Tofacitinib as Induction and Maintenance Therapy in Japanese Patients with Active Ulcerative Colitis

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Keywords

Janus kinase inhibitor · Japan · Japanese · Tofacitinib · Ulcerative colitis

Abstract

Background: Tofacitinib is an oral, small molecule Janus kinase inhibitor approved in Japan for the treatment of ulcerative colitis (UC). Differences in the safety profile of tofacitinib in Japanese patients versus the global population, such as a higher risk of herpes zoster, have been reported. **Objectives:** We conducted post hoc analyses of tofacitinib treatment in Japanese patients with moderate-to-severe UC in two global phase III studies. **Methods:** In OCTAVE Induction 1 (NCT01465763), 62 patients were randomized to placebo or tofacitinib 10 mg twice daily (b.i.d.). In OCTAVE Sustain (NCT01458574), 39 patients with clinical response in OCTAVE Induction 1 were re-randomized to placebo, tofacitinib 5 mg, or 10 mg b.i.d. Efficacy endpoints included: remission (primary endpoint; total Mayo score ≤ 2 ; no individual subscore > 1 ; rectal bleeding subscore 0); mucosal healing (Mayo endoscopic subscore ≤ 1); clinical response ($\geq 30\%$ and ≥ 3 -point decrease from induction study baseline total Mayo

score; decrease in rectal bleeding subscore ≥ 1 or absolute subscore ≤ 1). Adverse events (AEs) and clinical laboratory parameters were recorded. **Results:** At week 8 of OCTAVE Induction 1, 22.4% of patients achieved remission with tofacitinib (placebo, 7.7%). At week 52 of OCTAVE Sustain, 31.3% and 66.7% of patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, achieved remission (placebo, 9.1%). The occurrence of AEs or serious AEs in Japanese patients was generally similar to that in the global study population, with no new or unexpected safety risks observed. **Conclusions:** Although patient numbers were small, tofacitinib demonstrated numerically greater efficacy versus placebo among Japanese patients in OCTAVE Induction 1 and OCTAVE Sustain, with a safety profile consistent with that of the global study population.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract, characterized by alternating periods of disease activity and remission [1]. UC

can have a considerable impact upon patients' quality of life and imposes a significant health burden [2], requiring optimum disease management to improve clinical outcomes.

In Japan, the prevalence of UC is 0.16–1.95 cases per 100,000 person-years [3]. While this estimated prevalence is lower than that of Western countries (Europe, 4.9–505 cases per 100,000 person-years; North America, 37.5–248.6 cases per 100,000 person-years) [3], prevalence rates in the Asia-Pacific region, including Japan, are thought to be rising [4–6]. Current treatment options include 5-aminosalicylic acids (5-ASA), corticosteroids, thiopurines (azathioprine and 6-mercaptopurine [6-MP]), immunosuppressants (tacrolimus and cyclosporine), tumor necrosis factor inhibitors (TNFi), integrin inhibitors (vedolizumab), and Janus kinase (JAK) inhibitors (tofacitinib [7]), with treatment guided by the extent and severity of disease [8, 9]. Although conventional treatment options (5-ASA with/without corticosteroids) are available to Japanese patients with UC, with TNFi recommended in those with steroid-refractory or severe disease [10], patients with an inadequate response to TNFi [11] may require alternative treatment options. Consequently, studies evaluating the efficacy and safety of novel treatments in Japanese patients with UC are required.

Tofacitinib is an oral, small molecule JAK inhibitor approved in Japan for the treatment of UC. The efficacy and safety of tofacitinib for UC have been reported in a phase II study [12], two identically designed phase III induction studies (OCTAVE Induction 1 and 2) [13], a phase III maintenance study (OCTAVE Sustain) [13], and an ongoing, long-term, open-label extension study [14]. Differences in the safety profile of tofacitinib in Japanese patients versus the global population, such as a higher risk of herpes zoster, have been reported [15, 16]. Therefore, it is important to understand the efficacy and safety profiles of tofacitinib in Japanese patients with UC.

Here, we report the efficacy and safety of tofacitinib in Japanese patients in the OCTAVE Induction 1 and OCTAVE Sustain randomized controlled trials.

Methods

Patients

OCTAVE Induction 1 (<http://www.clinicaltrials.gov>, NCT01465763) and OCTAVE Sustain (<http://www.clinicaltrials.gov>, NCT01458574) were phase III, multicenter, randomized, double-blind, placebo-controlled studies of patients with moderately to severely active UC, conducted globally at 144 and 297 sites, respectively, between April 2012 and May 2016 [13].

Patients in OCTAVE Induction 1 must have failed or been intolerant to therapy with ≥ 1 of: corticosteroids, azathioprine, 6-MP, or TNFi (infliximab or adalimumab). Oral 5-ASA or oral corticosteroid (≤ 25 mg/day prednisone equivalent) therapy was permitted, provided dosing was stable throughout the study. Concomitant TNFi and immunomodulatory therapies (azathioprine, 6-MP, or methotrexate) were prohibited. Further details of inclusion and exclusion criteria are provided in the online supplementary material (see www.karger.com/doi/10.1159/000502144).

Patients completing OCTAVE Induction 1 with clinical response were eligible for OCTAVE Sustain (see online suppl. Table 1 for definitions of clinical response and other Mayo-score-based endpoints).

Study Design

Patients in OCTAVE Induction 1 were randomized 4:1 to receive tofacitinib 10 mg or placebo twice daily (b.i.d.) for up to 9 weeks [13]. OCTAVE Induction 1 initially included an additional 15 mg b.i.d. arm incorporating three Japanese patients, which was removed following a protocol amendment.

Patients in OCTAVE Sustain were re-randomized (1:1:1) to receive placebo, tofacitinib 5 mg, or tofacitinib 10 mg b.i.d. for up to 53 weeks [13].

Efficacy Assessment

Total Mayo score was determined at baseline and week 8 in OCTAVE Induction 1, and at weeks 24 and 52 in OCTAVE Sustain. Partial Mayo score was determined at baseline and weeks 2, 4, and 8 in OCTAVE Induction 1, and at weeks 4, 8, 16, 24, 32, 40, and 52 in OCTAVE Sustain. Efficacy analyses utilized centrally read endoscopic subscores [13].

In OCTAVE Induction 1, the primary efficacy endpoint was the proportion of patients in remission (total Mayo score ≤ 2 ; no individual subscore > 1 ; rectal bleeding subscore of 0) at week 8. The key secondary endpoint was the proportion of patients achieving mucosal healing (Mayo endoscopic subscore ≤ 1) at week 8.

In OCTAVE Sustain, the primary efficacy endpoint was the proportion of patients in remission at week 52. Key secondary endpoints were the proportion of patients with mucosal healing at week 52 and sustained steroid-free remission among patients in remission at baseline of OCTAVE Sustain. Efficacy data at week 8 in OCTAVE Induction 1 were used as baseline values for OCTAVE Sustain.

Health-related quality of life was assessed using the patient-reported Inflammatory Bowel Disease Questionnaire (IBDQ) at baseline, week 4, and week 8 in OCTAVE Induction 1, and at weeks 8, 16, 24, 32, 40, and 52 in OCTAVE Sustain. Change from baseline in total score and individual domain scores, IBDQ remission (total IBDQ score ≥ 170) and IBDQ response (≥ 16 -point increase from baseline IBDQ total score) were assessed.

Safety Assessment

Adverse events (AEs) and clinical laboratory parameters were recorded throughout both studies. Safety follow-up was out to week 13 post-baseline (OCTAVE Induction 1) and week 57 (OCTAVE Sustain) [13].

Pharmacokinetics

Plasma samples for population pharmacokinetic and exposure-response analyses were collected pre- and post-dose at weeks

Table 1. Demographics and baseline disease characteristics for the Japanese population of patients in OCTAVE Induction 1 and OCTAVE Sustain

	OCTAVE Induction 1		OCTAVE Sustain		
	Placebo (N = 13)	Tofacitinib 10 mg b.i.d. (N = 49)	Placebo (N = 11)	Tofacitinib 5 mg b.i.d. (N = 16)	Tofacitinib 10 mg b.i.d. (N = 12)
Male	10 (76.9)	29 (59.2)	8 (72.7)	9 (56.3)	6 (50.0)
Age, years	38.4±16.4	43.5±14.7	41.7±14.1	41.1±15.5	43.0±12.4
Weight, kg	57.3±12.2	60.3±12.4	60.8±6.8	56.7±8.6	63.8±14.0
Duration of disease, years	5.1 (2.9–15.2)	9.7 (0.8–25.5)	10.4 (1.0–25.2) ^a	9.5 (2.2–25.1) ^a	11.6 (2.7–24.0) ^a
Extent of disease					
Proctosigmoiditis	1 (7.7)	4 (8.2)	0 (0.0) ^b	1 (6.3) ^b	2 (16.7) ^b
Left-sided colitis	5 (38.5)	9 (18.4)	3 (27.3) ^b	3 (18.8) ^b	3 (25.0) ^b
Extensive colitis or pancolitis	7 (53.8)	36 (73.5)	8 (72.7) ^b	12 (75.0) ^b	7 (58.3) ^b
Total Mayo score	8.9±1.5	8.3±1.3	3.6±2.0 ^a	3.1±1.4 ^a	2.4±1.9 ^a
Partial Mayo score	6.2±1.2	5.6±1.0	1.8±1.5 ^a	1.4±0.8 ^a	1.3±1.1 ^a
IBDQ total score	141.9±23.4	150.0±29.1	184.1±27.4	185.7±23.1	184.6±16.6
Prior TNFi treatment	7 (53.8)	24 (49.0)	5 (45.5) ^b	6 (37.5) ^b	6 (50.0) ^b
Prior TNFi failure	6 (46.2)	23 (46.9)	5 (45.5) ^b	6 (37.5) ^b	5 (41.7) ^b
Prior immunosuppressant treatment	12 (92.3)	40 (81.6)	9 (81.8) ^b	13 (81.3) ^b	8 (66.7) ^b
Prior immunosuppressant failure	11 (84.6)	38 (77.6)	8 (72.7) ^b	12 (75.0) ^b	8 (66.7) ^b
Prior tacrolimus treatment	7 (53.8)	17 (34.7)	4 (36.4) ^b	6 (37.5) ^b	3 (25.0) ^b
Prior corticosteroid treatment	13 (100)	47 (95.9)	11 (100.0) ^b	15 (93.8) ^b	12 (100.0) ^b
Prior corticosteroid failure	10 (76.9)	34 (69.4)	9 (81.8) ^b	12 (75.0) ^b	8 (66.7) ^b
Corticosteroid use at baseline	7 (53.8)	20 (40.8)	7 (63.6) ^a	6 (37.5) ^a	4 (33.3) ^a
Smoking status					
Never smoked	7 (53.8)	29 (59.2)	3 (27.3) ^b	12 (75.0) ^b	8 (66.7) ^b
Current smoker	1 (7.7)	1 (2.0)	0 (0.0) ^b	0 (0.0) ^b	1 (8.3) ^b
Ex-smoker	5 (38.5)	19 (38.8)	8 (72.7) ^b	4 (25.0) ^b	3 (25.0) ^b

Data are presented as *n* (%), mean ± standard deviation, or median (range). ^a Indicated baseline values are as of date of randomization into OCTAVE Sustain. ^b Indicated baseline values are at baseline of the induction. b.i.d., twice daily; IBDQ, Inflammatory Bowel Disease Questionnaire; N, number of evaluable patients; *n*, number of patients in the specified category; TNFi, tumor necrosis factor inhibitor.

2 and 8 of OCTAVE Induction 1, and at weeks 8, 24, and 52 of OCTAVE Sustain.

Statistical Analyses

These post hoc analyses included data from patients enrolled in Japanese study centers. Efficacy data are presented for the full analysis set (all patients randomized to tofacitinib [10 mg dose only in OCTAVE Induction 1 full analysis set] or placebo) [13]. For binary efficacy endpoints, patients with missing data were treated as nonresponders. Remission, mucosal healing, and clinical response analyses were stratified by prior TNFi failure, corticosteroid use at baseline, and prior exposure to tacrolimus. Safety data are presented for all randomized patients who received ≥1 dose of study drug. Exposure-response relationships in Japanese patients were compared with results using all data [17, 18]. The exposure-response relationship between individual average plasma tofacitinib concentration (C_{avg}), predicted by the population pharmacokinetic model and achievement of remission in Japanese patients in OCTAVE Induction 1, was assessed using a logistic maximum effect (E_{max}) regression model. Descriptive statistics are presented for patients receiving placebo, tofacitinib 5 mg b.i.d. (OCTAVE Sustain only), and tofacitinib 10 mg b.i.d. The three

patients randomized to tofacitinib 15 mg b.i.d. in induction studies are not included in the induction study efficacy and safety evaluations, but are included in the OCTAVE Sustain efficacy and safety evaluations.

Ethical Approval

Studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines, and were approved by the Institutional Review Boards and/or Independent Ethics Committees at each participating center. All patients provided written informed consent [13].

Results

Patients

Globally, 614 patients were randomized in OCTAVE Induction 1 [13], of whom 62 were Japanese (placebo, *n* = 13; tofacitinib 10 mg b.i.d., *n* = 49; online suppl.

Fig. 1). Of these, 39 were re-randomized in OCTAVE Sustain to receive placebo, tofacitinib 5 mg or 10 mg b.i.d. ($n = 11$, $n = 16$, and $n = 12$, respectively; online suppl. Fig. 1). No large differences in baseline disease activity by total and partial Mayo score and IBDQ were observed between treatment groups in either study (Table 1). In both studies, a slightly higher proportion of patients receiving placebo had received prior tacrolimus versus the tofacitinib 10 mg b.i.d. group, although there were few patients in the placebo group in OCTAVE Induction 1, and in all groups in OCTAVE Sustain. Country of enrollment for patients randomized in the global OCTAVE Induction 1 and OCTAVE Sustain study populations is shown in online suppl. Table 2.

Efficacy Assessment

In OCTAVE Induction 1, 22.4% of Japanese patients receiving tofacitinib 10 mg b.i.d. (11/49) were in remission at week 8 versus 7.7% in the placebo group (1/13) (Fig. 1a). Similarly, response rates at week 8 were numerically greater with tofacitinib 10 mg b.i.d. versus placebo for mucosal healing (30.6% [15/49] versus 15.4% [2/13]; Fig. 1b) and clinical response (69.4% [34/49] versus 23.1% [3/13]; Fig. 1c).

In OCTAVE Sustain, both remission and mucosal healing rates at week 52 were 31.3% (5/16) and 66.7% (8/12) in Japanese patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, compared with remission and mucosal healing rates of 9.1% (1/11) and 18.2% (2/11), respectively, with placebo (Fig. 1a, b). Clinical response rates at week 52 were numerically greater with tofacitinib (5 mg b.i.d., 56.3% [9/16]; 10 mg b.i.d., 83.3% [10/12]); versus placebo (36.4% [4/11]) (Fig. 1c).

In OCTAVE Sustain, sustained steroid-free remission among patients in remission at baseline was achieved by 50.0% (3/6) and 66.7% (4/6) of Japanese patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, versus 0.0% (0/1) with placebo (online suppl. Fig. 2). Sustained remission and sustained mucosal healing rates in OCTAVE Sustain are also shown (online suppl. Fig. 2).

The proportions of patients achieving remission, mucosal healing, and clinical response at week 8 in OCTAVE Induction 1 and at week 52 in OCTAVE Sustain, grouped by prior TNFi failure, corticosteroid use at baseline, and prior tacrolimus treatment, are shown in online suppl. Figure 3. Generally, response rates were numerically greater with tofacitinib versus placebo for all subgroups. However, patient numbers in the subgroups, particularly for the placebo group, were low, and results were inconsistent across endpoints.

In OCTAVE Induction 1, 10.2% (5/49) of patients achieved endoscopic remission at week 8 with tofacitinib 10 mg b.i.d. versus none in the placebo group (Fig. 2a). Clinical remission at week 8 was achieved by 22.4% (11/49) of patients in the tofacitinib group versus 7.7% (1/13) with placebo (Fig. 2b). Symptomatic and deep remission rates at week 8 were also numerically greater with tofacitinib 10 mg b.i.d. (16.3% [8/49] and 10.2% [5/49], respectively) versus placebo (7.7% [1/13] and 0.0% [0/13], respectively) (Fig. 2c, d).

In OCTAVE Sustain, 18.8% (3/16) and 33.3% (4/12) of patients achieved endoscopic and deep remission at week 52 with tofacitinib 5 and 10 mg b.i.d., respectively, versus 9.1% (1/11) with placebo (Fig. 2a, d). Numerically higher clinical and symptomatic remission rates at week 52 were achieved in patients receiving tofacitinib 5 and 10 mg b.i.d. compared with placebo (Fig. 2b, c).

In OCTAVE Induction 1, mean change from baseline in partial Mayo score was greater with tofacitinib 10 mg b.i.d. versus placebo at weeks 2 (first post-baseline assessment), 4, and 8 (Fig. 3a). Efficacy was maintained at week 52 with tofacitinib 5 or 10 mg b.i.d. in OCTAVE Sustain (Fig. 3b).

Patient-Reported Outcomes

Mean changes from baseline in IBDQ total score and IBDQ domain scores were generally numerically greater with tofacitinib 10 mg b.i.d. versus placebo at week 4 and week 8 in OCTAVE Induction 1 (Fig. 4). Among patients who remained in the study, improvements were maintained over time in OCTAVE Sustain in all treatment groups (Fig. 4).

At week 8 of OCTAVE Induction 1, 73.5% of patients receiving tofacitinib 10 mg b.i.d. achieved IBDQ remission versus 38.5% receiving placebo (63.3% versus 38.5% at week 4). IBDQ response was achieved by 65.3% of patients receiving tofacitinib 10 mg b.i.d. versus 38.5% receiving placebo at week 8 (61.2% versus 46.2% at week 4).

In OCTAVE Sustain, 62.5% and 75.0% of patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, achieved IBDQ remission at week 52, versus 45.5% receiving placebo. At week 24, 50.0% and 75.0% of patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, achieved IBDQ remission versus 45.5% receiving placebo. IBDQ response at week 52 was achieved by 56.3% and 75.0% of patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, versus 18.2% with placebo. At week 24, 68.8% and 75.0% of patients receiving tofacitinib 5 and 10 mg b.i.d., respectively, achieved IBDQ response, versus 54.5% receiving placebo.

Fig. 1. Proportion of Japanese patients achieving remission (**a**), mucosal healing (**b**), and clinical response (**c**) at week 8 (OCTAVE Induction 1) and week 52 (OCTAVE Sustain). Data are full analysis set with nonresponder imputation, central read. Clinical response: $\geq 30\%$ and ≥ 3 -point decrease from baseline total Mayo score, plus decrease in rectal bleeding subscore ≥ 1 or absolute sub-

score ≤ 1 . Mucosal healing: endoscopic subscore ≤ 1 . Remission: total Mayo score ≤ 2 , no individual subscore > 1 , rectal bleeding subscore of 0. Δ , treatment difference; b.i.d., twice daily; N, number of evaluable patients in each subgroup; n, number of patients with response.

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Exposure-Response Profile

The exposure-response $E_{\max}$ regression model for Japanese patients in OCTAVE Induction 1 indicated a tofacitinib exposure-response profile similar to that for all (global) patients in OCTAVE Induction 1, with similar individual C_{avg} values between patients who were in remission and those who were not in remission at week 8 (online suppl. Fig. 4). Due to the limited number of patients, exposure-response modeling was not performed for Japanese patients in OCTAVE Sustain.

Safety

The proportion of patients with AEs was 69.2% (9/13) with placebo and 55.1% (27/49) with tofacitinib 10 mg b.i.d. in OCTAVE Induction 1. In OCTAVE Sustain, 72.7% (8/11), 87.5% (14/16), and 100.0% (12/12) of patients receiving placebo, tofacitinib 5 and 10 mg b.i.d., respectively, exhibited AEs (Table 2). In OCTAVE Induc-

tion 1, three serious AEs (SAEs; *Clostridium difficile* infection, UC/condition aggravation) were reported in two patients receiving tofacitinib 10 mg b.i.d.; no SAEs occurred in the placebo group. SAEs only occurred in the placebo group (18.2% [2/11]) in OCTAVE Sustain.

In OCTAVE Induction 1, one patient receiving tofacitinib 10 mg b.i.d. discontinued due to an AE (lymphopenia) and two discontinued due to insufficient clinical response (AEs of worsening UC [defined as AEs with a preferred term of “colitis ulcerative” reported by the investigator] leading to discontinuation were designated as insufficient clinical response); no patients receiving placebo discontinued (Table 2). In OCTAVE Sustain, four patients receiving placebo and four receiving tofacitinib 5 mg b.i.d. discontinued due to AEs; none discontinued due to AEs from the tofacitinib 10 mg b.i.d. group. Five patients receiving placebo, five receiving tofacitinib 5 mg b.i.d., and two receiving tofacitinib 10 mg b.i.d. dis-

Fig. 3. Change from baseline in partial Mayo score in Japanese patients at weeks 2, 4, and 8 in OCTAVE Induction 1, and at weeks 4, 8, 16, 24, 32, 40, and 52 in OCTAVE Sustain, by treatment group.

Data are full analysis set observed cases. b.i.d., twice daily; N, number of evaluable patients; SD, standard deviation.

Fig. 2. Proportion of Japanese patients achieving endoscopic remission (a), clinical remission (b), symptomatic remission (c), and deep remission (d) at week 8 (OCTAVE Induction 1) and week 52 (OCTAVE Sustain). Data are full analysis set with nonresponder imputation, central read. Clinical remission: total Mayo score of ≤ 2 points, with no individual subscore ≥ 1 . Deep remission: total Mayo score of ≤ 2 points, with no individual subscore > 1 point and

endoscopic and rectal bleeding subscores of 0. Endoscopic remission: Mayo endoscopic subscore of 0. Symptomatic remission: total Mayo score of ≤ 2 points with no individual subscore > 1 point, and both rectal bleeding and stool frequency subscore of 0. Δ , treatment difference; b.i.d., twice daily; N, number of evaluable patients in each subgroup; n, number of patients with response.

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continued due to insufficient clinical response in OCTAVE Sustain.

The most frequently reported AEs in any treatment group during OCTAVE Sustain were nasopharyngitis, colitis ulcerative (i.e., worsening of UC), increased blood cholesterol, and insomnia (Table 2).

In OCTAVE Induction 1, similar proportions of patients experienced infections in the tofacitinib and placebo groups, and one serious infection occurred in the tofacitinib group (*Clostridium difficile* infection; Table 2). Infections were the most frequent AE by system organ class in OCTAVE Sustain, although the only serious infection occurred in the placebo group (diverticulitis; Table 2). No herpes zoster cases, cardiovascular events, intestinal perforations, deaths, or malignancies were reported up to week 13 or week 57 in OCTAVE Induction 1 or OCTAVE Sustain.

Changes from baseline in clinical laboratory parameters in both studies are summarized in Table 3. At week 8 of OCTAVE Induction 1 and week 52 of OCTAVE Sustain, increases from baseline in cholesterol, high-density lipoprotein, creatine kinase, aspartate aminotransferase,

and alanine aminotransferase were numerically greater (or decreases from OCTAVE Sustain baseline were numerically smaller) with tofacitinib versus placebo. There was also a numerically greater increase from baseline in low-density lipoprotein in OCTAVE Induction 1 with tofacitinib versus placebo. Conversely, there was a numerically greater increase from baseline in low-density lipoprotein and triglycerides with placebo versus tofacitinib in OCTAVE Sustain. Percentage changes from baseline in triglycerides were similar between treatment groups in OCTAVE Induction 1. There were no clinically meaningful differences with tofacitinib versus placebo in clinical laboratory parameters, including hemoglobin count, absolute neutrophil count, and absolute lymphocyte count, at week 8 or at week 52 in either OCTAVE Induction 1 or OCTAVE Sustain, respectively (Table 3). In OCTAVE Induction 1, no patients had confirmed absolute neutrophil count $<750/\text{mm}^3$ and one patient receiving tofacitinib 10 mg b.i.d. had confirmed absolute lymphocyte count $<500/\text{mm}^3$. In OCTAVE Sustain, no patients had confirmed absolute neutrophil count $<750/\text{mm}^3$ or absolute lymphocyte count $<500/\text{mm}^3$.

Table 2. Summary of safety in Japanese patients in OCTAVE Induction 1 and OCTAVE Sustain

	OCTAVE Induction 1		OCTAVE Sustain		
	Placebo (N = 13)	Tofacitinib 10 mg b.i.d. (N = 49)	Placebo (N = 11)	Tofacitinib 5 mg b.i.d. (N = 16)	Tofacitinib 10 mg b.i.d. (N = 12)
AEs	9 (69.2)	27 (55.1)	8 (72.7)	14 (87.5)	12 (100.0)
SAEs	0 (0.0)	2 (4.1)	2 (18.2)	0 (0.0)	0 (0.0)
Discontinuations due to AEs	0 (0.0)	1 (2.0)	4 (36.4)	4 (25.0)	0 (0.0)
Discontinuations due to insufficient clinical response ^a	0 (0.0)	2 (4.1)	5 (45.5)	5 (31.3)	2 (16.7)
Infections	3 (23.1)	12 (24.5)	4 (36.4)	8 (50.0)	8 (66.7)
Serious infections	0 (0.0)	1 (2.0)	1 (9.1)	0 (0.0)	0 (0.0)
Most frequent AEs ^b					
Nasopharyngitis	3 (23.1)	6 (12.2)	2 (18.2)	4 (25.0)	5 (41.7)
Worsening of UC	0 (0.0)	1 (2.0)	4 (36.4)	5 (31.3)	0 (0.0)
Blood cholesterol increased	0 (0.0)	3 (6.1)	0 (0.0)	2 (12.5)	1 (8.3)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	1 (8.3)

Data are presented as *n* (%). ^a AEs of worsening UC leading to discontinuation were designated as insufficient clinical response. ^b Four most frequently occurring AEs in OCTAVE Sustain are reported for OCTAVE Induction 1. AE, adverse event; b.i.d., twice daily; N, number of evaluable patients; *n*, number of patients in the specified category; SAE, serious adverse event; UC, ulcerative colitis.

Fig. 4. Change from baseline in IBDQ total and domain scores (a–e) in Japanese patients at weeks 4 and 8 in OCTAVE Induction 1, and at weeks 8, 16, 24, 32, 40, and 52 in OCTAVE Sustain, by

treatment group. Data are full analysis set observed cases. b.i.d., twice daily; IBDQ, Inflammatory Bowel Disease Questionnaire; N, number of evaluable patients; SD, standard deviation.

Table 3. Change from baseline in clinical laboratory parameters at week 8 in Japanese patients in OCTAVE Induction 1 and week 52 in OCTAVE Sustain

	OCTAVE Induction 1		OCTAVE Sustain ^c		
	Placebo (N = 13)	Tofacitinib 10 mg b.i.d. (N = 49)	Placebo (N = 11)	Tofacitinib 5 mg b.i.d. (N = 16)	Tofacitinib 10 mg b.i.d. (N = 12)
Percentage change from baseline in lipid profile and creatine kinase					
Total cholesterol, mg/dL	3.4±9.9	21.3±18.6 ^a	-6.5±15.0	2.2±9.6	4.9±15.1
LDL, mg/dL	3.2±14.0	17.7±23.7 ^a	11.9±29.3	7.3±13.5	6.5±21.1
HDL, mg/dL	2.7±12.2	29.6±23.2 ^b	-19.7±9.1	-0.7±21.0	6.0±20.1
Triglycerides, mg/dL	12.4±35.7	13.6±63.5 ^a	16.6±53.6	7.1±37.4	5.2±24.7
Total cholesterol/HDL ratio	1.1±7.7	-5.8±13.7 ^b	16.5±15.9	5.7±16.7	0.7±15.5
LDL/HDL ratio	1.2±13.8	-8.9±17.3 ^b	39.7±37.3	12.8±29.8	3.0±24.4
Creatine kinase, U/L	13.8±114.4	73.5±230.4 ^a	-9.8±33.2	-16.5±38.9	6.9±42.2
Change from baseline in other laboratory parameters					
Hemoglobin, g/dL	-0.1±0.8	0.0±0.7 ^a	1.4±1.0	0.8±1.2	0.5±1.4
ALC, ×10 ³ /mm ³	-0.1±0.5	-0.1±0.7 ^b	-0.2±0.8	-0.1±0.3	-0.5±0.7
ANC, ×10 ³ /mm ³	-0.0±1.3	0.1±2.2 ^b	-1.0±3.8	0.5±1.2	-0.4±1.7
AST, IU/L	1.3±2.6	5.4±8.6 ^a	0.2±3.9	5.6±11.0	5.3±8.4
ALT, IU/L	-0.2±6.0	5.0±11.9 ^a	0.0±4.1	6.2±13.2	6.6±7.6

Data are presented as mean (median for creatine kinase) ± standard deviation. ^a N = 47. ^b N = 46. ^c Data from N = 6, N = 11, and N = 10 patients for placebo, tofacitinib 5 mg and tofacitinib 10 mg b.i.d., respectively. ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; b.i.d., twice daily; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of patients with non-missing data.

Discussion

There is unmet need in Japan consistent with the global unmet need for new UC therapies for patients with an inadequate response to current treatment options. Tofacitinib has demonstrated efficacy for UC treatment in global phase II/III induction, maintenance, and open-label, long-term extension studies [12–14]. Differences in the safety profile of tofacitinib in Japanese patients versus the global population have been reported [15, 16]. These post hoc analyses assessed efficacy and safety of tofacitinib 5 and 10 mg b.i.d. in Japanese patients with moderately to severely active UC.

Remission, mucosal healing, and clinical response rates in Japanese patients were numerically greater with tofacitinib 10 mg b.i.d. compared with placebo at week 8 in OCTAVE Induction 1. Efficacy for these endpoints was maintained at 52 weeks with tofacitinib 5 and 10 mg b.i.d., regardless of prior TNFi failure, corticosteroid use at baseline, or prior tacrolimus treatment. Exposure-response analyses using Japanese data from OCTAVE Induction 1 indicated a tofacitinib exposure-response profile similar to that for all (global) patients. However, this should be interpreted cautiously due to the small group size. In exposure-response subgroup analyses of the glob-

al population [13], race was not identified as a covariant factor for loss of efficacy due to decreased C_{avg} .

Rates of clinical remission, endoscopic remission, deep remission, and symptomatic remission were higher with tofacitinib 10 mg b.i.d. than with placebo at week 8 in OCTAVE Induction 1, and were maintained in OCTAVE Sustain.

Further support for early onset of treatment effect with tofacitinib 10 mg b.i.d. was demonstrated by numerically greater improvements in partial Mayo score as early as week 2 (first post-baseline assessment), and at weeks 4 and 8. Efficacy of tofacitinib 10 mg b.i.d. in the Japanese population was generally consistent with that observed in the global population in OCTAVE Induction 1 [13]. For example, globally, in OCTAVE Induction 1, rates of remission, mucosal healing, and clinical response with tofacitinib 10 mg b.i.d. versus placebo at week 8 were 18.5% versus 8.2%, 31.3% versus 15.6%, and 59.9% versus 32.8%, respectively [13].

The efficacy reported here for tofacitinib was of similar magnitude to that of biologic agents in Japanese patients. In a study of adalimumab in Japanese patients, remission rates at week 8 were similar whether patients received adalimumab 80/40 (14%; 80 mg at week 0, then 40 mg fortnightly), adalimumab 160/80 (10%; 160 mg at week 0, 80 mg at week 2, 40 mg at week 4 and week 6), or placebo

(11%), and at week 52 were significantly higher with adalimumab (23%) versus placebo (7%; $p = 0.001$) [19]. In a study of golimumab in Japanese patients, induction treatment (200 mg of golimumab at week 0, 100 mg at week 2) led to a week 6 clinical remission rate of 19%, and maintenance treatment (100 mg golimumab 4-weekly) led to a week 54 clinical remission rate of 56% versus 19% with placebo [20]. Although Japan-specific data are not available for infliximab, the ACT 1 and ACT 2 studies showed clinical remission rates (infliximab 5 or 10 mg versus placebo) of 28–39% versus 6–15% at week 8, and 42% versus 20% at week 54 [21].

The safety profile of tofacitinib in the Japanese UC population was generally consistent with findings in the global population, with no new or unexpected safety risks compared with tofacitinib treatment in rheumatoid arthritis [22, 23], psoriasis [24], or Crohn's disease [25, 26]. Nasopharyngitis was one of the most common AEs, both in this analysis of Japanese patients and in the global population [13]. In OCTAVE Induction 1, AE rates were higher with placebo than with tofacitinib 10 mg b.i.d., whereas SAE rates were higher with tofacitinib 10 mg b.i.d. versus placebo. In OCTAVE Sustain, AE rates were higher with tofacitinib versus placebo; however, SAEs appeared only in the placebo group.

As in the global analyses, there were treatment-related increases in serum lipid parameters and creatine kinase with tofacitinib 10 mg b.i.d. [13]. In OCTAVE Induction 1, infection rates were similar with tofacitinib 10 mg b.i.d. or placebo, whereas in the global analyses, infections occurred more frequently with tofacitinib [13]. No herpes zoster cases were reported in Japanese patients in these studies, although patient numbers were low. High incidence of herpes zoster with tofacitinib (4.07 per 100 patient-years) was reported for the global UC population [27], and a higher risk of herpes zoster with tofacitinib in Japanese patients versus the global population has been reported [15, 16] (e.g., 7.4 patients with events per 100 patient-years versus 4.3 patients with events per 100 patient-years in the tofacitinib rheumatoid arthritis program [28]). Furthermore, data from rheumatoid arthritis and psoriasis studies suggest that Asian patients are at greater risk than non-Asian patients of developing herpes zoster with tofacitinib treatment [29, 30]. Thus, a similar trend is anticipated in Japanese patients with UC receiving long-term tofacitinib treatment. While no deaths or malignancies were reported in this analysis, long-term monitoring with tofacitinib is required to assess safety outcomes.

The post hoc nature of these analyses, including the small number of patients (particularly in the placebo

group) and the lack of formal statistical analyses, limits the conclusions that can be drawn. The duration of OCTAVE Induction 1 was short, further limiting the safety profile characterization. The ongoing, open-label, long-term extension study (NCT01470612) will allow further characterization of the long-term safety profile of tofacitinib.

In summary, in these analyses of Japanese patients with moderately-to-severely active UC enrolled in the phase III OCTAVE Induction 1 and OCTAVE Sustain studies, tofacitinib was efficacious as induction and maintenance therapy and was well tolerated, with a safety profile consistent with that of the global study population.

Acknowledgment

The authors would like to thank the patients, investigators, and study teams involved in OCTAVE Induction 1 and OCTAVE Sustain. These studies were funded by Pfizer Inc. Medical writing support, under the guidance of the authors, was provided by Stephanie Johnson, PhD, and Sandrine M. Dupré, PhD, at CMC Connect, a division of McCann Health Medical Communications Ltd, Macclesfield, UK and was funded by Pfizer Inc, New York, NY, USA in accordance with Good Publication Practice (GPP3) guidelines (Ann Intern Med. 2015;163:461–464).

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

Y.S. has received lecture fees from AbbVie, EA Pharma, Kyorin, Mitsubishi Tanabe Pharma, Mochida, and Zeria; and scholarship donations from AbbVie, EA Pharma, JIMRO, Kissei, Mitsubishi Tanabe Pharma, Mochida, and Nippon Kayaku. M.W. has received lecture fees from Janssen, Mitsubishi Tanabe Pharma, Takeda, and Zeria; and scholarship donations from AbbVie, Asahi Kasei Kura-ray Medical, Astellas Pharma, Daiichi Sankyo, EA Pharma, Eisai, JIMRO, Kyorin, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, MSD, Otsuka, Pfizer Inc, Takeda, and Zeria. T.M. has received lecture fees from AbbVie and Eisai; and scholarship donations from Astellas and Mitsubishi Tanabe Pharma. S.M. has received lecture fees from Mitsubishi Tanabe Pharma; and research grants from AbbVie, Ajinomoto, AstraZeneca, Janssen, and Pfizer Inc. T. Hisamatsu has received lecture fees from AbbVie, EA Pharma, Janssen, Kyorin, Mitsubishi Tanabe Pharma, Mochida, and Takeda; and scholarship donations from AbbVie, Astellas Pharma, Daiichi Sankyo, EA Pharma, JIMRO, Kyorin, Mitsubishi Tanabe Pharma, Mochida, Nippon Kayaku, Otsuka, Pfizer Inc, and Takeda. T. Hibi has

received lecture fees from AbbVie, EA Pharma, Janssen, Kyorin, Mitsubishi Tanabe Pharma, Mochida, and Takeda; and scholarship donations from AbbVie, Astellas Pharma, EA Pharma, JIMRO, Kyorin, Mitsubishi Tanabe Pharma, Mochida, Nippon Kayaku, Otsuka, Pfizer Inc, and Takeda. S.A., J.T., N.I., S.T., and H.Y. are employees and shareholders of Pfizer Inc.

Funding Sources

These studies were funded by Pfizer Inc.

Author Contributions

H.Y., J.T., N.I., S.A., and S.T. conceived the manuscript; M.W., S.M., T. Hibi, T. Hisamatsu, T.M., and Y.S. contributed to data acquisition as investigators; and N.I. and S.T. performed the statistical analyses. All authors critically reviewed the manuscript and approved the final draft.

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Data Sharing Statement

Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals 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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