

## ORIGINAL ARTICLE

# Effect of tofacitinib withdrawal and re-treatment on patient-reported outcomes: results from a Phase 3 study in patients with moderate to severe chronic plaque psoriasis

C.E.M. Griffiths,<sup>1,\*</sup> R. Vender,<sup>2</sup> H. Sofen,<sup>3</sup> L. Kircik,<sup>4,5,6</sup> H. Tan,<sup>7</sup> S.T. Rottinghaus,<sup>7,†</sup> M. Bachinsky,<sup>7</sup> L. Mallbris,<sup>8,†</sup> C. Mamolo<sup>7</sup>

<sup>1</sup>The Dermatology Centre, Salford Royal Hospital, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

<sup>2</sup>Dermatrics Research Inc, Hamilton, ON, Canada

<sup>3</sup>UCLA School of Medicine, Los Angeles, CA, USA

<sup>4</sup>Icahn School of Medicine at Mount Sinai, New York, NY, USA

<sup>5</sup>Indiana School of Medicine, Indianapolis, IN, USA

<sup>6</sup>DermResearch PLLC, Louisville, KY, USA

<sup>7</sup>Pfizer Inc, Global Innovative Pharmaceuticals, Groton, CT, USA

<sup>8</sup>Pfizer Inc, Collegeville, PA, USA

\*Correspondence: C.E.M. Griffiths. E-mail: Christopher.Griffiths@manchester.ac.uk

## Abstract

**Background** Tofacitinib is an oral Janus kinase inhibitor being investigated for psoriasis. A Phase 3 withdrawal/re-treatment study (NCT01186744; OPT Retreatment) showed tofacitinib re-treatment was effective in patients with chronic plaque psoriasis.

**Objectives** To describe the effects of tofacitinib withdrawal/re-treatment on health-related quality of life (HRQoL) and disease symptoms measured by patient-reported outcomes (PROs).

**Methods** The study was divided into initial treatment, treatment withdrawal, and re-treatment periods. Initial treatment: patients were randomized to receive tofacitinib 5 ( $n = 331$ ) or 10 mg ( $n = 335$ ) BID for 24 weeks. Treatment withdrawal: patients who achieved both  $\geq 75\%$  reduction in Psoriasis Area and Severity Index (PASI) score from baseline and Physician's Global Assessment of 'clear'/'almost clear' at Week (W)24 received placebo (withdrawal) or the previous dose (continuous treatment). Re-treatment: at relapse ( $> 50\%$  loss of W24 PASI response) or at W40, patients received their initial tofacitinib dose. PROs included: Dermatology Life Quality Index (DLQI), Itch Severity Item (ISI), Short Form-36 (SF-36) and Patient's Global Assessment (PtGA).

**Results** After initial treatment with tofacitinib 5 and 10 mg BID, substantial and significant improvements were reported for mean DLQI (baseline: 12.6 and 12.6; W24: 5.1 and 2.6) and ISI (baseline: 6.7 and 6.9; W24: 2.9 and 1.6). Patients continuously treated with tofacitinib 5 and 10 mg BID maintained those improvements through Week 56 (DLQI: 3.0 and 2.1; ISI: 2.3 and 1.4). By W40, patients withdrawn from tofacitinib 5 and 10 mg BID showed worsening in DLQI (5.0 and 6.2) and ISI (3.7 and 4.0) scores; improvements were regained upon re-treatment (W56, DLQI: 3.4 and 2.4; ISI: 2.2 and 1.6). Similar results were reported for PtGA and SF-36.

**Conclusion** Continuous tofacitinib treatment provided sustained improvement in HRQoL and disease symptoms. Patients randomized to treatment withdrawal lost initial improvements. Upon re-treatment, improvements were recaptured to levels comparable to those seen with continuous treatment.

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## Conflicts of interest

C.E.M. Griffiths has received grant/research support and/or received honoraria from AbbVie, Actelion, Biotest, Celgene, Eli Lilly, Incyte, Janssen, Leo Pharma, MSD, Novartis, Pfizer Inc, Sandoz, Stiefel UK, Trident, UCB and Zymogenetics. R. Vender has served as an investigator and/or received honoraria from AbbVie, Amgen, Centocor, Celgene Dermira, Eli Lilly, Leo Pharma, Merck, Novartis, Pfizer Inc and Takeda. H. Sofen has served as a principal investigator and consultant for Amgen, Celgene, Eli Lilly, Janssen, Merck, Novartis and Pfizer Inc. L. Kircik has received grant/research support and/or received honoraria from 3M, Abbott Laboratories, Acambis, Allergan, Amgen, Anacor Pharmaceuticals, Assos Pharma, Astellas Pharma US, Asubio, Berlex Laboratories,

<sup>†</sup>Affiliation at the time of the study.

Biogen-Idec, Bioline, Biopelle, Breckinridge Pharma, Colbar, Celgene, Centocor Inc, ColloGenex, Combinatrix, Connecticut Corporation, Coria, Dermik Laboratories, Dow Pharmaceutical Sciences, Dusa, Eli Lilly, Embil Pharmaceutical, EOS, Ferndale Laboratories, Galderma Laboratories, Genentech Inc, GlaxoSmithKline, Innocutis, Innovail, Intendis, Johnson & Johnson, Laboratory Skin Care Inc, LEO Pharma, L-Oréal, Maruho, Medical International Technologies, Medicis Pharmaceutical Corp, Merck, Merz, Nano Bio, Novartis, Noven Pharmaceuticals, Nucryst Pharmaceuticals Corp, Obagi, Onset, OrthoNeutrogena, Pfizer Inc, PharmaDerm, Promius, PuraCap, QLT Inc, Quatrix, Serono, SkinMedica Inc, Stiefel Laboratories Inc, TolerRx, Triax, UCB, Valeant Pharmaceuticals Intl, Warner-Chilcott, XenoPort and ZAGE. H. Tan, M. Bachinsky and C. Mamolo are employees and shareholders of Pfizer Inc. S.T. Rottinghaus and L. Mallbris were employees of Pfizer Inc at the time of the study.

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### Introduction

Psoriasis is a chronic, immune-mediated disease affecting 1–9% of the global population.<sup>1</sup> There are several treatment options available for moderate to severe psoriasis that can provide improvements in clinical assessments of skin symptoms [e.g. Psoriasis Area and Severity Index (PASI) score and Physician's Global Assessment (PGA)]. However, moderate to severe psoriasis affects patients both physically<sup>2,3</sup> and psychologically,<sup>3–6</sup> leading to major health-related quality of life (HRQoL) impairment. Therefore, outcome assessments which encompass patient-reported outcomes (PROs) as well as clinical efficacy are required in order to reflect the complete patient experience.

Improvements in PROs, including measures of HRQoL, disease severity and pruritus, in patients with psoriasis can be achieved with a variety of therapies.<sup>7,8</sup> However, despite the available therapy options, a substantial proportion of patients with moderate to severe psoriasis are not receiving any treatment, or are under-treated.<sup>9,10</sup> Treatment options available to patients may be limited by contraindications, poor tolerability, adverse events and patient preference/tolerability for administration route.<sup>9,11,12</sup> In addition, not all patients are responsive to currently available treatments, or may lose their initial response over time. This can lead to high rates of treatment cycling (discontinuations or switching) over time.<sup>13</sup>

Optimal control of psoriasis usually requires adherence to continuous treatment.<sup>14</sup> Clinical trials have confirmed that continuous treatment with biologic therapies results in better maintenance of efficacy than does interrupted therapy.<sup>14–17</sup> Treatment interruption and re-treatment with biologic therapies has been associated with the development of antidrug antibodies, which increase the risk of failure to recapture efficacy.<sup>18</sup> However, in clinical practice, interruption of treatment for variable periods may occur due to various circumstances such as poor compliance, pregnancy, medically related or unrelated infections, reimbursement issues or surgery. Therefore, it is

important to understand the likelihood of disease recurrence after treatment withdrawal and whether improvements in disease severity and HRQoL can be recaptured following re-treatment.

Tofacitinib is an oral Janus kinase inhibitor that is under investigation for the treatment of psoriasis. In kinase assays, tofacitinib inhibits JAK1, JAK2 and JAK3 and, to a lesser extent, tyrosine kinase 2.<sup>19</sup> JAK inhibition by tofacitinib blocks signalling of key cytokines implicated in immune response and inflammation including the common gamma chain containing cytokines [interleukin (IL)-2, -4, -7, -9, -15 and -21], IL-6 and interferon- $\gamma$ .<sup>19,20</sup> The efficacy and safety of continuous tofacitinib treatment has been demonstrated in four Phase 3 studies of patients with moderate to severe plaque psoriasis.<sup>21–23</sup> One of these studies assessed the effect of tofacitinib withdrawal and re-treatment.<sup>21</sup> In this study, after initial treatment, PASI75 and PGA responses were achieved by ~40% and ~60% of patients who received tofacitinib 5 and 10 mg BID respectively. Continuous tofacitinib treatment effectively maintained responses in the majority of the patients. In patients who relapsed during treatment withdrawal, up to 60% recaptured a response upon re-treatment with tofacitinib. In addition, safety profiles were equivalent in both the continuous treatment group and re-treatment group. Here, we evaluate the effect of tofacitinib withdrawal and re-treatment on HRQoL and disease symptoms in patients who participated in this Phase 3 study in order to compare maintenance of response between patients receiving continuous treatment and those withdrawn from treatment, and to assess whether improvements in HRQoL and disease symptoms can be recaptured upon tofacitinib re-treatment.

### Materials and methods

#### Study design and patients

The study design and patient eligibility criteria have been previously described.<sup>21</sup> Briefly, this was a Phase 3, randomized,

double-blind, parallel-group, treatment-withdrawal and re-treatment study (NCT01186744; OPT Retreatment). Eligible patients were  $\geq 18$  years of age with moderate to severe plaque psoriasis for  $\geq 12$  months covering  $\geq 10\%$  of the total body surface area.

The study was divided into three periods: initial treatment, treatment withdrawal and re-treatment (Fig. 1). In the initial treatment period, patients were randomized (1 : 1) to receive tofacitinib 5 or 10 mg BID for 24 weeks. At the end of the initial treatment period, patients were classified as responders if they achieved both a 75% reduction from baseline in PASI score (PASI75) and PGA rating of 'clear' (score of 0) or 'almost clear' (score of 1). Non-responders were discontinued. Responders entered the treatment-withdrawal period, and were re-randomized (3 : 1) to receive either placebo or their previous tofacitinib dose. Patients were monitored for relapse ( $> 50\%$  reduction in the PASI improvement from baseline to Week 24), and those who relapsed entered the re-treatment period. After 16 weeks, all remaining patients in the treatment-withdrawal period progressed to re-treatment and returned to their original tofacitinib dose.

The study was performed in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided

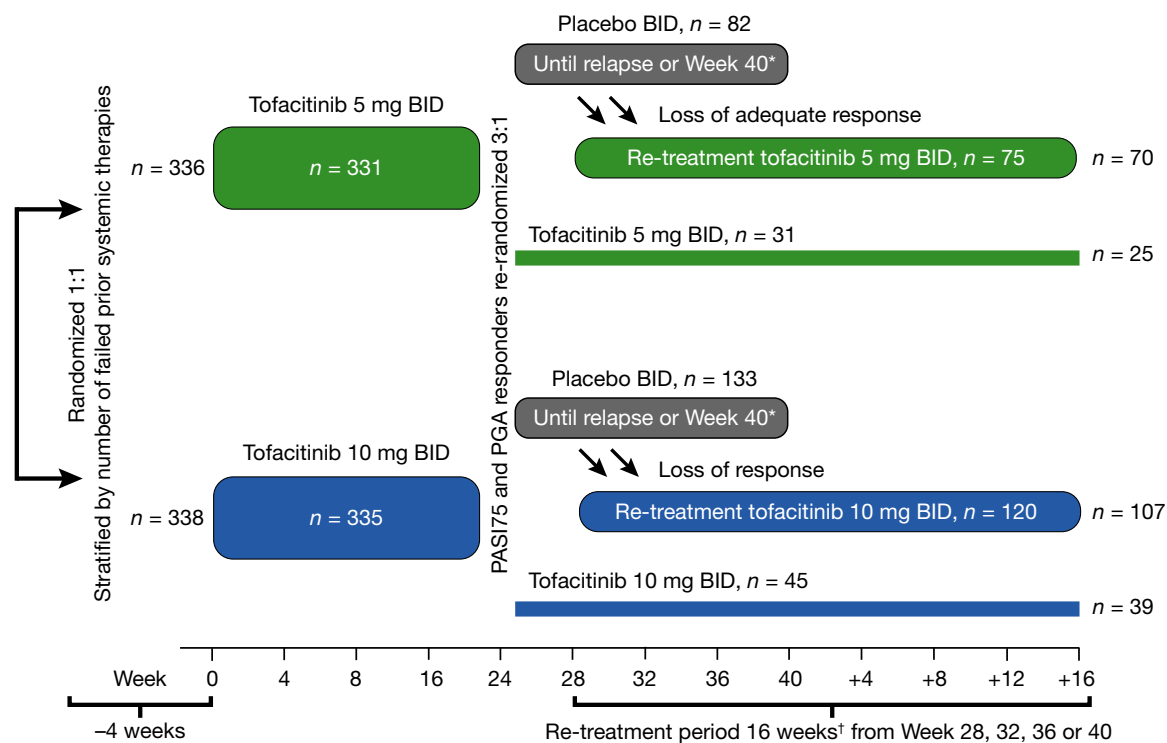
written informed consent. Institutional review boards or ethics committees approved the study protocol.

#### Patient-reported outcome measures

Severity of pruritus was assessed using the Itch Severity Item (ISI), a validated, single-item, horizontal numeric rating scale from 0 (no itching) to 10 (worst possible itching).<sup>24</sup> At each study visit, patients completed the ISI by rating their worst itching due to psoriasis over the previous 24 h.

The impact of a chronic skin condition on HRQoL was assessed with the Dermatology Life Quality Index (DLQI). The DLQI consists of 10 items and the total score ranges from 0 to 30; a score of 0 or 1 indicates no effect (of the skin condition) on the patient's life, while a score of 21–30 indicates an extremely large effect on the patient's life. The minimal clinically important difference for the DLQI has been estimated as a 2- to 5-point change from baseline;<sup>25</sup> here, a minimal clinically important difference of  $\geq 5$ -point change from baseline is used.

Physical and mental health functioning were assessed using the Short Form-36 (SF-36; version 2),<sup>26,27</sup> a widely used 36-item questionnaire measuring functional health status across eight domains. The physical and mental component scores (PCS and



**Figure 1** Study design and patient numbers. \*Patients were evaluated at Weeks 28, 32, 36 and 40. If patients experienced  $> 50\%$  loss of Week 24 PASI response at any time point, they advanced to the re-treatment period. All patients advanced to the re-treatment period by Week 40. †Study duration was 56 weeks. If a patient entered the re-treatment period before Week 40, the duration of the re-treatment period was  $> 16$  weeks; efficacy evaluations were carried out after 16 weeks of re-treatment. BID, twice daily; PASI, Psoriasis Area and Severity Index; PASI75,  $\geq 75\%$  reduction in PASI score from baseline; PGA, Physician's Global Assessment.

MCS respectively) are derived from the eight domain scores, and range from 0 to 100, with higher scores indicating better health functioning.<sup>26,27</sup> The mean score for the PCS and MCS is 50, with scores below 45 indicating impairment relative to the general population.<sup>28</sup>

Overall disease severity at a given time was assessed using the Patient's Global Assessment of psoriasis (PtGA), a single-item, 5-point rating scale (0 = clear, no psoriasis; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe).

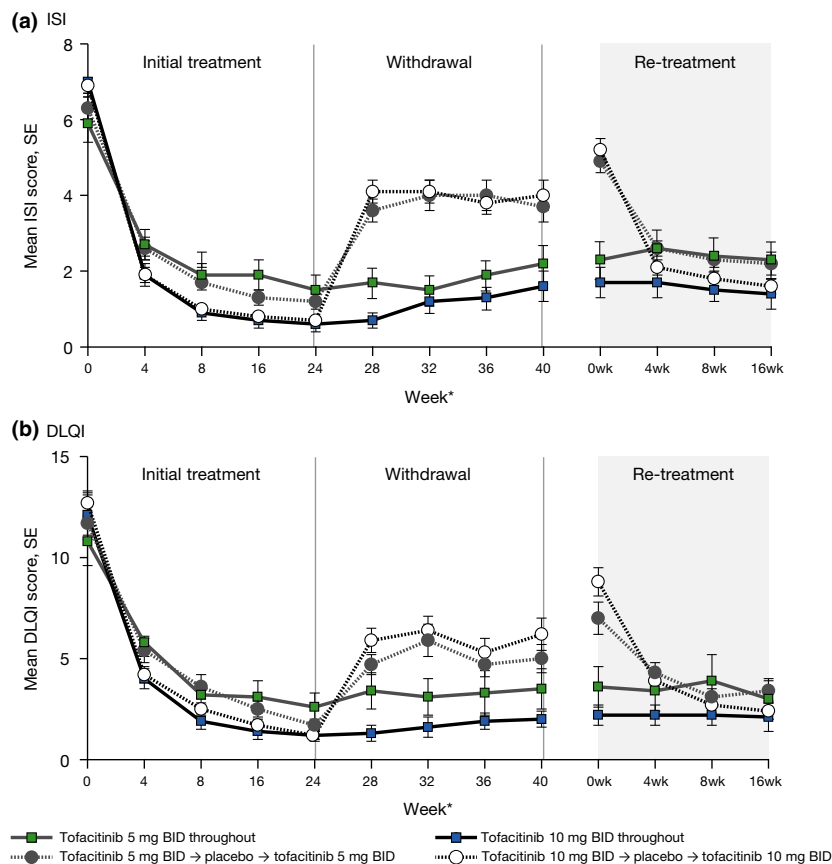
ISI, DLQI and PtGA were assessed at each study visit (once every 4 weeks). The SF-36 was completed at: baseline (Week 0); end of the initial treatment period (Week 24); start of the re-treatment period (Week 40, or at relapse); and after 16 weeks of re-treatment.

### Statistical analysis

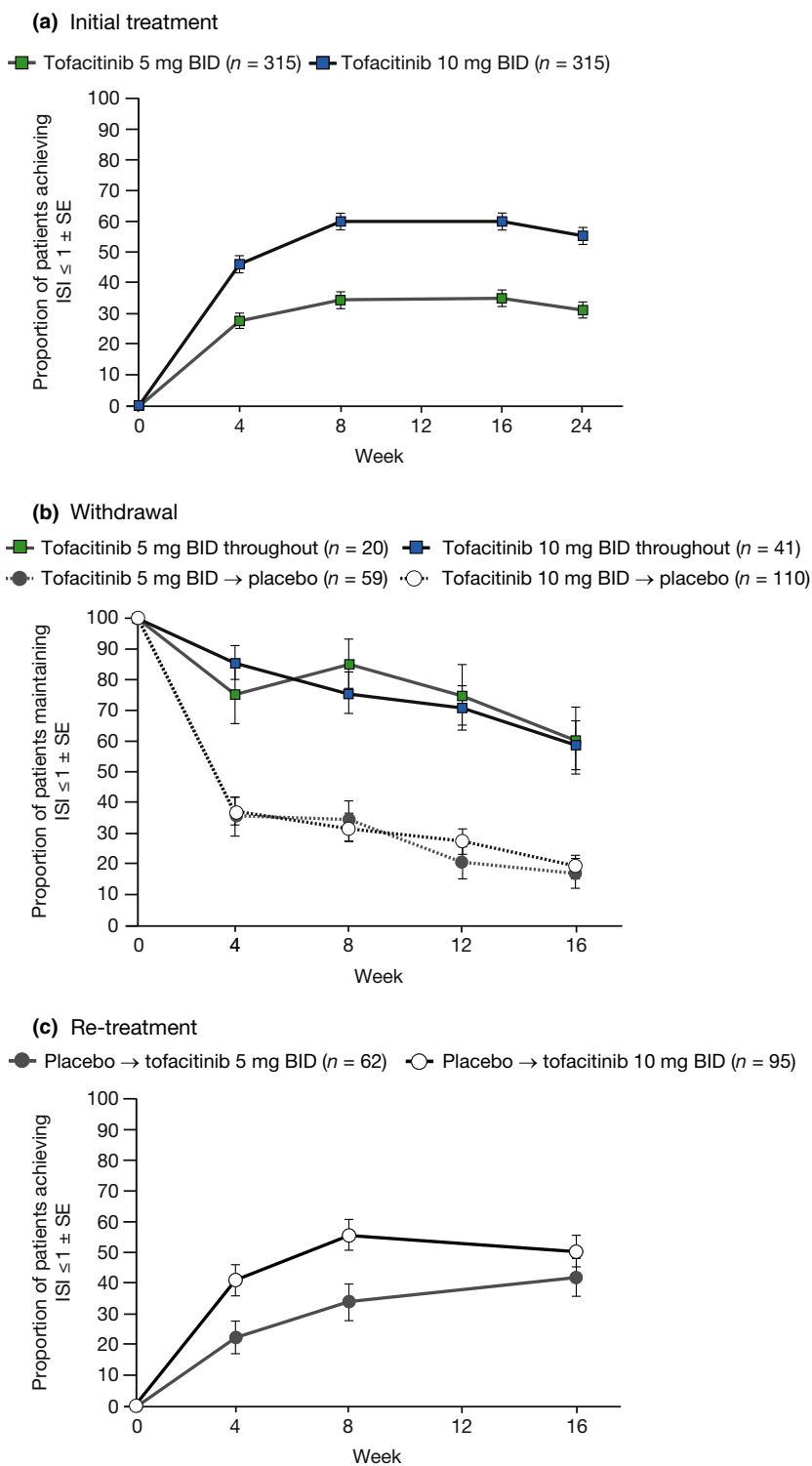
All analyses used the full analysis set: all patients who were randomized and received  $\geq 1$  dose of study drug. Two different reporting conventions were used: one was to report by each

period; the other was to report by treatment sequence over time. When reported by period, baseline values were taken as the last observation up to the first dosing date for each period. When reported by treatment sequence, baseline values at the time of initial randomization were used.

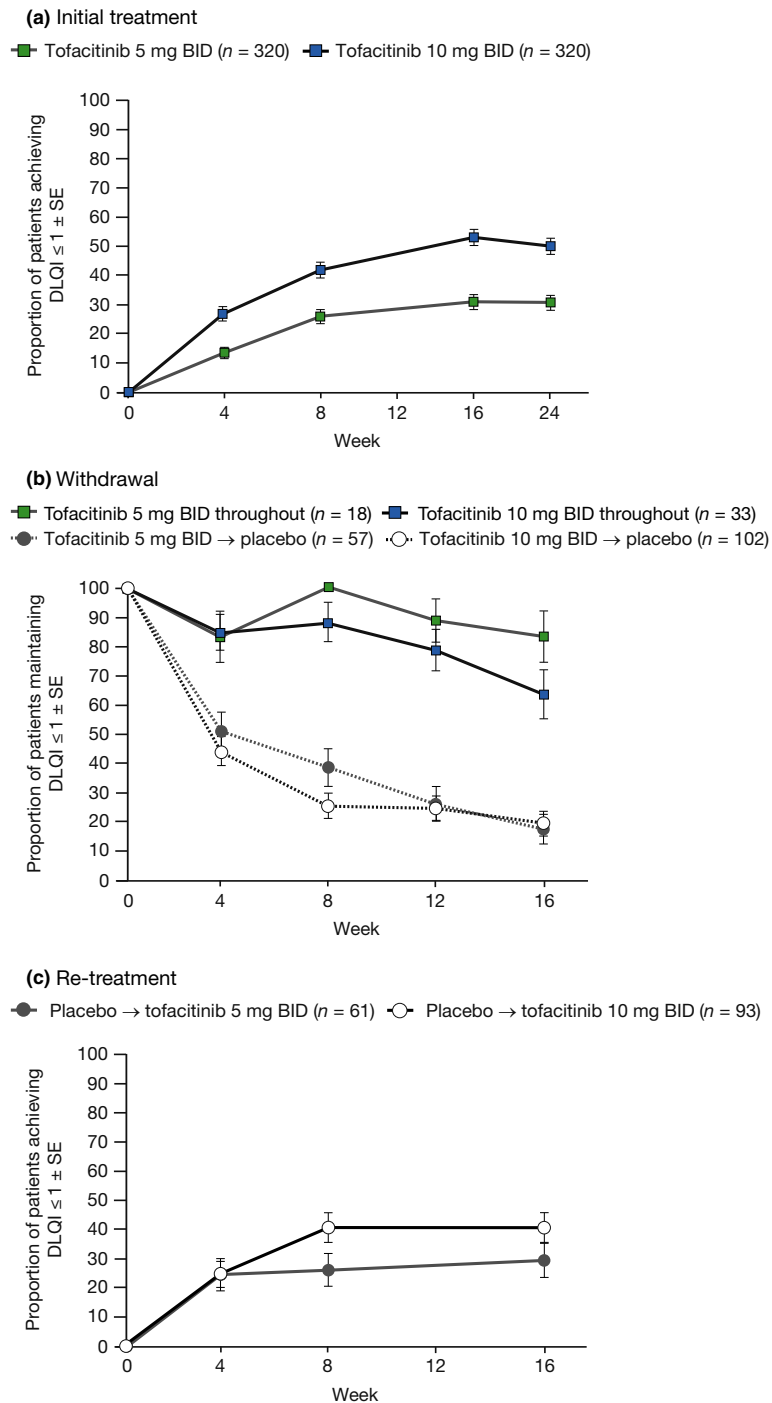
The criteria for entering the treatment withdrawal period were based on PASI75 and PGA responses and not on PRO responses. Therefore, only descriptive trends over time (by treatment sequence) are presented. The proportions of patients achieving and maintaining an ISI score  $\leq 1$  (little or no itching), ISI score = 0 (no itching), DLQI score  $\leq 1$  (no impact of psoriasis on HRQoL), a reduction from baseline in DLQI of  $\geq 5$  points (clinically meaningful response) and a PtGA of 'clear' or 'almost clear' were analysed using the normal approximation to the binomial distribution. Missing values for binary endpoints were handled using non-responder imputation. Change from baseline in the PCS and MCS scores were analysed using an analysis of covariance (ANCOVA) model.



**Figure 2** Mean score over time for (a) ISI and (b) DLQI (Full analysis set, observed case). \*Patients experiencing  $> 50\%$  loss of Week 24 PASI response advanced to re-treatment before Week 40. BID, twice daily; DLQI, Dermatology Life Quality Index; ISI, Itch Severity Item; PASI; Psoriasis Area and Severity Index; SE, standard error; wk, week.



**Figure 3** (a) Proportion of patients achieving ISI  $\leq 1$  (little or no pruritus) during the initial treatment period, among patients with baseline ISI  $> 1$ ; (b) Proportion of patients maintaining ISI  $\leq 1$  during treatment withdrawal, among patients with ISI  $\leq 1$  at the start of the withdrawal period; (c) Proportion of patients achieving ISI  $\leq 1$  during the re-treatment period, among patients with ISI  $> 1$  at the start of the re-treatment period (Full analysis set, non-responder imputation). BID, twice daily; ISI, Itch Severity Item; SE, standard error.



**Figure 4** (a) Proportion of patients achieving  $DLQI \leq 1$  (little to no impact of psoriasis on quality of life) during the initial treatment period, among patients with baseline  $DLQI > 1$ ; (b) Proportion of patients maintaining  $DLQI \leq 1$  during treatment withdrawal, among patients with  $DLQI \leq 1$  at the start of the withdrawal period; (c) Proportion of patients achieving  $DLQI \leq 1$  during the re-treatment period, among patients with  $DLQI > 1$  at the start of the re-treatment period (Full analysis set, non-responder imputation). BID, twice daily; DLQI, Dermatology Life Quality Index; SE, standard error.

**Table 1** SF-36 physical and mental component summary scores and the proportion of patients achieving score > 50 (normal population mean) (Full analysis set, observed case)

|   | Initial treatment    |               |                       |               | Re-treatment                    |              |                                 |               |
|---|----------------------|---------------|-----------------------|---------------|---------------------------------|--------------|---------------------------------|---------------|
|   | Tofacitinib 5 mg BID |               | Tofacitinib 10 mg BID |               | Placebo → Tofacitinib 5 mg BID  |              | Placebo → Tofacitinib 10 mg BID |               |
|   | Baseline             | Week 24       | Baseline              | Week 24       | Baseline (Week 40) <sup>†</sup> | Week 56      | Baseline (Week 40) <sup>†</sup> | Week 56       |
| <b>PCS</b>                                    |                      |               |                       |               |                                 |              |                                 |               |
| Mean score (SE)                               | 48.1 (0.5)           | 50.5 (0.5)*** | 47.8 (0.5)            | 52.9 (0.5)*** | 49.9 (1.1)                      | 52.7 (1.0)** | 49.7 (0.8)                      | 51.2 (0.9)*   |
| Proportion of patients with score ≥ 50, n (%) | 169 (51.2)           | 167 (50.6)    | 178 (53.1)            | 217 (64.8)    | 44 (53.0)                       | 48 (57.8)    | 69 (51.5)                       | 62 (46.3)     |
| <b>MCS</b>                                    |                      |               |                       |               |                                 |              |                                 |               |
| Mean score (SE)                               | 45.2 (0.7)           | 48.9 (0.6)*** | 46.1 (0.6)            | 51.2 (0.6)*** | 51.0 (1.1)                      | 50.9 (1.2)   | 48.3 (1.0)                      | 53.7 (0.8)*** |
| Proportion of patients with score ≥ 50, n (%) | 135 (40.9)           | 154 (46.7)    | 150 (44.8)            | 184 (54.9)    | 51 (61.5)                       | 46 (55.4)    | 63 (47.0)                       | 74 (55.2)     |

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  vs. baseline in the same treatment period; 50 = normal population mean.

<sup>†</sup>For patients who relapsed and were re-treated with tofacitinib before Week 40, baseline was taken as the last observation before the start of the re-treatment period.

BID, twice daily; MCS, mental component summary score; PCS, physical component summary score; SE, standard error; SF-36, Short Form-36.

## Results

### Patients

Patient numbers and demographics have been reported previously.<sup>21</sup> Briefly, a total of 674 patients were randomized in this study (tofacitinib 5 mg BID,  $n = 336$ ; 10 mg BID,  $n = 338$ ), and 666 received treatment. Of these patients, 293 were re-randomized in the treatment-withdrawal period, 264 entered the re-treatment period and 241 patients completed the study (Fig. 1). Of the patients who completed the re-treatment period ( $n = 241$ ), 25 and 39 received continuous treatment with tofacitinib 5 and 10 mg BID, respectively, and 70 and 107 patients had treatment withdrawn and were re-treated with tofacitinib 5 and 10 mg BID.

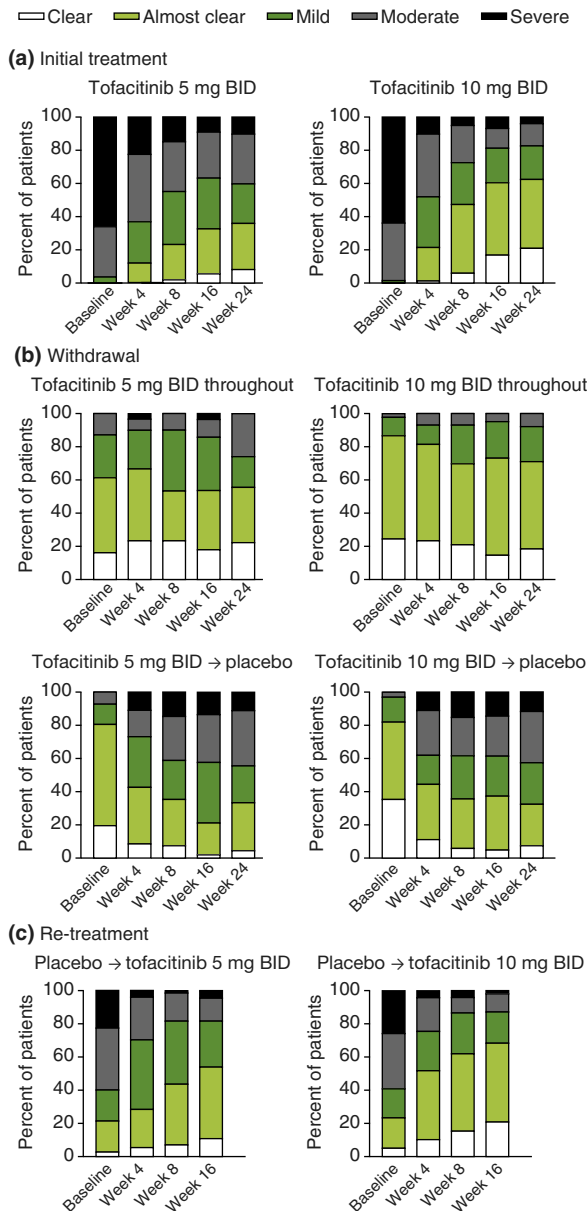
### Patient-reported outcomes

**Itch Severity Item** At baseline, mean [standard error (SE)] ISI scores for patients who were randomized and received treatment with tofacitinib 5 and 10 mg BID were 6.7 (0.1) and 6.9 (0.1), respectively, and the majority of the patients had an ISI score  $\geq 1$  (98.2% and 97.6% respectively), indicating that they experienced pruritus (ISI score of 0 indicates no pruritus). At the end of the initial treatment period, mean ISI scores showed substantial improvement with both tofacitinib doses (Fig. 2a). For patients who were randomized to receive continuous tofacitinib, improvements in itch severity observed at Week 24 were maintained for the duration of the study. In patients who were re-randomized to placebo, ISI score increased within the first 4 weeks of the treatment-withdrawal period, indicating worsening of pruritus. Upon re-treatment with tofacitinib (following

placebo), patients experienced significant improvement in ISI score after 4 weeks, resulting in similar scores to patients who had received continuous treatment (Fig. 2a).

After initial treatment with tofacitinib 5 and 10 mg BID, among patients with ISI > 1 at baseline, 98 (31.1%) and 174 (55.2%), respectively, achieved ISI  $\leq 1$  (little or no itching; Fig. 3a), and among those with ISI > 0 at baseline, 63 (19.4%) and 122 (37.3%) achieved ISI = 0 (no itching), respectively, at Week 24. The median [95% confidence interval (CI)] time to ISI  $\leq 1$  response was 16.4 (16.1, 24.6) and 8.0 (5.1, 8.1) weeks for patients treated with tofacitinib 5 and 10 mg BID respectively. During the withdrawal period, 12 (60%) and 24 (58.5%) patients continuously treated with tofacitinib 5 and 10 mg BID, respectively, maintained ISI  $\leq 1$ , compared with 10 (17.0%) and 21 (19.1%) patients who were withdrawn from tofacitinib (Fig. 3b). Among patients who reported ISI > 1 at the beginning of the re-treatment period, 26 (41.9%) and 48 (50.5%) achieved ISI  $\leq 1$  after 16 weeks of re-treatment with tofacitinib 5 and 10 mg BID respectively (Fig. 3c); among patients with ISI > 0 at the beginning of the re-treatment period, 11 (15.5%) and 30 (28.9%) patients achieved ISI = 0 (no itching). The median (95% CI) time to ISI  $\leq 1$  response for patients re-treated with tofacitinib 5 and 10 mg BID was similar to the initial treatment period, 16.1 (10.1, –) and 8.3 (6.0, 12.4) weeks respectively.

**Dermatology Life Quality Index** At baseline, mean (SE) DLQI scores were 12.6 (0.4) for both treatment groups, indicating a substantial burden on HRQoL. Mean DLQI scores showed clinically meaningful improvement following initial treatment with both doses of tofacitinib (mean change from baseline: –7.1 and –9.7 for 5 and 10 mg BID respectively; Fig. 2b); this



**Figure 5** Percentage of patients within each PtGA assessment category in (a) the initial treatment period; (b) the treatment-withdrawal period; (c) the re-treatment period (Full analysis set, observed case). BID, twice daily; PtGA, Patient's Global Assessment.

improvement was maintained throughout the study for patients who received continuous treatment. Mean DLQI scores increased by 3.6 and 5.4 points in patients withdrawn from tofacitinib 5 and 10 mg BID, respectively, indicating a worsening in HRQoL. However, after 4 weeks of re-treatment with tofacitinib (following placebo), improvement in DLQI score was

regained to a similar level as in patients who received continuous tofacitinib treatment (Fig. 2b).

After 24 weeks' initial treatment, among patients with a DLQI score  $> 1$  at baseline, 98 (30.6%) and 160 (50.0%) patients who received tofacitinib 5 and 10 mg BID, respectively, achieved DLQI  $\leq 1$  (no effect of psoriasis on HRQoL; Fig. 4a). Median (95% CI) time to response for DLQI  $\leq 1$  was 16.0 (8.0, 16.0) weeks with tofacitinib 10 mg BID, and  $> 24$  weeks with 5 mg BID. Of the patients with DLQI  $\leq 1$  and continuously treated with tofacitinib 5 and 10 mg BID, 15 (83.3%) and 21 (63.6%) patients, respectively, maintained DLQI  $\leq 1$  during the withdrawal period, compared with 10 (17.5%) and 20 (19.6%) patients who were withdrawn from tofacitinib (Fig. 4b). The median (95% CI) time to loss of DLQI  $\leq 1$  was calculated *post hoc* and estimated as 8.0 (4.0, 8.0) and 4.0 (4.0, 8.0) weeks for patients who were withdrawn from tofacitinib 5 and 10 mg BID respectively. After 16 weeks of re-treatment with tofacitinib 5 or 10 mg BID (after placebo), among patients with DLQI  $> 1$  at the start of the re-treatment period, 18 (29.5%) and 38 (40.9%) patients, respectively, achieved DLQI  $\leq 1$  (Fig. 4c). A similar pattern of results was reported for patients achieving a reduction in DLQI total score  $\geq 5$  points from baseline (i.e. clinically meaningful improvements).<sup>21</sup> After initial treatment, among patients with DLQI  $\geq 5$  at baseline, 59.9% and 73.0% of patients receiving tofacitinib 5 and 10 mg BID, respectively, reported clinically meaningful improvement in DLQI, and upon re-treatment after tofacitinib withdrawal, 47.5% and 64.5% of patients with DLQI  $\geq 5$  at the start of the re-treatment period reported clinically meaningful improvement in DLQI.

**Short Form-36 physical and mental component summary scores** At baseline, for both dose groups, mean (SE) SF-36 PCS [5 mg BID, 48.1 (0.5); 10 mg BID, 47.8 (0.5)] and MCS [5 mg BID, 45.2 (0.7); 10 mg BID, 46.1 (0.6)] scores were slightly below the general population mean (score of 50). After initial treatment, patients receiving both tofacitinib doses demonstrated significant improvements from baseline in PCS and MCS scores, and the proportion of patients with scores  $\geq 50$  increased (Table 1). For continuously treated patients, mean PCS and MCS scores were maintained above 50 throughout the study (data not shown). Upon re-treatment after placebo, significant improvements from baseline in PCS score were noted with both tofacitinib doses (Table 1), although the proportion of patients achieving PCS scores  $\geq 50$  increased upon re-treatment with tofacitinib 5 mg BID, but not 10 mg BID. Significant improvement from baseline in MCS score only occurred for patients re-treated with tofacitinib 10 mg BID. However, for tofacitinib 5 mg BID, MCS score was above 50 at the re-treatment period baseline. For MCS, the proportion of patients with scores  $\geq 50$  increased upon re-treatment with tofacitinib 10 mg BID, but not 5 mg BID (Table 1).



**Patient's Global Assessment** At baseline, 30–35% of patients classified their psoriasis as 'moderate' on the PtGA, and 64–66% as 'severe'. During the initial treatment period, 98 (29.6%) and 173 (51.6%) patients treated with tofacitinib 5 and 10 mg BID, respectively, achieved a PtGA response of 'clear' or 'almost clear' (Fig. 5a). The proportion of patients achieving a PtGA response of 'clear' or 'almost clear' was maintained with continuous tofacitinib treatment, but rapidly declined in patients withdrawn from tofacitinib (Fig. 5b). Among patients with PtGA of 'mild', 'moderate' or 'severe' after treatment withdrawal, who were re-treated with tofacitinib 5 and 10 mg BID, a large proportion of patients [26 (47.3%) and 53 (63.1%) respectively] regained PtGA response after 16 weeks (Fig. 5c).

## Discussion

In this randomized Phase 3 treatment-withdrawal and re-treatment study of patients with moderate to severe psoriasis, tofacitinib led to significant, substantial and clinically meaningful improvements in several domains that are important to patients, including pruritus (ISI), HRQoL (DLQI), physical and mental health status (SF-36 PCS and MCS scores) and overall disease severity (PtGA). The data clearly demonstrate that continuous treatment with tofacitinib is preferable and leads to sustained improvements in all of the reported PROs. Upon treatment withdrawal, improvements in PROs were either reduced or lost. However, during the 16-week withdrawal period, PRO scores did not return to the original baseline (Week 0) levels, and no worsening of any PRO endpoint was observed compared with the original baseline. Furthermore, the majority of patients who withdrew from treatment regained improvements in HRQoL measures upon re-treatment with tofacitinib, to a similar level as that seen in patients receiving continuous tofacitinib treatment. The results presented here are consistent with previously reported primary efficacy measures,<sup>21</sup> indicating that continuous use of tofacitinib is preferable to maintain PRO improvements; however, when necessary, treatment can be stopped and re-started.

In this study, baseline PRO assessments indicated that patients had a substantial burden of disease, with mean baseline DLQI scores of 12.6 (indicating a large effect on HRQoL). At baseline, more than 90% of patients reported their disease as moderate or severe on the PtGA. These findings are in line with results from previous studies, which demonstrate the substantial impact of psoriasis on the mental and physical health of patients.<sup>29–31</sup>

Pruritus has been reported in 64–84% of patients with psoriasis across different geographical regions,<sup>32,33</sup> and at baseline in this study, over 90% of patients experienced pruritus. Tofacitinib treatment led to a substantial reduction in pruritus severity, with approximately 50% of patients who reported pruritus (ISI > 0) at baseline achieving an ISI score ≤ 1 (little or no itching) after either continuous treatment or re-treatment with tofacitinib. In addition, improvements in pruritus severity were

rapid, both upon initial treatment and upon re-treatment. This finding is particularly pertinent given recent reports from a population-based survey, in which 43% of more than 3000 patients with psoriasis indicated that pruritus was the most bothersome symptom.<sup>10,34</sup> In addition, pruritus is more likely to result in the absence from work than pain or scaling, and leads to reduced productivity.<sup>35</sup> Therefore, for patients with psoriasis who are distressed by pruritus, tofacitinib may potentially represent an important future treatment option.

As reported in other studies, SF-36 PCS and MCS scores were not substantially impaired at baseline;<sup>3</sup> however, significant improvements from baseline to values above the normal population were reported with tofacitinib treatment. In addition, unlike other inflammatory diseases such as rheumatoid arthritis and psoriatic arthritis, which affect the joints, in this study of patients with psoriasis, MCS was impaired to a greater extent than PCS at baseline.<sup>3</sup>

One limitation of this study was that there was no placebo arm during the initial treatment or re-treatment periods. However, the response for all PROs was large and clinically meaningful, and therefore is unlikely to be due to a placebo effect. In addition, other Phase 3 studies have demonstrated the greater efficacy of tofacitinib on PROs compared with placebo in patients with psoriasis.<sup>31,36</sup> Another limitation was that patient entry into the treatment-withdrawal and re-treatment periods was selected based on PASI and PGA responses, and not on PRO criteria. This may have biased PRO results, as a population selection based on clinical efficacy measures is unlikely to align exactly with a population based on PRO endpoints.

In summary, continuous treatment with tofacitinib provided sustained, clinically meaningful improvements in measures of HRQoL and pruritus in patients with chronic plaque psoriasis, consistent with results previously reported with clinical efficacy data such as PASI and PGA. Should treatment interruptions be required (e.g. due to patient choice, surgery or life events), PRO improvements are likely to be reduced; however, the majority of patients re-treated with tofacitinib after withdrawal experienced improvements in their HRQoL to a similar level as that seen in patients who received continuous treatment.

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