyond were analysed separately.

The median time and time for the 25th percentile of patients to experience pain improvements were calculated using a non-parametric Kaplan-Meier method (LIFETEST procedure (SAS V.9.4, SAS Institute); all treatment arms)^{28 29}; patients who did not achieve an improvement of $\geq 30\%$ or $\geq 50\%$ were censored at last observation. For these endpoints, data from OPAL Broaden and OPAL Beyond were pooled. To determine time to pain improvement in patients receiving adalimumab, data from OPAL Broaden were also evaluated independently.

A test of equality over strata log-rank test^{28 30 31} was performed to detect any significant differences between the tofacitinib 5 mg twice daily arm versus the placebo-to-tofacitinib 5 mg twice daily arm, and the adalimumab arm versus the placebo-to-tofacitinib 5 mg twice daily arm, regarding time to initial/continued pain improvement of $\geq 30\%$ or $\geq 50\%$ relative to baseline. Significance was declared for $p \leq 0.05$ without multiple comparison adjustments.

Analysis of the impact of baseline pain severity on pain response (tofacitinib arm)

A parametric model referred to as a 'parametric model to failure time data'³² (LIFEREG procedure (SAS V.9.4, SAS Institute)) determined whether baseline pain severity was significantly and meaningfully predictive of the time to $\geq 30\%$ or $\geq 50\%$ improvement in pain in patients receiving tofacitinib 5 mg twice daily (data pooled across OPAL Broaden and OPAL Beyond). The parametric model was defined as:

$$Y = a + bX + e$$

where Y is the response corresponding to the natural log of time to an improvement, a is the intercept, b is the slope, X is baseline pain (the predictor variable) and e is the random disturbance term. Different distributions (exponential, log-logistic, log-normal, logistic, normal, Weibull) were investigated, and the model with best fit

based on the lowest Akaike information criterion (AIC) value was carried forward.

RESULTS

Patients

In total, OPAL Broaden and OPAL Beyond enrolled 238 patients randomised to tofacitinib 5 mg twice daily, 118 randomised to placebo-to-tofacitinib 5 mg twice daily and 106 randomised to adalimumab 40 mg once every 2 weeks. Patient demographics and baseline disease characteristics have been previously reported^{25 26} and were generally similar between treatment groups (table 1). However, among OPAL Broaden participants, those assigned to adalimumab had slightly lower pain scores, Leeds Enthesitis Index Scores and Dactylitis Severity Scores, reduced swollen and tender/painful joint counts and shorter PsA durations at baseline compared with those assigned to tofacitinib 5 mg twice daily and placebo-to-tofacitinib 5 mg twice daily.

In OPAL Beyond, one and three patients assigned to tofacitinib 5 mg twice daily, and one and three patients assigned to placebo-to-tofacitinib 5 mg twice daily had a past or present diagnosis of fibromyalgia, respectively. In OPAL Broaden, no patients in any of the treatment arms included in this analysis had a past or present diagnosis of fibromyalgia.

Most patients receiving tofacitinib 5 mg twice daily had baseline VAS pain scores between 30 and 80 mm; approximately 10% of patients had baseline scores < 30 mm and baseline scores > 80 mm (pooled across OPAL Broaden and OPAL Beyond; online supplemental table 1).

Proportion of patients with $\geq 30\%$ and $\geq 50\%$ improvements in pain at each study visit (tofacitinib, placebo-to-tofacitinib and adalimumab arms)

In OPAL Broaden, 56.3% (58/103) and 47.6% (49/103) of patients receiving tofacitinib 5 mg twice daily experienced $\geq 30\%$ and $\geq 50\%$ improvements in pain from baseline at month 3, respectively. In contrast, 34.6% (18/52) and 21.2% (11/52) of patients receiving placebo experienced $\geq 30\%$ and $\geq 50\%$ improvements in pain at month 3 (figure 1). Pain improvements with tofacitinib 5 mg twice daily were observed as early as month 1, when 42.9% (45/105) and 30.5% (32/105) of patients experienced $\geq 30\%$ and $\geq 50\%$ improvements in pain, respectively, compared with placebo (25.5% (13/51) and 15.7% (8/51), respectively). Similar to tofacitinib 5 mg twice daily, improvements in pain were observed with adalimumab 40 mg once every 2 weeks at month 3, whereby 58.0% (58/100) and 41.0% (41/100) experienced $\geq 30\%$ and $\geq 50\%$ improvements in pain, respectively (figure 1). At month 1, numerically higher proportions of patients experienced pain improvements with adalimumab 40 mg once every 2 weeks versus tofacitinib 5 mg twice daily (figure 1).

In OPAL Beyond, similar pain improvements were observed to those in OPAL Broaden; briefly, more patients experienced $\geq 30\%$ and $\geq 50\%$ improvements in

Table 1 Selected demographics and baseline disease characteristics for patients with PsA from OPAL Broaden and OPAL Beyond for all treatment arms included in this post hoc analysis*

	OPAL Broaden		OPAL Beyond	
	Tofacitinib 5mg BID (N=107)	Placebo→tofacitinib 5mg BID (N=52)	Adalimumab 40mg Q2W (N=106)	Tofacitinib 5mg BID (N=131)
Patient demographics				
Age, years, mean (SD)	49.4 (12.6)	46.1 (10.4)	47.4 (11.3)	49.5 (12.3)
Female, n (%)	57 (53.3)	28 (53.8)	50 (47.2)	64 (48.9)
White race, n (%)	105 (98.1)	52 (100.0)	103 (97.2)	121 (92.4)
BMI, kg/m ² , mean (SD)	29.0 (5.2)	30.0 (6.3)	28.8 (5.3)	30.5 (7.1)
Baseline disease characteristics				
PsA duration, years, mean (SD)	7.3 (8.2)	7.8 (7.7)	5.3 (5.3)	9.6 (7.6)
VAS pain score, mm				
Mean (SD)	55.7 (22.8)	56.1 (21.8)	50.7 (21.7)‡	56.4 (24.1)§
Median (range) (IQR)	54.0 (3.0–97.0) (44.0–76.0)	57.5 (13.0–97.0) (42.0–71.5)	52.0 (3.0–92.0) (37.0–67.0)‡	58.0 (1.0–99.0) (40.0–74.0)§
LEI score, mean (SD) (n)†	2.5 (1.4) (75)	2.7 (1.4) (31)	2.3 (1.2) (76)	3.0 (1.6) (83)
DSS, mean (SD) (n)†	9.1 (8.0) (61)	10.5 (9.5) (29)	8.0 (7.4) (58)	7.8 (9.9) (66)
Swollen joint count (of 66 joints assessed), mean (SD)	12.9 (9.9)	11.0 (7.9)	9.8 (7.9)	12.1 (10.6)
Tender/painful joint count (of 68 joints assessed), mean (SD)	20.5 (12.6)	21.9 (16.2)	17.1 (11.2)	20.5 (13.0)
				21.0 (16.2)

*Further details are available elsewhere.^{25,26}

†For patients with score >0 at baseline.

‡N=105.

§N=130.

BID, twice daily; BMI, body mass index; DSS, Dactylitis Severity Score; LEI, Leeds Enthesitis Index; N, total number of patients in that group; n, number of patients with characteristic; PsA, psoriatic arthritis; Q2W, once every 2 weeks; VAS, Visual Analogue Scale.

pain with tofacitinib 5 mg twice daily than with placebo (up to month 3), and these improvements were observed as early as month 1 (figure 1).

For patients in the placebo-to-tofacitinib 5 mg twice daily arms (OPAL Broaden and OPAL Beyond), pain improvement was comparable with that in the tofacitinib 5 mg twice daily treatment arm by month 6 (figure 1). Patients receiving active treatment maintained pain improvements over the 6-month or 12-month trial duration (figure 1).

Median time and time to the 25th percentile to improvements in pain (tofacitinib, placebo-to-tofacitinib and adalimumab arms)

As the proportions of patients experiencing $\geq 30\%$ or $\geq 50\%$ pain improvements were similar between OPAL Broaden and OPAL Beyond (figure 1), data from both studies were pooled to compare time to pain improvement with tofacitinib 5 mg twice daily versus placebo-to-tofacitinib 5 mg twice daily. For the pooled trial data, median days (95% CI) to initial/continued pain improvements of $\geq 30\%$ and $\geq 50\%$ from baseline, respectively, were 55 (29–57)/60 (57–85) and 85 (57–92)/171 (90–not estimable (NE)) for tofacitinib 5 mg twice daily versus 106 (64–115)/126 (113–173) and 169 (120–189)/NE for placebo-to-tofacitinib 5 mg twice daily (table 2). Similarly, the times to the 25th percentile to initial/continued $\geq 30\%$ and $\geq 50\%$ improvements

in pain were shorter with tofacitinib 5 mg twice daily versus placebo-to-tofacitinib 5 mg twice daily. Statistical significance favouring tofacitinib 5 mg twice daily versus placebo-to-tofacitinib 5 mg twice daily was obtained for initial/continued pain improvements of $\geq 30\%$ and $\geq 50\%$ from baseline (figure 2 and table 2).

For data from OPAL Broaden only, the median times and times to the 25th percentile to initial/continued pain improvements from baseline of $\geq 30\%$ or $\geq 50\%$ were shorter with tofacitinib 5 mg twice daily and adalimumab 40 mg once every 2 weeks versus placebo-to-tofacitinib 5 mg twice daily (table 2). Statistical significance favouring tofacitinib 5 mg twice daily versus placebo-to-tofacitinib 5 mg twice daily was demonstrated for initial pain improvements of $\geq 30\%$ and $\geq 50\%$ from baseline (figure 3 and table 2). Additionally, statistical significance favouring adalimumab versus placebo-to-tofacitinib 5 mg twice daily was yielded for initial/continued improvements of $\geq 30\%$ (figure 3 and table 2). In some instances, the median time and the time to the 25th percentile to initial/continued pain improvements from baseline of $\geq 30\%$ and $\geq 50\%$ were shorter in patients treated with adalimumab 40 mg once every 2 weeks compared with those that received tofacitinib 5 mg twice daily (table 2).

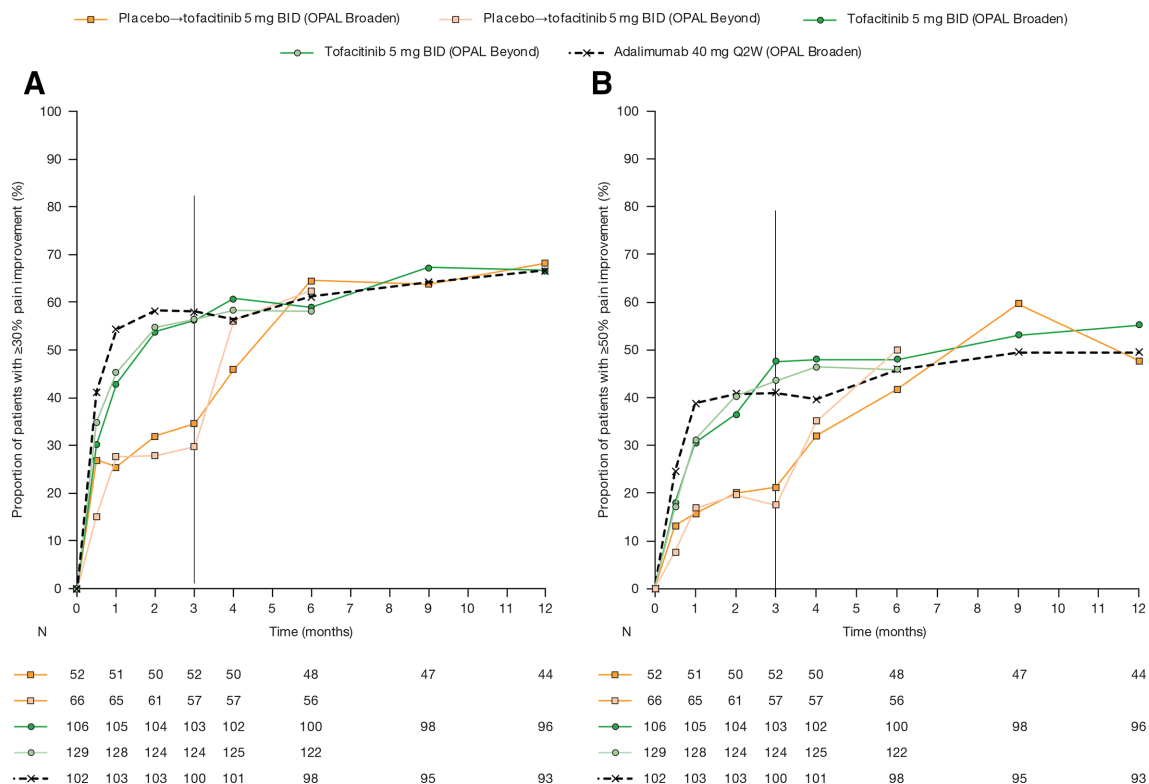


Figure 1 Proportion of patients with PsA receiving tofacitinib 5 mg BID, placebo-to-tofacitinib 5 mg BID (OPAL Broaden and OPAL Beyond) or adalimumab 40 mg Q2W (OPAL Broaden only) reporting (A) $\geq 30\%$ and (B) $\geq 50\%$ improvements in pain from baseline at each study visit. The vertical line represents the point at which patients receiving placebo switched to tofacitinib 5 mg BID (month 3). BID, twice daily; N, number of patients evaluable at the timepoint; PsA, psoriatic arthritis; Q2W, once every 2 weeks.

Table 2 Median time and time to the 25th percentile to initial and continued pain improvement from baseline in patients with PsA receiving tofacitinib 5 mg BID or placebo-to-tofacitinib 5 mg BID (pooled across OPAL Broaden and OPAL Beyond); tofacitinib 5 mg BID, placebo-to-tofacitinib 5 mg BID or adalimumab 40 mg Q2W (OPAL Broaden only)

	Pooled across OPAL Broaden and OPAL Beyond			OPAL Broaden				
	Tofacitinib 5 mg BID (N=236)	Placebo→tofacitinib 5 mg BID at month 3 (N=118)	Log-rank test, p value*	Tofacitinib 5 mg BID (N=107)	Adalimumab 40 mg Q2W (N=105)	Placebo→tofacitinib 5 mg BID at month 3 (N=52)	Log-rank test, p value (tofacitinib)*	Log-rank test, p value (adalimumab)*
Time to ≥30% pain improvement, days (95% CI)								
Initial improvement								
Median	55.0 (29.0 to 57.0)	106.0 (64.0 to 115.0)	0.0132	57.0 (29.0 to 57.0)	29.0 (17.0 to 57.0)	113.0 (57.0 to 169.0)	0.0465	0.011
25th percentile	15.0 (15.0 to 16.0)	29.0 (15.0 to 37.0)		15.0 (15.0 to 28.0)	15.0 (NE)	19.0 (15.0 to 57.0)		
Continued improvement								
Median	60.0 (57.0 to 85.0)	126.0 (113.0 to 173.0)	0.0067	64.0 (57.0 to 113.0)	57.0 (29.0 to 85.0)	168.0 (112.0 to 252.0)	0.1791	0.045
25th percentile	16.0 (15.0 to 28.0)	58.0 (29.0 to 106.0)		18.0 (15.0 to 33.0)	15.0 (15.0 to 17.0)	47.0 (15.0 to 112.0)		
Time to ≥50% pain improvement, days (95% CI)								
Initial improvement								
Median	85.0 (57.0 to 92.0)	169.0 (120.0 to 189.0)	0.0068	64.0 (57.0 to 92.0)	57.0 (29.0 to 157.0)	171.0 (113.0 to 253.0)	0.0328	0.1028
25th percentile	29.0 (27.0 to 31.0)	57.0 (29.0 to 106.0)		29 (20.0 to 31.0)	26 (15.0 to 29.0)	57 (15.0 to 113.0)		
Continued improvement								
Median	171.0 (90.0–NE)	NE (247.0–NE)	0.005	176.0 (85.0–NE)	169.0 (60.0–NE)	253.0 (169.0–NE)	0.2892	0.1991
25th percentile	51.0 (29.0 to 57.0)	115.0 (88.0 to 169.0)		56.0 (28.5 to 58.0)	29.0 (15.0 to 56.0)	113.0 (29.0 to 169.0)		

Median time to initial/continued improvement was estimated via a non-parametric Kaplan-Meier method.

*Initial improvement was defined as the first post-baseline day with a pain improvement of ≥30% or ≥50% relative to baseline. 'Continued' improvement was defined as the first post-baseline visit where there was pain improvement of ≥30% or ≥50% relative to baseline that was maintained up to the next visit (ie, two consecutive observations).

*Versus placebo switching to tofacitinib 5 mg BID at month 3.

BID, twice daily; N, total number of patients in that group; NE, not estimable, as the time was beyond duration of the study; PsA, psoriatic arthritis; Q2W, once every 2 weeks.

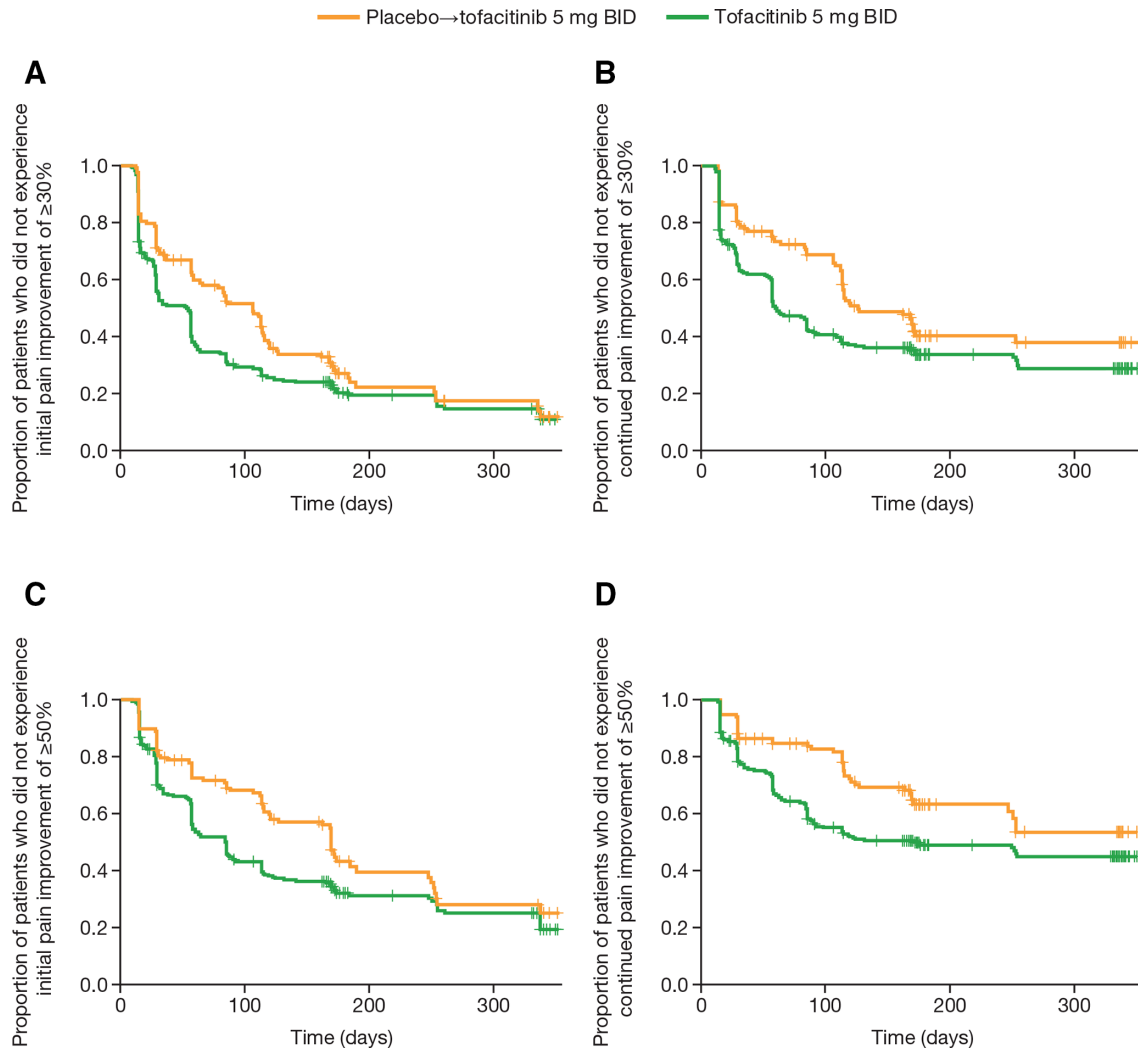


Figure 2 Probability of patients with PsA not experiencing (A) an initial and (B) continued $\geq 30\%$ pain improvement, and (C) an initial and (D) continued $\geq 50\%$ pain improvement, from baseline, with tofacitinib 5 mg BID or placebo-to-tofacitinib 5 mg BID (pooled across OPAL Broaden and OPAL Beyond). Tick marks indicate censored patients. BID, twice daily; PsA, psoriatic arthritis.

Heat maps indicated that initial pain improvements of $\geq 30\%$ or $\geq 50\%$ from baseline in patients receiving tofacitinib 5 mg twice daily and adalimumab 40 mg once every 2 weeks were generally maintained across subsequent timepoints (online supplemental figure 1 and 2).

Impact of baseline pain severity on pain response (tofacitinib arm only)

Based on time-to-event data for both $\geq 30\%$ and $\geq 50\%$ improvement in pain in patients receiving tofacitinib 5 mg twice daily (data pooled across OPAL Broaden and OPAL Beyond), the log-normal distribution was identified as the parametric model with best fit (lowest AIC value; online supplemental table 2).

Results from the final selected parametric model indicated that the median time to $\geq 30\%$ and $\geq 50\%$ pain improvement from baseline with tofacitinib 5 mg twice daily decreased with higher baseline pain (figure 4). For example, in patients with

baseline VAS pain scores of 30 or 80 mm, predicted median times to a $\geq 30\%$ improvement in pain were 68.2 or 43.0 days, respectively (figure 4 and online supplemental table 3); the predicted median times to a $\geq 50\%$ improvement in pain were 101.3 days for those with a baseline VAS pain score of 30 mm and 81.1 days for those with a baseline VAS pain score of 80 mm (figure 4 and online supplemental table 3).

DISCUSSION

More patients with PsA experienced $\geq 30\%$ and $\geq 50\%$ improvements in pain with tofacitinib 5 mg twice daily (OPAL Broaden and OPAL Beyond) and adalimumab 40 mg once every 2 weeks (OPAL Broaden) than with placebo in the first 3 months of treatment; pain improvements with active treatment were generally maintained for the duration of each trial. In OPAL Broaden, the proportion of patients reporting $\geq 30\%$ and $\geq 50\%$ improvements in pain was

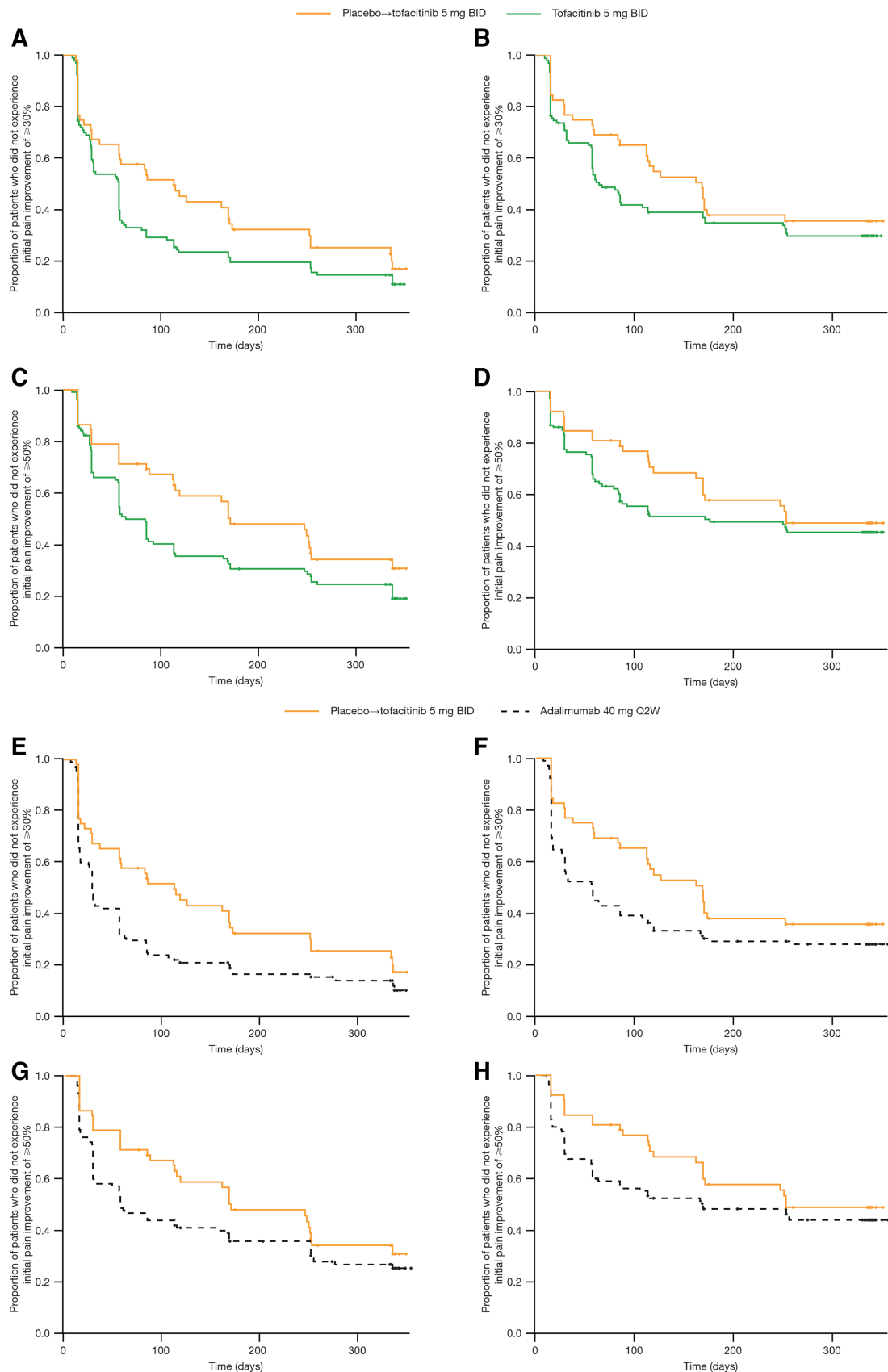


Figure 3 Probability of patients with PsA not experiencing (A) an initial and (B) continued $\geq 30\%$ pain improvement, and (C) an initial and (D) continued $\geq 50\%$ pain improvement, from baseline, with tofacitinib 5 mg BID or placebo-to-tofacitinib 5 mg BID; and (E) an initial and (F) continued $\geq 30\%$ pain improvement, and (G) an initial and (H) continued $\geq 50\%$ pain improvement, from baseline, with adalimumab 40 mg Q2W or placebo-to-tofacitinib 5 mg BID (OPAL Broaden only). Tick marks indicate censored patients. BID, twice daily; PsA, psoriatic arthritis; Q2W, once every 2 weeks.

numerically higher for adalimumab 40 mg once every 2 weeks versus tofacitinib 5 mg twice daily at month 1; although, by month 3, the proportion of patients with pain improvements with these two treatments was similar. Median times to initial/continued pain improvement were shorter with tofacitinib 5 mg twice daily (OPAL Broaden and OPAL Beyond) and adalimumab 40 mg once every 2 weeks (OPAL Broaden) versus placebo-to-tofacitinib 5 mg twice daily. Our findings suggest that, after initiating tofacitinib 5 mg twice daily treatment, half of patients could experience initial/continued pain improvements of $\geq 30\%$ and $\geq 50\%$, respectively, by 55/60 days and 85/171 days. Moreover, our data indicate that 25% of patients could experience initial $\geq 30\%$ pain improvements by approximately 2 weeks following initiation of tofacitinib 5 mg twice daily. In OPAL Broaden, time to initial/continued pain improvements appeared to be shorter, in some instances, with adalimumab 40 mg once every 2 weeks versus tofacitinib 5 mg twice daily; it is possible that adalimumab had a slightly faster onset of pain reduction relative to tofacitinib in this study, but further statistical analyses across additional timepoints would be required to make a definitive conclusion.

In patients receiving tofacitinib 5 mg twice daily (OPAL Broaden and OPAL Beyond), the predicted median time to $\geq 30\%$ and $\geq 50\%$ improvement in pain decreased in patients with higher baseline pain (parametric time-to-event analysis). Based on the results of this post hoc analysis, it may be deduced that 50% of patients with higher baseline pain (eg, 60–90 mm) will achieve clinically meaningful improvements in pain of $\geq 30\%$ within 39–52 days, and improvements of $\geq 50\%$ within 78–89 days of initiating treatment with tofacitinib 5 mg twice daily. Patients with lower baseline pain (eg, 20–40 mm) will likely achieve $\geq 30\%$ and $\geq 50\%$ improvement in pain within 62–75 and 97–106 days, respectively.

The results of this post hoc analysis suggest that time to pain improvement with tofacitinib 5 mg twice daily in patients with PsA may be affected by their level of baseline pain severity. It is possible that substantial and/or rapid reductions in pain following treatment may not be as detectable in patients with low baseline pain levels as there is less room for pain improvement in these patients. However, it should be noted that, in OPAL Broaden, patients assigned to adalimumab had lower pain scores and shorter PsA disease durations at baseline but shorter times to initial/continued pain improvements in some cases, relative to those assigned to tofacitinib 5 mg twice daily and placebo-to-tofacitinib 5 mg twice daily. The effect of baseline pain levels on pain improvements in patients with PsA treated with adalimumab has yet to be evaluated.

The findings from the current analysis could guide physicians in their management of patient expectations with respect to pain reduction and, in particular, when patients with PsA may expect to notice meaningful

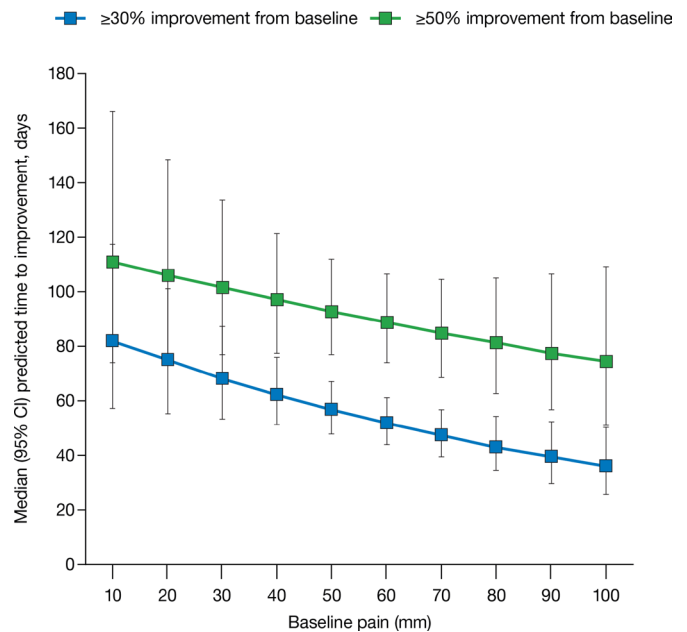


Figure 4 Predicted median (95% CI) time (days) to pain improvement as a function of baseline pain severity in patients with PsA receiving tofacitinib 5 mg twice daily. Results from the parametric model (final selected model (log-normal distribution) with the smallest AIC). AIC, Akaike information criterion; PsA, psoriatic arthritis.

improvements with tofacitinib. Because the VAS is widely used as a means of measuring pain,³³ its utilisation in this study may help translate these findings to clinical practice. In a previous analysis of data from OPAL Broaden and OPAL Beyond, improvements in VAS pain score of ≥ 20 mm were achieved by significantly more patients in the tofacitinib 5 mg twice daily arm versus placebo at month 3, with improvements sustained to 6 months.³⁴ The pain improvement thresholds of $\geq 30\%$ and $\geq 50\%$ used here²⁴ provide reasonable thresholds to determine how clinically meaningful pain improvement is to patients, in addition to the MCID of ≥ 10 mm improvement in VAS pain^{22 23}; however, further studies are required to specifically validate all of these cut-off values for detecting pain improvements in patients with PsA.

A recent study investigated pain relief with baricitinib (a JAK 1/2 inhibitor), adalimumab and placebo in patients with rheumatoid arthritis and an inadequate response to methotrexate.³⁵ For the baricitinib treatment arm, the proportion of patients achieving a $\geq 30\%$ pain improvement at month 3 was 73% and the median time to $\geq 30\%$ pain improvement was 2 weeks. However, due to differences in disease (rheumatoid arthritis vs PsA), outcome measures and the frequency of pain reporting, it is difficult to compare these findings with those of the current study. Moreover, to our knowledge, data regarding pain reduction specifically as a function of baseline pain severity are very limited.

In a separate analysis, median days (95% CI) to clinically meaningful improvements from baseline in Health Assessment Questionnaire-Disability Index and Functional

Assessment of Chronic Illness Therapy-Fatigue, respectively, were 30.0 (27.0–57.0 (OPAL Broaden))/37.0 (29.0–61.0 (OPAL Beyond)) and 31 (29.0–43.0 (OPAL Broaden))/32 (30.0–85.0 (OPAL Beyond)) for patients with PsA receiving tofacitinib 5 mg twice daily.³⁶ These data, taken together with the results of the current analysis, suggest that patients with PsA can expect to experience clinically meaningful improvements in fatigue, quality of life and pain within the first 3 months of tofacitinib initiation.

This analysis was limited by several factors. The trial designs incorporated comparisons with placebo only to month 3, which is not particularly meaningful in ‘time-to-event’ analyses and thus impacts on the practical clinical relevance of the findings. Additionally, direct comparisons between adalimumab and tofacitinib were not made in this post hoc analysis, as OPAL Broaden was not designed for non-inferiority/superiority comparisons between these treatments. In OPAL Broaden and OPAL Beyond, pain was measured at a limited number of predefined visits, with increasing intervals between visits as the trials progressed; therefore, potential effects of tofacitinib on pain may have been missed at the timepoints at which no measurements were obtained. Importantly, the definition of ‘continued improvement’ used here is not universally agreed on and was limited to initial improvement over two consecutive visits; therefore, it was not always possible to determine exactly when patients achieved clinically important pain relief that was maintained throughout treatment. Heat maps indicated that initial pain improvements in patients receiving tofacitinib 5 mg twice daily and adalimumab 40 mg once every 2 weeks were typically maintained across subsequent study visits. It is important to acknowledge that pain is complex and multifaceted; therefore, a unidimensional scale such as a pain VAS may not fully capture all the components of pain experienced by patients with PsA. VAS scales are susceptible to anchoring as well as floor and ceiling effects,³⁷ which can impact comparisons of percent changes in scores from baseline between patients with high versus low baseline scores. As such, it may have been beneficial to consider absolute VAS pain scores in addition to percentage changes in VAS scores in our analysis. Baseline VAS pain was the only predictor of time to pain improvement evaluated in this post hoc study of patients with PsA receiving tofacitinib. Finally, the data used here were obtained from clinical trials, where the inclusion/exclusion criteria would rule out other factors such as certain comorbidities (ie, fibromyalgia, history of severe neurological disorders) that could potentially affect the pain experienced, and which may play a role in patient pain in the clinical setting.

In conclusion, in patients with active PsA, clinically important improvements in pain were experienced by more patients, and more rapidly, with tofacitinib 5 mg twice daily and adalimumab 40 mg once every 2 weeks compared with placebo. Patients receiving active treatment maintained pain improvements throughout the trials. In those receiving tofacitinib 5 mg twice daily, higher baseline pain was associated with faster pain improvements. This analysis provides information on when clinically meaningful improvements

in pain may be expected in patients with PsA receiving tofacitinib or adalimumab, and how baseline pain severity may impact response to tofacitinib, which is of value in clinical practice.

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Competing interests KdV is a consultant for Lilly and Pfizer Inc. AO has served as a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Corrona, Gilead, Janssen, Lilly, Novartis, Pfizer Inc, Takeda and UCB, and has received grant/research support from Amgen, Novartis and Pfizer Inc. AO's husband has received royalties from Novartis. RF is a consultant for AbbVie, Acea, Amgen, Bristol-Myers Squibb, Celltrion, Genentech, Gilead, GSK, Janssen, Lilly, Novartis, Pfizer Inc, Sanofi-Aventis and UCB, and has received grant/research support from AbbVie, Acea, Amgen, AstraZeneca, Bristol-Myers Squibb, Celltrion, Genentech, GSK, Janssen, Lilly, Novartis, Pfizer Inc, Sanofi-Aventis and UCB. PCT is a consultant for AbbVie, Biogen, Bristol-Myers Squibb, Fresenius, Galapagos, Gilead, Janssen, Lilly, Pfizer Inc, Roche, Sanofi-Aventis and UCB, and has received grant/research support from Celgene, Galapagos, Gilead and Lilly. VA is a consultant for AbbVie, Merck-Serono, Novartis and Pfizer Inc, and has received grant/research support from AbbVie, Lilly, Genentech, GSK, Pfizer Inc and UCB. PJM is a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Corrona, Janssen, Lilly, Merck, Novartis, Pfizer Inc, Sun, UCB and Zynerva, and has received grant/research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, Pfizer Inc, Sun and UCB. AGB, JCC, LF and JW are employees and shareholders of Pfizer Inc.

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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.

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