ORIGINAL ARTICLE

Tofacitinib versus etanercept or placebo in patients with moderate to severe chronic plaque psoriasis: patient-reported outcomes from a Phase 3 study

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Abstract

Background Tofacitinib is an oral Janus kinase inhibitor that is being investigated for psoriasis. Psoriasis impacts on physical and psychological well-being; improvements in health-related quality of life (HRQoL) with etanercept in psoriasis are well documented.

Objective To evaluate HRQoL with tofacitinib, vs. placebo or etanercept, in the Phase 3, randomized, placebo-controlled, non-inferiority, Oral-treatment Psoriasis Trial (OPT) Compare Study (NCT01241591).

Methods Adults with moderate to severe chronic plaque psoriasis were randomized 3:3:3:1 to tofacitinib 10 or 5 mg twice daily (BID), etanercept 50 mg twice weekly or placebo, for 12 weeks. Patient-reported outcomes (PROs) included Dermatology Life Quality Index (DLQI), Itch Severity Item and Patient Global Assessment of psoriasis.

Results At baseline, 83.4% (911/1092) of patients had a DLQI score ranging between 6 and 30, indicating a substantial burden of disease. By Week 12, 47.3%, 43.6% and 30.9% of patients in the tofacitinib 10 mg BID, etanercept and tofacitinib 5 mg BID groups, respectively, had a DLQI score of 0 or 1 (no effect of psoriasis on QoL) vs. 7.8% for placebo (all $P < 0.0001$). Tofacitinib significantly reduced itch vs. placebo ($P < 0.05$ both doses) and etanercept ($P < 0.0001$ both doses) within 1 day of starting treatment. Furthermore, reductions in itch were greater with tofacitinib 10 mg BID, vs. etanercept, at Weeks 2–12 (all time points $P < 0.05$). At Week 2, an Itch Severity Item score of 'little or no itch' was more frequent with tofacitinib 10 mg (68.6%) vs. etanercept (57.4%) and placebo (12.2%), and the PtGA response rate was significantly greater with tofacitinib 10 mg vs. placebo ($P < 0.05$).

Conclusion Oral tofacitinib provided significant improvements across multiple PROs by Week 12. Improvements with tofacitinib 10 mg BID were comparable to etanercept, and improvements in itch were greater and more rapid with tofacitinib 10 mg BID.

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Conflicts of interest

F.V. has been a principal investigator, member of a scientific advisory board or speaker for AbbVie, Janssen, Eli-Lilly, Merck, Novartis and Pfizer Inc. C.P. has been a consultant or investigator for AbbVie, Amgen, Boehringer, Celgene, Eli-Lilly, Janssen-Cilag, Novartis and Pfizer Inc. H.T., J.P., H.V. and C.M. are employees and stockholders of Pfizer Inc. L.M. was an employee and stockholder of Pfizer Inc at the time of the analysis.

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Introduction

Moderate to severe plaque psoriasis has a recognized impact on the physical and emotional well-being of patients.[1] Some existing treatments for plaque psoriasis can achieve a ≥ 75% reduction in Psoriasis Area Severity Index (PASI75 response) in over half of patients.[2–4] However, such clinical efficacy endpoints do not reflect the complete patient experience. For example, itch is a major symptom of psoriasis and is known to negatively impact the health-related quality of life (HRQoL).[5,6] In addition,

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patients with psoriasis often suffer from impaired physical and/or mental health.[7,8] Thus, despite a variety of clinically efficacious therapeutic options, treatment dissatisfaction remains common in patients with psoriasis.[9]

In order to improve the patient experience, a more holistic approach to outcomes assessment is required, which encompasses patient-reported outcomes (PROs) as well as physician efficacy assessment. Thus, clinical evaluation of treatment efficacy in psoriasis should include measures that evaluate the totality of symptoms and patient perceptions. Etanercept, a biologic agent, has shown improvements in patient-reported measures of HRQoL in psoriasis.[10] However, head-to-head studies that compare clinical efficacy and PROs with an oral small-molecule agent vs. a biologic agent in the psoriasis setting are limited.[11,12]

Tofacitinib is an oral Janus kinase inhibitor that is being investigated for psoriasis. In the Phase 3 Oral-treatment Psoriasis Trial (OPT) Compare Study, tofacitinib 10 mg twice daily (BID) demonstrated non-inferiority to etanercept 50 mg twice weekly (BIW) and superiority to placebo, with regard to PASI75 and Physician Global Assessment (PGA), at Week 12. Non-inferiority to etanercept was not demonstrated for tofacitinib 5 mg BID. Both tofacitinib (5 and 10 mg BID) and etanercept were well tolerated.[13] Specific HRQoL data were collected during the OPT Compare Study[13] and are being presented here, separately from the primary efficacy results, to allow for a more detailed assessment and discussion.

The objective of the present analysis was to examine the impact of tofacitinib (an orally administered small molecule) compared with etanercept (an established, frequently used biologic) or placebo on PROs and HRQoL in patients with moderate to severe psoriasis, using data from the Phase 3 OPT Compare Trial.

Materials and methods

Study design, patients and treatment

The study design and methods have been described previously (clinicaltrials.gov; NCT01241591).[13] Briefly, the OPT Compare Study was a Phase 3, randomized, double-blind, double-dummy, placebo-controlled, active comparator study in adult patients with moderate to severe chronic plaque psoriasis (duration $\geq$ 12 months) and with a PASI score of 12 or higher, a PGA score of 'moderate' or 'severe' (on a five-point severity scale of: 0 'clear'; 1 'almost clear'; 2 'mild'; 3 'moderate'; 4 'severe') and at least 10% affected body surface area. Patients had failed to respond, had contraindication or were intolerant to at least one conventional systemic psoriasis therapy. Patients were randomized (3 : 3 : 3 : 1) to receive oral tofacitinib 5 or 10 mg BID, subcutaneous etanercept 50 mg BIW or placebo (matched dosing schedule) for 12 weeks, with an additional 2- to 4-week follow-up period after the end of the treatment. Primary endpoints included the proportion of patients achieving PASI75 at Week 12 and the proportion of patients achieving a PGA score of 'clear' or 'almost clear' at Week 12. PROs were evaluated as secondary endpoints.

Assessment of patient-reported outcomes

The Dermatology Life Quality Index (DLQI) is a 10-item questionnaire that assesses the impact of chronic skin conditions on HRQoL. Higher scores indicate greater impairment.[14] The DLQI was measured at Day 1 (baseline), Week 4 and Week 12. In addition to the PASI75 endpoint, a composite endpoint of PASI75 or 50–75% reduction from baseline in PASI (PASI50–75) and DLQI score $\leq$ 5, used in psoriasis guidelines as a threshold to determine treatment continuation,[15] was also evaluated at Week 4 and Week 12.

Each patient made a daily assessment of itch severity using the validated Itch Severity Item (ISI);[16] this was recorded in a diary each evening (concurrent with the evening dose of study drug) from 1 week before baseline to Day 15 postbaseline. Thereafter, ISI was assessed in the clinic at Weeks 2, 4, 8 and 12 (or the end of treatment). With the ISI, patients rated the severity of itch due to psoriasis during the previous 24 h using a numeric rating scale, where 0 indicated 'no itch' and 10 indicated 'worst possible itch'.

Patients evaluated their overall cutaneous disease using the Patient Global Assessment of psoriasis (PtGA), which was assessed on Day 1 (baseline) and at Weeks 2, 4, 8 and 12 (or the end of treatment) using a single-item, five-point scale. Category labels were the same as for the PGA: severe, moderate, mild, almost clear, and clear (no psoriasis). PtGA response was defined as 'clear' or 'almost clear'.

The Short-Form Health Survey (SF-36) version 2 acute form measures health status by assessing eight domains of functional health and well-being: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, social functioning, mental health, role limitations due to emotional problems and vitality.[8,17] Physical component summary (PCS) and mental component summary (MCS) scores are calculated from the domain scores; higher scores indicate better HRQoL. Age- and gender-matched normative values were calculated for use as a benchmark comparison and adjusted for a mean value of 50.[18] The SF-36 version 2 acute form, with a 1-week recall period, was utilized and administered at Day 1 (baseline) and Week 12 (or the end of treatment).

Statistical analyses

The full analysis set (FAS) was used for all analyses of PROs and included all patients who were randomized in the trial and received at least 1 dose of randomized investigational drug (tofacitinib, etanercept or placebo). For continuous endpoints, the change from baseline was analyzed using a mixed-effect, repeated-measures model. The least-squares (LS) mean

differences between tofacitinib and etanercept, or placebo, and the associated 95% confidence intervals were derived from this model. Binary endpoints were analyzed using the normal approximation for the difference in binomial proportions between tofacitinib and etanercept, or placebo, with missing values handled by non-responder imputation. No adjustments were made for multiple testing, and nominal *P* values were displayed.

Results

Baseline characteristics and the results of the primary analysis, including PASI75 response, PGA response and clinically meaningful reduction in DLQI, have been reported previously.[13]

PRO measurements at baseline indicated a substantial burden of psoriasis, with 67.1% of patients (733/1093) reporting a PtGA score of 'severe' and 29.6% (324/1093) reporting a score of 'moderate' (Table 1). In comparison, physicians generally rated patients' disease less severely and assigned a PGA score of 'severe' to 16.9% of patients and a score of 'moderate' to 81.6% of patients. Similar to the PtGA data, baseline DLQI scores reflected an impact of psoriasis on HRQoL: 14.9% (163/1092) of patients had a DLQI score of 21–30 (extremely large effect), 45.7% (499/1092) had a DLQI score of 11–20 (a very large effect), and a further 22.8% (249/1092) had a DLQI score of 6–10 (a moderate effect).[19] The mean (standard error [SE]) baseline ISI for treatment groups ranged from 5.2 (0.3) to 5.3 (0.2); an ISI score > 1 at baseline was reported by 93.6% of patients (959/1025). Mean SF-36 PCS and MCS scores for all treatment groups were below the normative mean value of 50: 46.8–48.3 for the PCS and 39.8–42.0 for the MCS, indicating impairments in physical and mental health.

Table 1 Patient-reported outcome measurements at baseline

	Tofacitinib 5 mg BID (*N* = 329)	Tofacitinib 10 mg BID (*N* = 330)	Etanercept 50 mg BIW (*N* = 335)	Placebo (*N* = 107)
n	328	326	332	106
DLQI, mean (SE)	13.0 (0.4)	13.3 (0.4)	12.7 (0.4)	12.3 (0.7)
n	305	308	305	107
ISI, mean (SE)	5.2 (0.2)	5.3 (0.2)	5.2 (0.2)	5.2 (0.3)
n	328	328	330	107
PtGA, *n* (%)				
Almost clear	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
Mild	11 (3.4)	5 (1.5)	14 (4.2)	4 (3.7)
Moderate	106 (32.3)	99 (30.2)	94 (28.5)	25 (23.4)
Severe	211 (64.3)	223 (68.0)	221 (67.0)	78 (72.9)
n	327	327	327	105
SF-36, mean (SE)				
PCS	47.4 (0.5)	48.3 (0.5)	47.5 (0.5)	46.8 (1.0)
MCS	42.0 (0.6)	41.2 (0.6)	42.0 (0.7)	39.8 (1.2)

BID, twice daily; BIW, twice weekly; DLQI, Dermatology Life Quality Index; ISI, Itch Severity Item; MCS, mental component summary; PCS, physical component summary; PtGA, Patient Global Assessment of psoriasis; SE, standard error; SF-36, Short-Form Health Survey version 2 (acute).

DLQI

At Week 12, mean (SE) DLQI scores were 3.5 (0.3) with tofacitinib 10 mg BID, 3.8 (0.3) with etanercept, 5.6 (0.4) with tofacitinib 5 mg BID and 10.3 (0.8) with placebo, which represented substantial reductions from baseline in active treatment groups; a DLQI score of 2–5 indicates only a small effect of psoriasis on patients' lives.[19] Shifts in DLQI score from baseline to Week 12 are illustrated in Fig. 1. Improvements from baseline in LS mean DLQI scores were all statistically significant with tofacitinib (both doses) and etanercept vs. placebo (all $P < 0.0001$). In addition, 47.3% (151/319), 43.6% (142/326) and 30.9% (98/317) of patients in the tofacitinib 10 mg BID, etanercept 50 mg BIW and tofacitinib 5 mg BID groups, respectively, met the more stringent criterion of 'no effect of psoriasis on quality of life' (DLQI score of 0 or 1) at Week 12: $P < 0.0001$ for all comparisons vs. placebo (8/102; 7.8%) (Fig. 2).

Composite PASI75 or PASI50–75 response with DLQI ≤ 5

At Week 12, the proportion of patients who achieved PASI75 or PASI50–75 with a DLQI score ≤ 5 was 73.6% (243/330) with tofacitinib 10 mg BID, compared with 73.7% (247/335), 55.3% (182/329) and 12.2% (13/107) for etanercept 50 mg BIW, tofacitinib 5 mg BID and placebo, respectively. Improvements with active treatment were significant vs. placebo ($P < 0.0001$ for all comparisons).

Itch

A rapid and substantial decrease from baseline in itch (measured by ISI) was observed in patients receiving tofacitinib 10 and 5 mg BID (Fig. 3). Within 1 day of starting treatment, both tofacitinib doses demonstrated statistically significant reductions from baseline in LS mean (SE) ISI score: −1.0 (0.1) for both tofacitinib 5 and 10 mg BID (both $P < 0.05$ vs. placebo). Significant improvements in itch with active treatment (vs. placebo) were maintained through Weeks 2, 4, 8 and 12 ($P < 0.001$ for etanercept at Week 2 and $P < 0.0001$ for all other comparisons; Fig. 3). Reductions in itch with tofacitinib 10 mg BID were significantly larger vs. etanercept ($P < 0.05$ for all time points; Fig. 3).

Of those patients with an ISI score > 1 at baseline, the proportion who achieved 'little or no itch' (ISI ≤ 1) increased steadily in all active treatment groups over time, with the most rapid and substantial improvements observed with tofacitinib 10 mg BID, followed by tofacitinib 5 mg BID and etanercept 50 mg BIW (Fig. 4). Furthermore, a greater proportion of patients achieved 'little or no itch' at Week 2 onwards with tofacitinib 10 mg BID than with etanercept 50 mg BIW ($P < 0.05$ at all subsequent time points). At Week 12, the highest proportion of patients with 'little or no itch' was observed in the tofacitinib 10 mg BID group (68.6% [186/271]), followed by etanercept 50 mg BIW (57.4% [160/279]), tofacitinib 5 mg BID (55.6% [153/275]) and placebo (12.2% [12/98]).

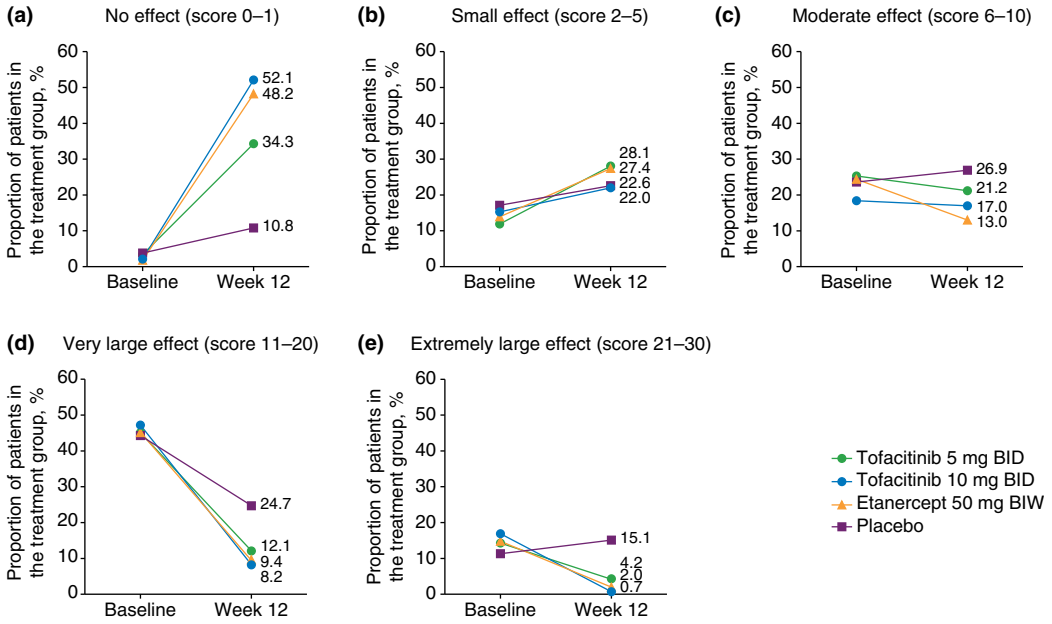

Figure 1 Proportion of patients in DLQI categories at baseline and Week 12, categorized according to the effect of the disease on patients' lives as per previously described classification[19] (FAS, observed cases). BID, twice daily; BIW, twice weekly; DLQI, Dermatology Life Quality Index; FAS, full analysis set.

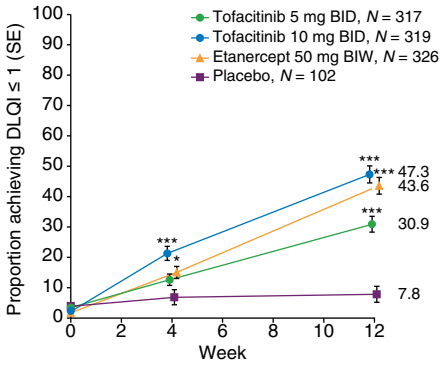

Figure 2 Proportion of patients at baseline, Week 4 and Week 12 with a DLQI score of ≤ 1, indicating 'no effect of psoriasis on quality of life' (FAS, NRI). *$P < 0.05$, ***$P < 0.0001$ vs. placebo. BID, twice daily; BIW, twice weekly; FAS, full analysis set; DLQI, Dermatology Life Quality Index; NRI, non-responder imputation; SE, standard error.

PtGA

The PtGA response rate in the tofacitinib 10 mg BID group was significantly greater vs. placebo at Week 2 ($P < 0.05$), indicating a rapid onset of effect (Fig. 5). From Week 4 onwards, the response rate for all active treatment groups was significantly greater than with placebo ($P < 0.0001$ for all comparisons). In addition, there was a higher proportion of responders in the tofacitinib 10 mg BID group vs. etanercept 50 mg BIW group at Week 4 and Week 8 ($P < 0.05$ for both comparisons). By Week 12, the response rates were similar in the tofacitinib 10 mg BID and etanercept groups (51.8% and 49.0%, respectively) compared with 30.4% for tofacitinib 5 mg BID and 0.9% for placebo.

SF-36 PCS and MCS scores

Improvements in PCS and MCS scores were observed in all groups at Week 12 (Table 2). In active treatment groups, mean PCS exceeded the mean age- and gender-matched normative value, whereas in the placebo group, they remained below this value. Similarly, MCS scores in active treatment groups approached normative values, while corresponding values in the placebo group remained low (data not shown). A highly significant improvement from baseline in health status was observed for all eight domains and scores of the SF-36 in all active treatment groups at Week 12, compared with the placebo group ($P < 0.001$ for 'general health' and 'health transition score'; $P < 0.0001$ for all other domains and scores; Table 2).

Discussion

From a patient perspective, the importance of PROs in psoriasis management should not be understated. Improvements in PROs are not only associated with better HRQoL for the patient[20] but also have a positive secondary impact on the lives of patients' relatives and partners.[21] Nevertheless, studies on patient perspectives suggest a disconnect with physicians regarding the

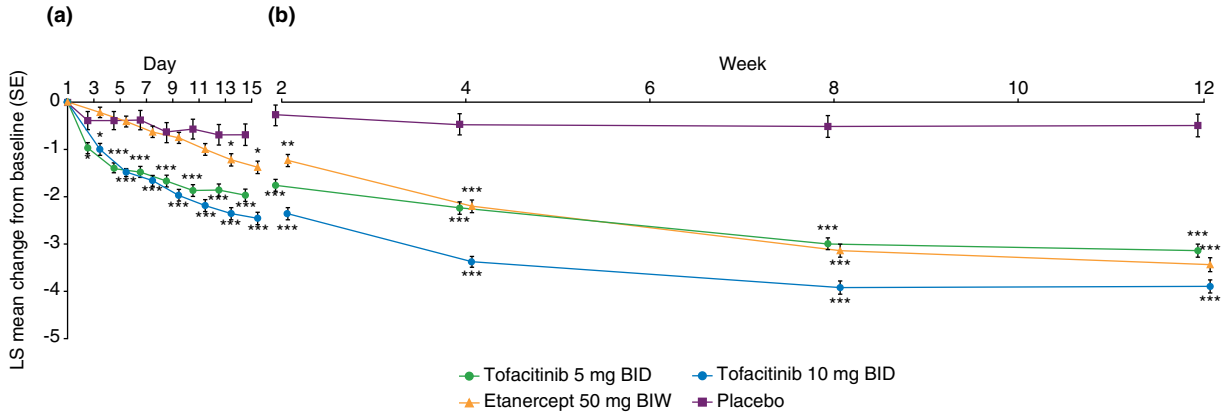

Figure 3 LS mean change in itch (measured by ISI) from (a) baseline to Day 15 (patient diary entries) and (b) from Week 2 to Week 12 (clinic assessments) (FAS, observed cases).
The last patient diary entry was scheduled for the evening before the Week 2 visit. However, not all patients completed the diary for the entirety of the intended period. Also, the window for the Week 2 visit was Day 15 ± 3 days; hence, the Week 2 visit did not necessarily take place on Day 15 for all participants. The Week 2 assessment was made for all patients at the clinic, and these differences account for the apparent difference in ISI values between Day 15 and Week 2.
Days 1–15: tofacitinib 5 mg BID $N = 291$, tofacitinib 10 mg BID $N = 296$, etanercept $N = 290$, placebo $N = 104$. Week 2–12: tofacitinib 5 mg BID $N = 304$, tofacitinib 10 mg BID $N = 306$, etanercept $N = 304$, placebo $N = 107$.
*$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$ vs. placebo.
BID, twice daily; BIW, twice weekly; FAS, full analysis set; ISI, itch severity item; LS, least squares; SE, standard error.

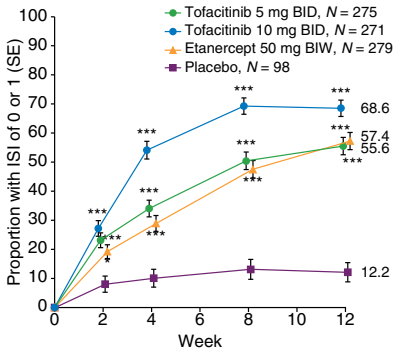

Figure 4 Proportion of patients with a baseline ISI score > 1 who reported 'little or no itch' (score of 0 or 1) at a subsequent visit (FAS, NRI).
*$P < 0.05$, ***$P < 0.0001$ vs. placebo.
BID, twice daily; BIW, twice weekly; FAS, full analysis set; ISI, itch severity item; NRI, non-responder imputation; SE, standard error.

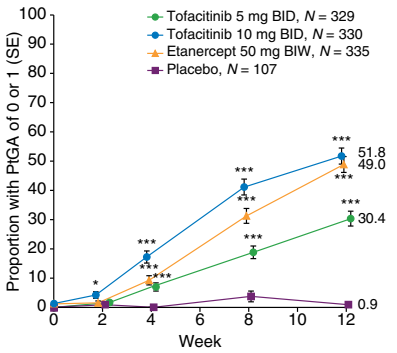

Figure 5 Mean (SE) proportion of patients with a PtGA score of 0 'clear' or 1 'almost clear' (FAS, NRI).
*$P < 0.05$, ***$P < 0.0001$ vs. placebo.
BID, twice daily; BIW, twice weekly; FAS, full analysis set; NRI, non-responder imputation; PtGA, Patient Global Assessment; SE, standard error.

extent of disease that patients experience.[22,23] Here, we found that patients rate their disease more severely than physicians do, highlighting the need for greater physician–patient communication in order to fully understand the patient experience.

The Phase 3 OPT Compare Study in patients with moderate to severe psoriasis was the first direct head-to-head comparison of the oral small-molecule tofacitinib with the biologic agent etanercept (the standard-of-care treatment in this setting). In this analysis, significant improvements in patient-reported measures of disease severity and improvements across multiple domains of HRQoL were observed with tofacitinib by Week 12 and often considerably earlier. Compared with etanercept, the magnitude of improvements in PROs with tofacitinib was comparable in patients dosed with 5 mg BID and greater in patients dosed with 10 mg BID – findings that complement the observed primary efficacy outcomes.[13] It should be noted that the dose of

Table 2 LS mean changes from baseline in SF-36 PCS, MCS and individual domain scores, at Week 12 (FAS, observed cases)

SF-36 domain score, mean change (SE)	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Etanercept 50 mg BIW	Placebo
n	301	302	301	93
PCS	4.0 (0.4)***	5.4 (0.4)***	5.0 (0.4)***	0.5 (0.7)
n	301	302	301	93
MCS	5.2 (0.5)***	7.6 (0.5)***	5.9 (0.5)***	0.7 (0.9)
n	305	304	304	94
Physical functioning	3.4 (0.4)***	4.1 (0.4)***	3.7 (0.4)***	0.3 (0.7)
n	306	304	304	94
Role physical	5.1 (0.4)***	6.7 (0.4)***	5.9 (0.4)***	0.9 (0.7)
n	305	304	304	95
Bodily pain	6.9 (0.5)***	9.3 (0.5)***	8.0 (0.5)***	1.2 (0.9)
n	304	302	304	94
General health	2.7 (0.4)**	5.4 (0.4)***	4.5 (0.4)***	-0.2 (0.7)
n	305	304	304	95
Vitality	4.2 (0.4)***	5.7 (0.5)***	4.6 (0.5)***	0.4 (0.8)
n	305	304	304	95
Social functioning	6.1 (0.5)***	9.0 (0.5)***	7.5 (0.5)***	0.5 (0.9)
n	305	304	304	94
Role emotional	5.7 (0.5)***	7.3 (0.5)***	5.8 (0.5)***	1.2 (0.9)
n	305	304	304	95
Mental health	4.7 (0.5)***	7.1 (0.5)***	5.9 (0.5)***	0.5 (0.9)
n	306	303	306	95
Health transition score	−0.5 (<0.1)**	−0.6 (<0.1)***	−0.6 (<0.1)***	−0.2 (0.1)

**$P < 0.001$, ***$P < 0.0001$ vs. placebo.
BID, twice daily; BIW, twice weekly; FAS, full analysis set; LS, least squares; MCS, mental component score; PCS, physical component score; SE, standard error; SF-36, Short-Form Health Survey version 2 (acute).

etanercept evaluated in the trial (50 mg BIW) is the highest dose approved by the US Food and Drug Administration and European Medicines Agency for the treatment of psoriasis[24] and may be given for up to 12 weeks.[25]

The reliability and validity of the DLQI in a psoriasis population has been well documented.[26] In addition, the minimally important difference (MID) in DLQI has been estimated as a ≥ 5-point change from baseline,[27] which was achieved by 66.3% (tofacitinib 5 mg BID), 78.2% (tofacitinib 10 mg BID) and 74.7% (etanercept) of patients in this trial.[13] A recent reassessment of the MID in DLQI led to the recommendation that the MID should be lowered to 4,[28] which would mean that an even greater proportion of patients in this trial achieved a clinically significant improvement in DLQI.

In addition to PASI75 responders, we also examined a composite endpoint defined by European consensus guidelines for the treatment goals of moderate to severe psoriasis.[15] These guidelines recommend that in patients who achieve an improvement in PASI score ≥ 50% but < 75%, treatment should be continued if DLQI is ≤ 5 or modified if the DLQI score is > 5 at the end of induction therapy or during maintenance therapy. In our study, more than 70% of patients receiving tofacitinib 10 mg BID or etanercept 50 mg BIW, and more than 50% of patients receiving tofacitinib 5 mg BID, achieved this composite endpoint of PASI75 or PASI50–75 with DLQI ≤ 5.

Itch is considered by patients to be the most bothersome symptom of psoriasis[29] and is more likely to cause absence from work and reduced work productivity than psoriasis-related pain or scaling.[30] In the present study, a rapid onset of treatment effect on itch was observed as early as within 1 day of starting treatment; improvements in itch were seen earlier with tofacitinib 10 mg BID than with etanercept. Given the considerable burden that itch represents for patients with psoriasis, and that itch relief can often be slow even with treatment, this finding indicates that tofacitinib may be associated with more effective and quicker relief from itch compared with etanercept, which would be of great importance to patients.

Potential limitations of this study include its relatively short duration of 12 weeks. Long-term studies of tofacitinib in moderate to severe psoriasis are ongoing; 1-year data show sustained improvements in DLQI and itch (measured by ISI) with tofacitinib.[31]

In conclusion, this study demonstrates that tofacitinib is effective across a range of signs and symptoms of moderate to severe plaque psoriasis, including PROs and HRQoL. In general, improvements in PROs and HRQoL observed with tofacitinib 10 mg BID were comparable with etanercept. However, improvements in itch were greater and more rapid with tofacitinib 10 mg BID vs. etanercept, suggesting that tofacitinib may

represent a potential future treatment option for patients with moderate to severe plaque psoriasis.

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