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ORIGINAL ARTICLE

Tofacitinib for the treatment of moderate to severe chronic plaque psoriasis in Japanese patients: Subgroup analyses from a randomized, placebo-controlled phase 3 trial

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ABSTRACT

Tofacitinib is an oral Janus kinase inhibitor. These post-hoc analyses assessed tofacitinib efficacy and safety in Japanese patients with psoriasis enrolled in a 52-week global phase 3 study. Patients received tofacitinib 5 mg, tofacitinib 10 mg or placebo twice daily (b.i.d.); placebo-treated patients advanced to tofacitinib at week 16. Primary efficacy end-points were the proportions of patients with 75% or more reduction from baseline Psoriasis Area and Severity Index (PASI-75) and Physician's Global Assessment (PGA) of "clear" or "almost clear" (PGA response) at week 16. Other end-points included: Itch Severity Item (ISI), Dermatology Life Quality Index (DLQI) score and Nail Psoriasis Severity Index (NAPSI). Adverse events (AEs) were recorded throughout the study. Overall, 58 Japanese patients were included in this analysis (tofacitinib 5 mg b.i.d., $n = 22$; 10 mg b.i.d., $n = 24$; placebo, $n = 12$); 29 completed the study. At week 16, significantly more patients receiving tofacitinib 5 and 10 mg b.i.d. versus placebo achieved PASI-75 (50% and 75% vs 0%, $P < 0.01$) and PGA response (59% and 75% vs 0%, $P < 0.001$). Substantial improvements in ISI, DLQI and NAPSI score were observed with both tofacitinib doses. Over 52 weeks, similar rates of AEs were reported across treatment groups; one serious AE occurred with tofacitinib 10 mg b.i.d. Herpes zoster occurred in three patients receiving tofacitinib 10 mg b.i.d. No deaths, serious infections, malignancies or gastrointestinal perforations were reported. Results were generally consistent with global analysis, suggesting sustained efficacy and a manageable safety profile, with increased herpes zoster incidence, of tofacitinib in Japanese patients with psoriasis.

Key words: **Janus kinase inhibitor, Japanese, oral medicine, plaque psoriasis, tofacitinib.**

INTRODUCTION

Psoriasis is a chronic, systemic, inflammatory disease. The most common form is plaque psoriasis, which accounts for approximately 90% of all cases.[1] Psoriasis is associated with an increased incidence of chronic comorbid conditions, and psoriasis patients are at higher risk of hypertension, type 2 diabetes and cardiovascular mortality than the general population.[2–5] The effect of psoriasis on the patient includes psychosocial as well as physical manifestations, and can result in stigmatization, anxiety and depression, and affect interpersonal relationships.[6,7]

The prevalence of psoriasis in the Japanese population has been reported to be 0.34%.[8] Although this is lower than reported in other regions, which range from 1% in the USA to 8.5% in Norway,[9] there are currently more than 400 000 Japanese patients with psoriasis.[8] Given the prevalence, together with the consequences of the disease, psoriasis represents a substantial health issue in Japan.

In Japan, therapies currently approved for treatment of psoriasis include topical corticosteroids and vitamin D_3, phototherapy, the oral systemic agents etretinate and cyclosporin and the injectable/infusible biologics infliximab, adalimumab, ustekinumab, secukinumab, brodalumab and ixekizumab; methotrexate is not available as a treatment option for psoriasis in Japan.[10–13] Topical therapies have limited effectiveness, particularly in moderate to severe disease, and are also considered inconvenient by many patients.[14,15] The effectiveness

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and convenience of phototherapy have also been reported to be lower than many systemic treatments.[14,15] Side-effects, including renal failure and hypertension, limit the long-term use of cyclosporin.[16] Although biologics have a high level of therapeutic effect,[10] use of some biologic agents has been associated with an increased risk of serious infections.[17] In addition, some biologics can also lose efficacy over time due to the development of anti-drug antibodies,[18] and the requirement for parenteral administration may be an issue for some patients.[19] Because of these limitations, there remains an unmet need for safe and effective oral therapies with unique mechanisms of action for treatment of psoriasis.

Tofacitinib is an oral Janus kinase (JAK) inhibitor. The efficacy and safety of tofacitinib 5 and 10 mg twice daily (b.i.d.) in patients with moderate to severe chronic plaque psoriasis has been demonstrated in global phase 3 trials[20–23] of up to 56 weeks' duration, and in a long-term extension (LTE) study with efficacy end-points reported through 24 months and safety reported over 33 months of exposure.[23] The efficacy and safety of tofacitinib has also been studied in several other immune-mediated inflammatory diseases, including rheumatoid arthritis,[24–29] psoriatic arthritis (NCT01877668, NCT01882439, NCT01976364), ankylosing spondylitis,[30] Crohn's disease[31] (NCT01393626, NCT01393899, NCT01470599) and ulcerative colitis.[32,33]

The phase 3 OPT Pivotal 1 study in psoriasis included sites in Japan; here, we report the results of post-hoc analyses of data for the Japanese patients enrolled in OPT Pivotal 1. The objective of these analyses was to describe the efficacy, safety and tolerability of tofacitinib over 52 weeks in Japanese patients with chronic moderate to severe plaque psoriasis.

METHODS

Study design

Post-hoc analyses were conducted using data from Japanese patients enrolled in an international, randomized, double-blind, placebo-controlled phase 3 study, OPT Pivotal 1 (NCT01276639).[22] Patients were randomized 2:2:1 to treatment with tofacitinib 5 mg b.i.d., tofacitinib 10 mg b.i.d., or placebo b.i.d. Placebo-treated patients were re-randomized at week 16 to tofacitinib 5 mg b.i.d. or 10 mg b.i.d. At week 28, patients who had not achieved either 75% or more reduction from baseline in the Psoriasis Area and Severity Index (PASI-75) or a Physician's Global Assessment of "clear" or "almost clear" (PGA response) discontinued study treatment. Tofacitinib treatment was continued up to week 52 for all patients remaining in the study. Eligible patients could enroll in an open-label LTE study, otherwise a follow-up visit was performed 2–4 weeks after the patient's last dose of study medication.

The study was conducted in compliance with the Declaration of Helsinki, the Good Clinical Practice Guidelines established by the International Conference on Harmonisation, and local country regulations relevant to the use of new therapeutic agents. The final protocol, all amendments and informed consent documentation were reviewed and approved by the institutional review boards and/or the independent ethics committees of the investigational centers. Patients provided written, informed consent.

Patients

Full inclusion and exclusion criteria for the OPT Pivotal 1 study have been described previously.[22] Briefly, patients were aged 18 years or older, with a diagnosis of plaque-type psoriasis 12 months or more prior to study entry, a PASI score of 12 or more, a PGA score of 3 (moderate) or 4 (severe), and 10% or more affected body surface area at baseline. Concomitant use of phototherapy, topical therapy or systemic treatments other than study medication was not allowed. Patients were excluded if they had non-plaque forms of psoriasis or drug-induced psoriasis; a recent systemic or local infection; evidence of active, latent or inadequately treated *Mycobacterium tuberculosis* infection; or a known malignancy or history of malignancies (except for adequately treated or excised basal/squamous cell carcinoma or cervical carcinoma *in situ*).

Assessments and outcomes

Efficacy

The primary efficacy end-points were the proportions of patients achieving PASI-75 and PGA responses at week 16. Other end-points included: Itch Severity Item (ISI) score, Dermatology Life Quality Index (DLQI) score and Nail Psoriasis Severity Index (NAPSI) score; and the proportions of patients achieving 90% or more reduction from baseline PASI score (PASI-90), at least 75% reduction from baseline NAPSI score (NAPSI-75), a score of 1 or less on the DLQI (indicating psoriasis has no effect on the patient's life),[34] and a score of 1 or less on the ISI (indicating "little or no itch").[35] All end-points were assessed at baseline and at weeks 2, 4, 8, 12, 16, 20, 28, 40 and 52, with the exception of NAPSI, which was assessed at baseline, and weeks 8, 16, 20, 28, 40 and 52.

Safety

Safety end-points included the incidence of adverse events (AEs), serious AEs, discontinuations due to AEs, and deaths. AEs of special interest, including serious infection events (defined as infections requiring parenteral antimicrobial therapy or hospitalization for treatment, or meeting other criteria requiring classification as a serious AE), herpes zoster infection (HZ), gastrointestinal perforations, major adverse cardiovascular events (MACE) and malignancies were reported. Cardiovascular events, opportunistic infections and hepatic events were adjudicated by an independent, external committee of experts. Changes in clinical laboratory parameters were assessed.

Statistical analyses

Post-hoc efficacy analyses were performed on the full analysis set of Japanese patients, which comprised all randomized patients who received one or more dose of study drug. Safety analyses were performed on the safety analysis set of Japanese patients, which comprised all patients who received one or more dose of study drug.

For the primary end-points, PASI-75 and PGA responses at week 16, statistical comparisons of the differences between treatment groups were evaluated using Barnard's test. There was no adjustment for multiple comparisons as these were post-hoc efficacy analyses. Non-responder imputation (NRI) was applied to missing data. For other end-points, descriptive statistics are presented for patients receiving tofacitinib 5 mg b.i.d., tofacitinib 10 mg b.i.d. and placebo.

RESULTS

Patients

The OPT Pivotal 1 study included 900 patients in the full analysis set, of whom 58 (6.4%) were Japanese and were included in these post-hoc analyses. Twenty-two Japanese patients were randomized to receive tofacitinib 5 mg b.i.d., 24 to receive tofacitinib 10 mg b.i.d. and 12 to receive placebo. Only two Japanese patients randomized to receive placebo continued in the study after week 16; both were re-randomized to receive tofacitinib 5 mg b.i.d.

In total, 29 Japanese patients completed the study and 29 discontinued. During weeks 0–16, two patients receiving tofacitinib 5 mg b.i.d. (9%) and four receiving placebo (33%) discontinued due to lack of efficacy; a further six patients receiving tofacitinib 5 mg b.i.d. and three receiving tofacitinib 10 mg b.i.d. discontinued for this reason between weeks 16 and 52. A total of 14 patients discontinued due to AEs.

Demographics and baseline characteristics of Japanese patients were similar across treatment groups, although four patients (16.7%) in the tofacitinib 10 mg b.i.d. group reported a medical history of psoriatic arthritis, compared with one (8.3%) in the placebo group and none in the tofacitinib 5 mg b.i.d. group (Table 1).

Efficacy

A significantly greater proportion of patients achieved PASI-75 at week 16 with tofacitinib 5 mg b.i.d. (11/22, 50%; $P < 0.01$) and tofacitinib 10 mg b.i.d. (18/24, 75%; $P < 0.0001$) versus placebo (0/12) (Fig. 1a). The proportions of patients achieving PGA response at week 16 were also significantly greater with tofacitinib 5 mg b.i.d. (13/22, 59.1%; $P < 0.001$) and tofacitinib 10 mg b.i.d. (18/24, 75.0%; $P < 0.0001$) versus placebo (0/12; Fig. 1b). PASI-75 and PGA responses were generally sustained to week 52 (Fig. 1). At week 52, 45.5% and 66.7% of patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, achieved PASI-75, and 40.9% and 62.5% of patients achieved a PGA response. For the two patients who advanced from placebo to tofacitinib 5 mg b.i.d. at week 16, both achieved PASI-75 and PGA response at all subsequent time points up to week 52.

Numerically greater proportions of patients achieved PASI-90 at week 16 with tofacitinib 5 mg b.i.d. (18.2%) and tofacitinib 10 mg b.i.d. (66.7%) versus placebo (0%), based on NRI. PASI-90 responses were generally sustained to week 52 for patients who received tofacitinib 5 mg b.i.d. (27.3%) and tofacitinib 10 mg b.i.d. (50.0%).

There was a substantial improvement in pruritus by week 16 with both tofacitinib doses (Fig. 2a). At week 16, mean decreases from baseline in ISI were −4.2 with tofacitinib 5 mg b.i.d. and −3.7 with tofacitinib 10 mg b.i.d., versus −0.1 with placebo. Improvements in ISI were generally maintained through week 52 with both tofacitinib doses (Fig. 2a). At week 16, based on NRI, the proportions of patients achieving ISI of 1 or less were 50.0% (11/22) and 72.7% (16/22) for the tofacitinib 5 mg and 10 mg b.i.d. doses, respectively, versus 8.3% (1/12) for placebo.

At week 16, there was also a substantial decrease in DLQI score, indicating improvement in health-related quality of life (HRQoL), with both tofacitinib 5 mg (−8.2) and 10 mg (−4.7) b.i.d., compared with an increase in mean DLQI score in patients receiving placebo (6.0; Fig. 2b). Improvement in DLQI with tofacitinib versus placebo was seen as early as week 2, with decreases in DLQI score of 2.9 and 3.4 with tofacitinib 5 and 10 mg b.i.d., respectively, at this time, versus 0.2 with placebo. Improvements in DLQI were maintained through week 52 with both tofacitinib doses (Fig. 2b). At week 16, based on

Table 1. Baseline demographic and disease characteristics (FAS)

	Tofacitinib 5 mg b.i.d. (*N* = 22)	Tofacitinib 10 mg b.i.d. (*N* = 24)	Placebo (*N* = 12)	Total (*N* = 58)
Median age, years (Q1, Q3)	47.5 (41.0, 58.0)	47.5 (37.0, 58.0)	51.5 (43.0, 59.0)	50.0 (40.0, 58.0)
Male, *n* (%)	18 (81.8)	20 (83.3)	10 (83.3)	48 (82.8)
Median weight, kg (Q1, Q3)	71.6 (61.0, 81.4)	68.5 (62.8, 77.4)	70.0 (57.5, 77.5)	70.0 (61.0, 79.2)
Median BMI, kg/m^2 (Q1, Q3)	24.6 (22.7, 27.9)	24.6 (23.1, 27.6)	26.5 (22.0, 28.8)	25.1 (22.8, 28.2)
Current smoker, *n* (%)	13 (59.1)	13 (54.2)	8 (66.7)	34 (58.6)
Median psoriasis duration, years (Q1, Q3)	10.2 (6.0, 17.0)	9.6 (4.0, 19.0)	11.9 (9.0, 19.0)	10.3 (6.0, 17.0)
Median PASI score (Q1, Q3)	25.2 (20.4, 38.6)	22.4 (17.6, 30.6)	31.1 (18.8, 37.5)	22.8 (19.5, 36.9)
Median BSA, % (Q1, Q3)	38.5 (31.0, 60.0)	35.0 (27.5, 53.0)	44.3 (24.8, 57.0)	37.0 (28.0, 57.0)
PGA moderate, *n* (%)	19 (86.4)	23 (95.8)	11 (91.7)	53 (91.4)
PGA severe, *n* (%)	3 (13.6)	1 (4.2)	1 (8.3)	5 (8.6)
Median DLQI (Q1, Q3)	8.5 (5.0, 15.0)	5.5 (3.5, 8.0)	13.0 (5.5, 15.0)	8.0 (4.0, 12.0)
Psoriatic arthritis, *n* (%)	0 (0)	4 (16.7)	1 (8.3)	5 (8.6)
Nail psoriasis, *n* (%)	16 (72.7)	20 (83.3)	10 (83.3)	46 (79.3)

BMI, body mass index; BSA, body surface area affected by psoriasis; DLQI, Dermatology Life Quality Index; FAS, full analysis set; ISI, Itch Severity Item; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; Q, quartile.

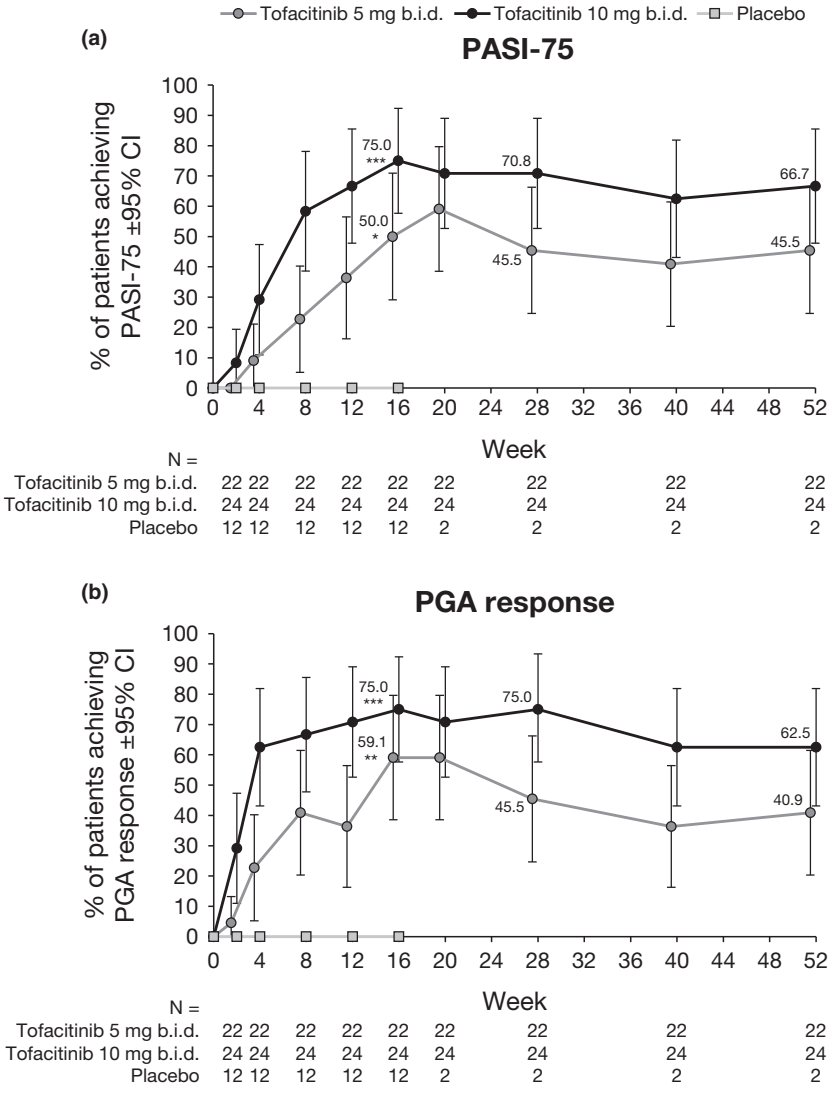

Figure 1. Proportion of patients achieving (a) PASI-75 and (b) PGA response through week 52 (FAS, NRI). *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$ vs placebo, Barnard's test. Patients initially assigned to placebo moved to active treatment at week 16; only two patients advanced from placebo (to tofacitinib 5 mg b.i.d.), both achieved PASI-75 and PGA response at all subsequent time points, data are not shown for weeks 20–52 for these patients. At week 28, patients who did not achieve PASI-75 or PGA response were withdrawn from the study. Eligible patients could enroll in an open-label LTE study; otherwise, a follow-up visit was performed 2–4 weeks after the patient's last dose of study medication. CI, confidence interval; FAS, full analysis set; LTE, long-term extension; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PASI-75, 75% or more reduction from baseline in PASI score; PGA, Physician's Global Assessment; PGA response, "clear" or "almost clear".

NRI, the proportions of patients achieving DLQI of 1 or less were 38.1% (8/21) and 54.2% (13/24) with tofacitinib 5 and 10 mg b.i.d., respectively, versus 0% (0/11) for placebo.

Greater reductions from baseline in NAPSI score were observed at week 16 with both tofacitinib 5 mg (−18.4%) and 10 mg (−37.2%) b.i.d. versus placebo (50.0%; Fig. 2c). NAPSI scores continued to decrease through week 52 with both tofacitinib dose groups (Fig. 2c). At week 16, of those patients with nail psoriasis at baseline, NAPSI-75 was achieved by 4/21 (19.1%) patients who received tofacitinib 10 mg b.i.d., and 1/11 (9.1%) patients who received placebo, based on NRI. None of the 18 patients with nail psoriasis who received tofacitinib 5 mg b.i.d. achieved NAPSI-75 at week 16. By week 52, 4/18 (22.2%) and 10/21 (47.6%) patients who received tofacitinib 5 and 10 mg b.i.d., respectively, achieved NAPSI-75.

Safety

The percentage of patients experiencing AEs during the 16-week placebo-controlled period ranged from 77% with tofacitinib 5 mg b.i.d. to 92% with placebo across treatment groups (Table 2). Up

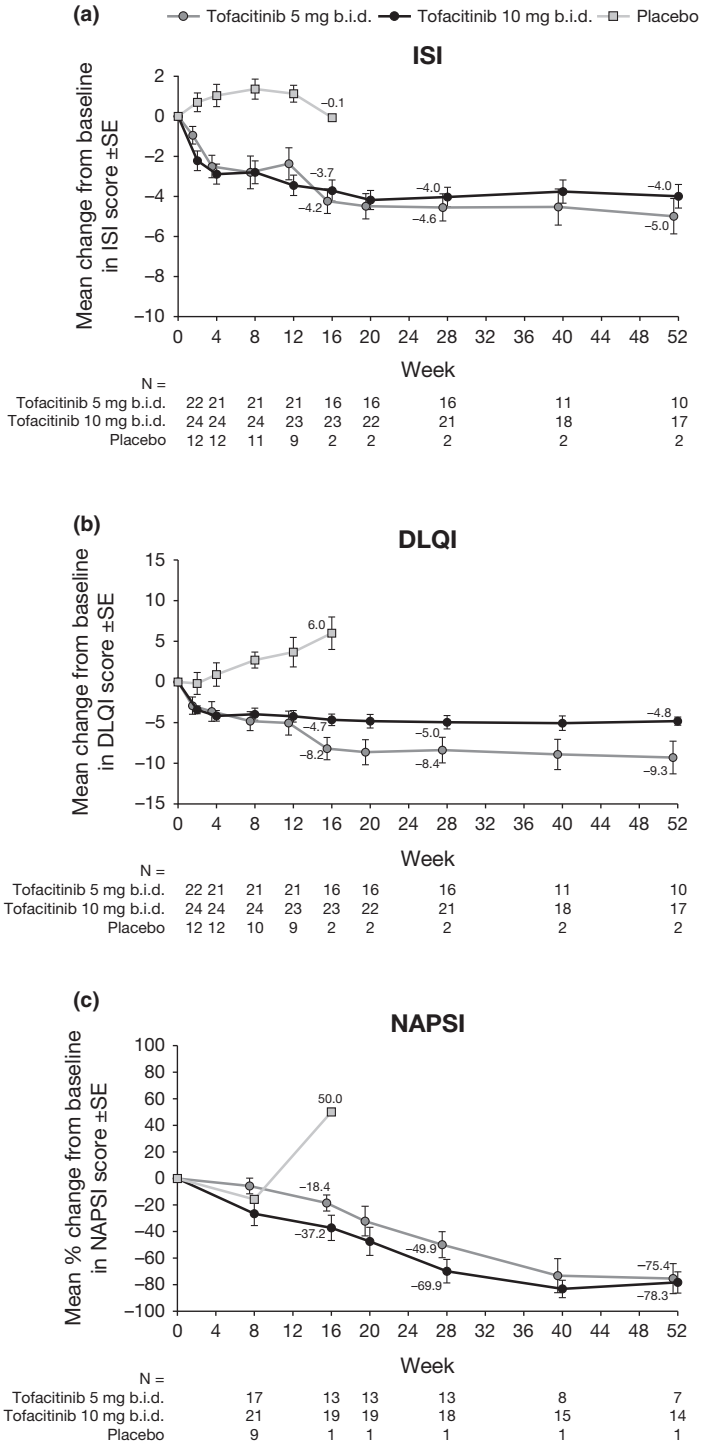

Figure 2. Change from baseline in (a) ISI and (b) DLQI, and (c) percent change from baseline in NAPSI over 52 weeks (FAS, observed cases). Patients initially assigned to placebo moved to active treatment at week 16; only two patients advanced from placebo (to tofacitinib 5 mg b.i.d.), data are not shown for weeks 20–52 for these patients. At week 28, patients who did not achieve PASI-75 or PGA response were withdrawn from the study. Eligible patients could enroll in an open-label LTE study; otherwise, a follow-up visit was performed 2–4 weeks after the patient's last dose of study medication. DLQI, Dermatology Life Quality Index; FAS, full analysis set; ISI, Itch Severity Item; LTE, long-term extension; NAPSI, Nail Psoriasis Severity Index; PASI-75, 75% or more reduction from baseline in PASI score; PGA, Physician's Global Assessment; SE, standard error.

to week 16, AEs resulting in discontinuation occurred in four patients receiving tofacitinib 5 mg b.i.d., four receiving tofacitinib 10 mg b.i.d. and six receiving placebo. No further discontinuations due to AEs occurred between weeks 16 and 52 (Table 2). Up to week 16, most AEs (96.9%) were mild to moderate; four severe AEs were reported, all in placebo-treated patients. No severe AEs were reported after week 16. Nasopharyngitis was the most commonly reported AE throughout the 52 weeks' observation. In addition, there was a relatively high rate of AEs related to laboratory parameter abnormalities (Table 2).

One serious AE was reported: a patient receiving tofacitinib 10 mg b.i.d. suffered a cerebral infarction prior to week 16, which was adjudicated as a MACE. The patient was discontinued from the study. This AE was determined by the investigator not to be related to the study drug. No deaths, serious infections, malignancies or gastrointestinal perforations were reported. Three patients experienced HZ infections; all were receiving tofacitinib 10 mg b.i.d. One case was reported in weeks 0–16 and two in weeks 16–52. One case was mild and two were moderate in severity. No patients were hospitalized due to HZ and no serious HZ events were reported.

Small mean increases in low-density lipoprotein cholesterol (LDL-C) were observed by week 4 after initiation of tofacitinib treatment, with mean levels increasing by 13.9 mg/dL from 102.6 mg/dL at baseline with tofacitinib 5 mg b.i.d., and by 18.6 mg/dL from 111.7 mg/dL at baseline with tofacitinib 10 mg b.i.d. (Fig. 3). Similar increases at week 4 were also observed in high-density lipoprotein cholesterol (HDL-C); mean levels increased by 9.6 mg/dL from 53.6 mg/dL at baseline with tofacitinib 5 mg b.i.d., and by 14.0 mg/dL from 54.5 mg/dL at baseline with tofacitinib 10 mg b.i.d. (Fig. 3). For both LDL-C and HDL-C, levels were generally stable from week 4 through week 52 (Fig. 3).

One patient, with a baseline lymphocyte count of $1.22 \times 10^3/mm^3$, receiving tofacitinib 5 mg b.i.d., had a confirmed lymphocyte count below $0.5 \times 10^3/mm^3$ during the study. Two patients had confirmed decreased hemoglobin levels (defined as a decrease from baseline of 3 g/dL or more or hemoglobin absolute value of 7 g/dL or less) during the study. One patient receiving tofacitinib 10 mg b.i.d., with a baseline hemoglobin level of 18.6 g/dL, had values of more than 3 g/dL below baseline levels reported at each visit from day 85 onward. The second patient was receiving placebo, and had a baseline value of 14.8 g/dL. Reduction in hemoglobin of more than 3 g/dL was reported on study day 30, but returned to within 3 g/dL of the baseline value by day 57. No patients had a confirmed neutrophil count below $1.2 \times 10^3/mm^3$ or alanine or aspartate aminotransferase levels of $\times 3$ or more the upper limit of normal.

DISCUSSION

In these post-hoc analyses, the efficacy and safety of tofacitinib, an oral JAK inhibitor, was analyzed in Japanese patients with moderate to severe plaque psoriasis who had participated in the phase 3 OPT Pivotal 1 study.

Table 2. Adverse events through week 52 (safety analysis set)

	Weeks 0–16			Weeks 0–52	
	Tofacitinib 5 mg b.i.d. (*N* = 22)	Tofacitinib 10 mg b.i.d. (*N* = 24)	Placebo (*N* = 12)	Tofacitinib 5 mg b.i.d. (*N* = 22)	Tofacitinib 10 mg b.i.d. (*N* = 24)
Patients with AEs, *n* (%)	17 (77.3)	21 (87.5)	11 (91.7)	20 (90.9)	23 (95.8)
Patients with SAEs, *n* (%)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (4.2)
Patients discontinued due to AEs, *n* (%)	4 (18.2)	4 (16.7)	6 (50.0)	4 (18.2)	4 (16.7)
Patients with SIEs, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with HZ, *n* (%)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	3 (12.5)
Most common AEs,[†] *n* (%)					
Nasopharyngitis	4 (18.2)	4 (16.7)	3 (25.0)	7 (31.8)	13 (54.2)
Blood cholesterol increased	4 (18.2)	5 (20.8)	0 (0.0)	5 (22.7)	5 (20.8)
Blood CPK increased	2 (9.1)	2 (8.3)	0 (0.0)	5 (22.7)	4 (16.7)
γ-GT increased	2 (9.1)	1 (4.2)	0 (0.0)	4 (18.2)	4 (16.7)
LDL increased	4 (18.2)	2 (8.3)	0 (0.0)	5 (22.7)	3 (12.5)
Psoriasis	4 (18.2)	1 (4.2)	8 (66.7)	5 (22.7)	1 (4.2)
Hyperlipidemia	0 (0.0)	4 (16.7)	0 (0.0)	0 (0.0)	5 (20.8)
Influenza	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	5 (20.8)
Back pain	1 (4.5)	1 (4.2)	1 (8.3)	3 (13.6)	1 (4.2)
Blood triglycerides increased	0 (0.0)	3 (12.5)	1 (8.3)	0 (0.0)	3 (12.5)
Gout	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)
HZ	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	3 (12.5)
Folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (12.5)
Pruritus	1 (4.5)	0 (0.0)	2 (16.7)	1 (4.5)	0 (0.0)

[†]By Medical Dictionary for Regulatory Activities (MedDRA) preferred term; occurring in more than 10% of patients. AE, adverse event; CPK, creatine phosphokinase; γ-GT, γ-glutamyltransferase; HZ, herpes zoster; LDL, low-density lipoprotein; SAE, serious adverse event; SIE, serious infection event.

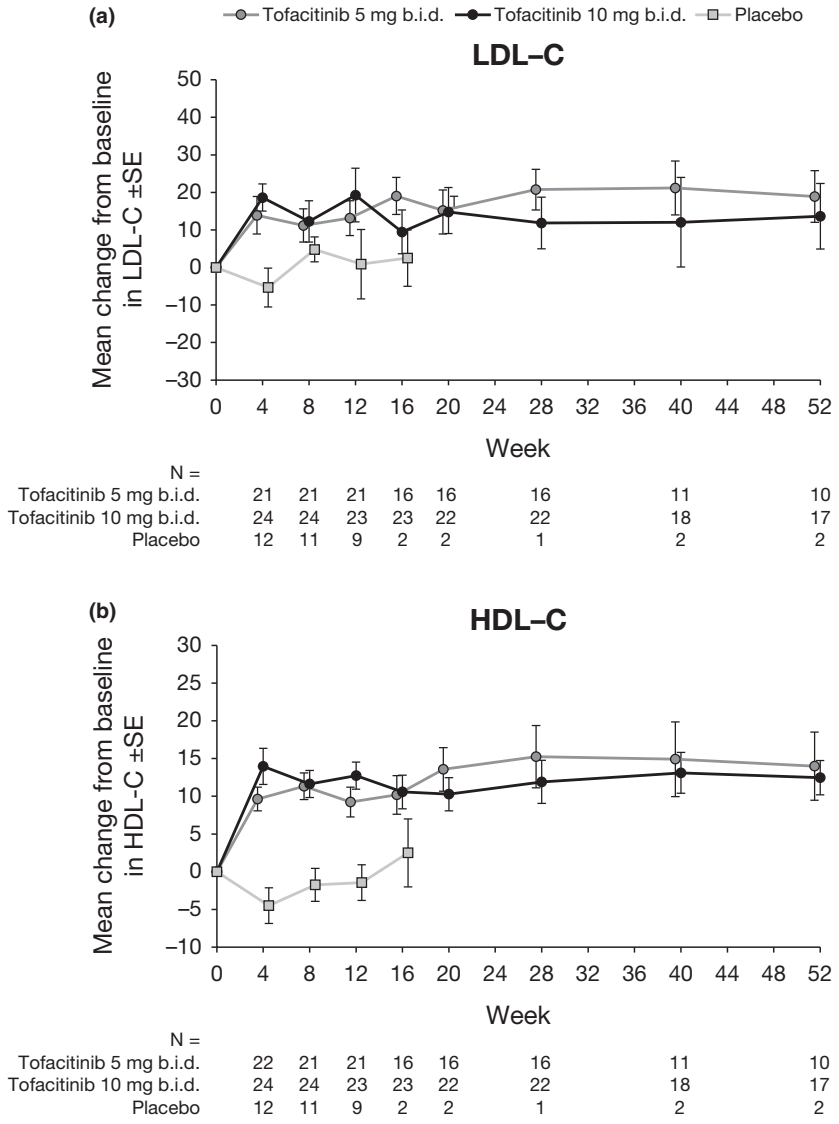

Figure 3. Change from baseline in (a) LDL-C and (b) HDL-C over 52 weeks (FAS, observed cases). Patients initially assigned to placebo moved to active treatment at week 16; only two patients advanced from placebo (to tofacitinib 5 mg b.i.d.), data are not shown for weeks 20–52 for these patients. FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SE, standard error.

Significant improvement in the signs and symptoms of psoriasis with tofacitinib 5 mg and 10 mg b.i.d. compared with placebo were demonstrated, as measured by patients achieving PASI-75 or PGA response at week 16; improvements were sustained up to 52 weeks. Numerically greater response rates were seen with tofacitinib 10 mg b.i.d. compared with 5 mg b.i.d. Improvements were seen in other efficacy outcomes, including HRQoL, pruritus and nail psoriasis. Changes were clinically meaningful; at week 16, 50% and 73% of patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, achieved an ISI score of 1 or less, equating to "little or no itch",[35] and 38% and 54% of patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, achieved DLQI of 1 or less, indicating psoriasis had no effect on the patient's quality of life.[34]

Efficacy was somewhat higher in Japanese patients receiving tofacitinib than the global population. The proportions of Japanese patients achieving PASI-75 at week 16 were 50%, 75% and 0% with tofacitinib 5 mg b.i.d., tofacitinib 10 mg b.i.d. and placebo, respectively, compared with 40% (145/363), 59% (213/360) and 6% (11/177) for the global population of OPT Pivotal 1.[22] At week 16, 59%, 75% and 0% of Japanese patients receiving tofacitinib 5 mg b.i.d., tofacitinib 10 mg b.i.d. and placebo, respectively, achieved PGA response; in the OPT Pivotal 1 global population, these proportions were 42%

(152/363), 59% (213/360) and 9% (16/177).[22] A similar trend of higher efficacy in Japanese patients compared with the global population was also reported in a randomized, double-blind, multicenter, phase 3 study conducted in Japan.[36] In this study, 63% (27/43) and 73% (32/44) of patients receiving tofacitinib 5 mg b.i.d. and 10 mg b.i.d., respectively, achieved PASI-75, and 67% (29/43) and 68% (30/44) achieved PGA response at week 16.

Comparison of the efficacy of tofacitinib with other psoriasis treatments in Japanese patients is challenging, as only one study has directly compared tofacitinib with an active comparator (etanercept) in a head-to-head study; however, that study did not include sites in Japan.[20] Based on indirect comparisons, tofacitinib appears to have efficacy within the range of biologic therapies in Japanese patients. For example, in a phase 2/3 study of adalimumab (80 mg loading dose followed by 40 mg every other week) in Japanese patients with psoriasis, 63% (27/43) of patients achieved PASI-75 at week 16,[37] and in a study of Japanese patients receiving infliximab (5 mg/kg at weeks 0, 2 and 6, and then every 8 weeks), 72% (26/36) and 54% (15/28) of patients achieved PASI-75 after 10 and 50 weeks of treatment, respectively.[38] In tumor necrosis factor inhibitor-naive Japanese patients receiving ustekinumab for 16 weeks, 88% (7/8) achieved PASI-75.[39] Similarly, in a subanalysis of Japanese patients from a global study of patients with psoriasis receiving secukinumab 150 mg or 300 mg (once weekly for 4 weeks and then once every 4 weeks), PASI-75 and PGA responses at week 12 were achieved by 86% (25/29) and 55% (16/29), respectively, of patients receiving 150 mg, and by 83% (24/29) and 55% (16/29) of those receiving 300 mg.[40]

No unexpected safety findings were observed in Japanese patients during the 52-week treatment period; commonly reported AEs were generally consistent with studies of tofacitinib for moderate to severe plaque psoriasis in global populations[20–23] and in a phase 3 multicenter Japanese study.[36] The proportions of patients reporting treatment-emergent AEs, serious AEs and discontinuing due to AEs during the initial 16-week placebo-controlled period appeared to be somewhat higher in the Japanese than in the global population of OPT Pivotal 1,[22] and higher than reported in the phase 3 study conducted in Japan;[36] however, it is difficult to interpret these findings given the limited number of patients included in these post-hoc analyses. Changes in laboratory parameters and the incidence of laboratory test abnormalities were similar to previous reports of tofacitinib in both the phase 3 global and Japanese studies.[22,36]

In these analyses, the incidence of HZ infection over 52 weeks of treatment in patients receiving tofacitinib 10 mg b.i.d. (12.5%) was higher than in the global population (5/360, 1.4%);[22] no cases were reported in Japanese patients receiving tofacitinib 5 mg b.i.d. compared with 0.8% (3/363 patients) in the global studies. In a previous phase 3 study in Japanese patients with psoriasis,[36] HZ was reported in 17.0% (16/94) of patients. An increased incidence of HZ in Japanese patients compared with those from other regions has also been reported in previous studies of tofacitinib in rheumatoid arthritis[41] and in psoriasis.[42] However, the reason behind these regional differences is currently unclear. These findings should be considered alongside reports of an increased risk of HZ infection in patients with inflammatory disease, including psoriasis, treated with some biologics.[43–47] Although there has been some controversy around the level of HZ risk associated with biologics for inflammatory disease,[44,48–50] there appears to be strong evidence suggesting an increased risk with monoclonal tumor necrosis factor-α inhibitors,[46,47] and particularly with infliximab.[43] However, an analysis of US health plan data suggested that the HZ risk associated with tofacitinib in rheumatoid arthritis patients was approximately double that with biologics.[51] An increased incidence of HZ infection in Japanese patients receiving biologic treatment for psoriasis, above that observed in the general population, has also been reported.[52]

Limitations of these post-hoc analyses include the relatively small sample size of the Japanese subpopulation; 58 Japanese patients enrolled, and only 29 completed the study. This high level of discontinuation leads to some difficulties in interpreting findings. The discontinuation rate is much higher than that seen in the phase 3 study in Japanese patients with psoriasis[36] and in the global population in the OPT Pivotal 1 study;[22] there is no clear reason for this difference. In addition, the requirement for discontinuation of non-responders at week 28, although necessary to ensure appropriate patient care, does limit the conclusions that can be drawn with regard to efficacy between weeks 28 and 52.

In conclusion, oral tofacitinib demonstrated efficacy that appeared to be sustained over 52 weeks with a manageable safety profile in Japanese patients with moderate to severe chronic plaque psoriasis; results were generally consistent with the global studies.

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