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Safety and efficacy of long-term tofacitinib treatment in East Asian patients with ulcerative colitis in OCTAVE Open

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Key words
herpes zoster, Janus kinase inhibitors, ulcerative colitis.

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Abstract

Background and Aim: Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). We present safety and efficacy data from patients from East Asia (Japan, Korea, and Taiwan) in OCTAVE Open, an open-label, long-term extension study.

Methods: Patients in remission at OCTAVE Open baseline received tofacitinib 5 mg twice daily (BID); all others received tofacitinib 10 mg BID. Proportions and IRs (unique patients with events/100 patient-years) were calculated for adverse events (AEs) of special interest. Efficacy endpoints were evaluated up to 36 months.

Results: In OCTAVE Open, 105/944 patients were from East Asia (tofacitinib 5 mg BID, $n = 22$; tofacitinib 10 mg BID, $n = 83$). Overall, 87.6% and 24.8% of patients had AEs and serious AEs, respectively; IRs (95% CI) for AEs of special interest were herpes zoster (HZ; non-serious and serious), 6.07 (3.40–10.02); serious infections, 1.47 (0.40–3.76); opportunistic infections, 1.91 (0.62–4.45); major cardiovascular adverse events, 0.37 (0.01–2.04); malignancies (excluding non-melanoma skin cancer [NMSC]), 0.37 (0.01–2.04); and NMSC, 0.00 (0.00–1.35). No deaths, venous thromboembolic events, or gastrointestinal perforations occurred. At month 36, 68.2% and 54.2% of patients had a clinical response, 68.2% and 53.0% had endoscopic improvement, and 63.6% and 49.4% were in remission with tofacitinib 5 and 10 mg BID, respectively.

Conclusions: The HZ IR in East Asian patients was numerically higher *versus* the global study population; excluding HZ, tofacitinib safety and efficacy were consistent with the global study population.

Declaration of conflict of interest: Katsuyoshi Matsuoka has served as a scientific adviser for EA Pharma, has served on advisory boards for Boehringer Ingelheim, Bristol-Myers Squibb, and Eli Lilly, has received personal fees from AbbVie, EA Pharma, Janssen, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Pfizer Inc, Takeda Pharmaceutical, and Zeria Pharmaceutical, and has received research grants from AbbVie, EA Pharma, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, and Takeda Pharmaceutical. Tadakazu Hisamatsu has received lecture fees from AbbVie, EA Pharma, Janssen, Kyorin, Mitsubishi Tanabe Pharma, Mochida, and Takeda, and has received scholarship donations from AbbVie, Astellas Pharma, Daiichi Sankyo, EA Pharma, JIMRO, Kyorin, Mitsubishi Tanabe Pharma, Mochida, Nippon Kayaku, Otsuka, Pfizer Inc, and Takeda. Hyo Jong Kim has no conflicts of interest to declare. Byong Duk Ye has served on advisory boards for AbbVie Korea, Celltrion, Daewoong Pharma, Ferring Korea, Janssen Korea, Pfizer Korea, Shire Korea, and Takeda Korea, has received research grants from Celltrion and Pfizer Korea, has received consulting fees from Chong Kun Dang Pharm., CJ Red BIO, Cornerstones Health, Daewoong Pharma, Kangstem Biotech, Korea United Pharm. Inc., Medtronic Korea, NanoEntek, and Takeda, and has received speaker fees from AbbVie Korea, Celltrion, Ferring Korea, IQVIA, Janssen Korea, Pfizer Korea, Shire Korea, Takeda, and Takeda Korea. Shoko Arai, Masato Hoshi, Hirotoshi Yuasa, Junichi Tabira, Shigeyuki Toyoizumi, and Nanzhi Shi are employees and stockholders of Pfizer Japan Inc. Joon-suk Woo is an employee and stockholder of Pfizer Korea Inc. Toshifumi 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.

Ethical approval: This study was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice Guidelines and was approved by the Institutional Review Boards and/or Independent Ethics Committees at each of the investigational centers participating in the studies or a central Institutional Review Board.

Informed consent: All patients provided written informed consent.

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disorder of the colon.[1] The incidence of UC has stabilized in Europe and North America;[2] however, while lower than rates in Western countries, the incidence and prevalence of UC in East Asia are increasing.[3]

Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of UC. In the global UC clinical program, the efficacy and safety of tofacitinib were demonstrated in a phase 2 induction study (NCT00787202),[4] two identical phase 3 induction studies (OCTAVE Induction 1 and 2; NCT01465763, NCT01458951), and one phase 3 maintenance study (OCTAVE Sustain; NCT01458574).[5]

Following reports of differences in the safety profiles of tofacitinib in patients from East Asia *versus* the global study population, including a higher risk of herpes zoster (HZ) in patients in Asia,[6] the efficacy and safety of tofacitinib in participants from East Asia in OCTAVE Induction 1 and 2, and OCTAVE Sustain, were evaluated.[7,8] These analyses demonstrated that, in the short term, tofacitinib was efficacious and had a safety profile comparable to that in the global study population.[7,8] The long-term safety of tofacitinib 5 and 10 mg twice daily (BID) in the global study population has been evaluated up to 7.0 years in a phase 3, multicenter, open-label, long-term extension study (OCTAVE Open; NCT01470612).[9]

We conducted a post-hoc analysis of the safety and efficacy of tofacitinib, including incidence rates (IRs) of HZ, in the subpopulation of patients from East Asia enrolled in OCTAVE Open.

Methods

Patients and study design. Safety and efficacy data for patients from East Asia (patients from study centers in Japan, Korea, and Taiwan) who participated in OCTAVE Open are presented. Patients previously enrolled in OCTAVE Induction 1 and 2, and OCTAVE Sustain, were eligible for OCTAVE Open. OCTAVE Open was conducted from October 2012 to August 2020; however, duration of participation for individual patients varied (from ~4 to 7 years) depending on when they enrolled. Full study design details for OCTAVE Open have been reported.[9]

Patients were eligible to enroll in OCTAVE Open if they were non-responders after completing OCTAVE Induction 1 or 2 or had completed or withdrawn early (after experiencing treatment failure) from OCTAVE Sustain. Tofacitinib dose assignment in OCTAVE Open was based on baseline remission status: patients who completed OCTAVE Sustain in remission were assigned to tofacitinib 5 mg BID, while patients who completed OCTAVE Sustain not in remission and those who withdrew early from OCTAVE Sustain due to treatment failure or who were non-responders after completing OCTAVE Induction 1 or 2 were assigned to tofacitinib 10 mg BID.[9] After the initial 8 weeks' treatment in OCTAVE Open, tofacitinib dose adjustments were permitted: patients receiving tofacitinib 5 mg BID could have the dose increased to 10 mg BID if they were experiencing a disease flare, while patients receiving tofacitinib 10 mg BID could have the dose reduced to 5 mg BID if they were in remission, met specific laboratory criteria, or if risk factors for pulmonary embolism were identified.

Patients who enrolled in OCTAVE Open as non-responders following completion of OCTAVE Induction 1 and 2 and who failed to demonstrate a clinical response at month 2 were required to withdraw from the study.

In OCTAVE Open, concomitant treatment with oral 5-aminosalicylates, sulfasalazine, or corticosteroids was permitted. Corticosteroid tapering was mandatory at the beginning of OCTAVE Open, although doses < 10 mg/day were permitted.

Efficacy and safety evaluation. Full details of the safety and efficacy evaluations performed in OCTAVE Open have been reported.[9] The primary objective of OCTAVE Open was to assess the safety and tolerability of long-term tofacitinib therapy in patients with UC. Adverse events (AEs) and clinical laboratory parameters were recorded throughout the study. Serious AEs (SAEs) were defined as any events that resulted in death; were life-threatening; resulted in a persistent or significant disability or incapacity; required patient hospitalization or prolongation of existing hospitalization; or resulted in a congenital anomaly or birth defect. Severe AEs were defined as AEs that interfered significantly with the patient's usual functioning. AEs of special interest (AESI) analyzed in this subpopulation included HZ (non-serious and serious), serious infections, opportunistic infections, malignancies (excluding non-melanoma skin cancer [NMSC]), NMSC, major adverse cardiovascular events (MACE; a composite endpoint comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke), gastrointestinal perforation, deep vein thrombosis, and pulmonary embolism. Serious infections were defined as infections that required parenteral antimicrobial therapy or met SAE reporting criteria. Cardiovascular, malignancy, hepatic, opportunistic infection, and gastrointestinal perforation events were adjudicated by independent specialist review committees. HZ events adjudicated as multidermatomal (defined as non-adjacent or > 2 adjacent dermatomes that were not considered disseminated) or disseminated (defined as any of: diffuse rash [> 6 dermatomes], encephalitis, pneumonia, or other non-skin organ involvement) were classified as opportunistic infections.

The secondary objective of OCTAVE Open was to evaluate the efficacy of long-term tofacitinib therapy using the endpoints of clinical response, endoscopic improvement, and remission (Table S1). In OCTAVE Open, there was no primary efficacy endpoint and the secondary efficacy endpoints were the proportions of patients with clinical response, endoscopic improvement, or remission at months 2, 12, 24, and 36.

Statistical analysis. Analyses were based on initial treatment assignment to the tofacitinib 5 and 10 mg BID groups in the full analysis set, which included all patients who received ≥ 1 dose of tofacitinib in OCTAVE Open. Numbers and percentages of patients with AEs, SAEs, and severe AEs were evaluated. Proportions and IRs (the number of unique patients with events per 100 patient-years [PY] of follow-up) of AESI were also evaluated, with 95% confidence intervals (CIs).

Efficacy endpoints were derived from the Mayo score per local read of endoscopic scores, which were summarized based on the observed-case data and with non-responder imputation (NRI) and last observation carried forward (LOCF) imputation. NRI was used for missing data before discontinuation; however, for

patients who advanced to a follow-up study (RIVETING [NCT03281304] or Japan post-marketing surveillance studies), LOCF was used up to the visit they would have reached if they had stayed in OCTAVE Open (NRI-LOCF).

Study ethics and patient consent. This study was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice Guidelines and approved by the Institutional Review Boards and/or Independent Ethics Committees at each of the investigational centers participating in the studies or a central Institutional Review Board. All patients provided written informed consent.

Results

Patients. Globally, 944 patients were enrolled in OCTAVE Open. This subpopulation analysis included 105 patients from East Asia who received ≥ 1 dose of tofacitinib. At OCTAVE Open baseline, 22 and 83 patients were assigned tofacitinib 5 and 10 mg BID, respectively.

Demographics were generally similar between the tofacitinib 5 and 10 mg BID groups (Table 1). All patients in remission on entering OCTAVE Open were assigned tofacitinib 5 mg BID at baseline, and mean total Mayo score was lower in these patients than those assigned tofacitinib 10 mg BID at baseline (0.9 and 7.2, respectively). Only non-responders from OCTAVE Induction 1 or 2, and OCTAVE Sustain treatment failures, were permitted baseline corticosteroids. At OCTAVE Open baseline, all patients who were receiving corticosteroids were in the tofacitinib 10 mg BID group (15/105 [14.3%]). The extent of disease was most commonly extensive colitis/pancolitis in both the tofacitinib 5 and 10 mg BID groups. A higher proportion of patients in the tofacitinib 10 mg BID group had prior tumor necrosis factor inhibitor (TNFi) failure and immunosuppressant failure (45/83 [54.2%] and 73/83 [88.0%], respectively) *versus* the tofacitinib 5 mg BID group (9/22 [40.9%] and 17/22 [77.3%], respectively).

Safety

Adverse events, serious adverse events, and discontinuations. The total PY of exposure in the tofacitinib 5 and 10 mg BID groups were 74.6 and 199.2, respectively. Of the patients in the tofacitinib 5 and 10 mg BID groups, 18.2% and 12.0% discontinued treatment due to AEs, and 4.5% and 36.1% due to insufficient clinical responses, respectively (Table 2).

The proportions of treatment-emergent AEs (TEAEs) and SAEs were similar across the two study groups (Table 2). The most frequent TEAEs by system organ class were infections and infestations (68/105 [64.8%] patients) and gastrointestinal disorders (48/105 [45.7%] patients). When evaluated by Medical Dictionary

Table 1 Baseline demographics and disease characteristics for patients from East Asia in OCTAVE Open

	Tofacitinib 5 mg BID (*N* = 22)	Tofacitinib 10 mg BID (*N* = 83)	Tofacitinib All (*N* = 105)
Remission, *n* (%)[†,‡]	22 (100.0)	0 (0.0)	22 (21.0)
Total Mayo score, mean (SD)[‡]	0.9 (0.8)	7.2 (2.5)	5.9 (3.4)
Age (years), mean (SD)	44.9 (15.6)	41.6 (13.3)	42.3 (13.8)
Male, *n* (%)	13 (59.1)	51 (61.4)	64 (61.0)
Site location, *n* (%)			
Japan	13 (59.1)	40 (48.2)	53 (50.5)
Korea	9 (40.9)	42 (50.6)	51 (48.6)
Taiwan	0 (0.0)	1 (1.2)	1 (1.0)
Weight (kg), mean (SD)[§]	65.7 (11.0)	60.3 (12.2)	61.5 (12.1)
BMI (kg/m^2), mean (SD)[¶]	23.9 (3.0)	22.2 (3.6)	22.6 (3.5)
Disease duration (years), median (range)[‡]	9.5 (3.2–25.0)	6.4 (1.0–26.2)	7.1 (1.0–26.2)
Corticosteroid use, *n* (%)[‡]	0 (0.0)	15 (18.1)	15 (14.3)
5-ASA use, *n* (%)[‡]	21 (95.5)	71 (85.5)	92 (87.6)
Prior TNFi exposure, *n* (%)[††]	10 (45.5)	48 (57.8)	58 (55.2)
Prior TNFi failure, *n* (%)[††]	9 (40.9)	45 (54.2)	54 (51.4)
Prior immunosuppressant use, *n* (%)[††]	18 (81.8)	76 (91.6)	94 (89.5)
Prior immunosuppressant failure, *n* (%)[††]	17 (77.3)	73 (88.0)	90 (85.7)
Extent of disease, *n* (%)[††]			
Proctosigmoiditis	3 (13.6)	5 (6.0)	8 (7.6)
Left-sided colitis	7 (31.8)	17 (20.5)	24 (22.9)
Extensive colitis/pancolitis	12 (54.5)	61 (73.5)	73 (69.5)
Proctitis	0 (0.0)	0 (0.0)	0 (0.0)

[†]Based on centrally read endoscopic subscore.

[‡]Baseline and clinical characteristics data per data from baseline of OCTAVE Open.

[§]From the last patient visit in the previous study.

[¶]BMI was calculated using weight (from the last patient visit in the previous study) and height (from screening of the induction studies).

[††]Baseline and clinical characteristics data per data from baseline of induction studies.

5-ASA, 5-aminosalicylates; BID, twice daily; BMI, body mass index; *N*, number of patients in the treatment group; *n*, number of patients within the given category; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

Table 2 Summary of safety in patients from East Asia in OCTAVE Open

	Tofacitinib 5 mg BID (*N* = 22)	Tofacitinib 10 mg BID (*N* = 83)[†]	Tofacitinib All (*N* = 105)
Total PY of exposure	74.6	199.2	273.8
Discontinuations, *n* (%)	15 (68.2)	79 (95.2)	94 (89.5)
Due to AEs	4 (18.2)	10 (12.0)	14 (13.3)
Dose reduced or temporary discontinuation due to AEs	2 (9.1)	7 (8.4)	9 (8.6)
Due to insufficient clinical response	1 (4.5)	30 (36.1)	31 (29.5)
Due to enrollment in another study/regulatory approval			
Enrolled in RIVETING (NCT03281304)	0 (0.0)	28 (33.7)	28 (26.7)
Enrolled in post-marketing surveillance (Japan only)	8 (36.4)	4 (4.8)	12 (11.4)
Regulatory approval in Japan	1 (4.5)	2 (2.4)	3 (2.9)
Dose adjustments, *n* (%)			
Dose escalation	4 (18.2)	–	–
Dose de-escalation	–	17 (20.5)	–
All-causality TEAEs, *n* (%)			
AEs	20 (90.9)	72 (86.7)	92 (87.6)
SAEs	5 (22.7)	21 (25.3)	26 (24.8)
Severe AEs	2 (9.1)	9 (10.8)	11 (10.5)
All-causality TEAEs, by MedDRA preferred term occurring in ≥ 10% of patients in any treatment group, *n* (%)			
Nasopharyngitis	12 (54.5)	35 (42.2)	47 (44.8)
Worsening UC	5 (22.7)	14 (16.9)	19 (18.1)
Arthralgia	3 (13.6)	12 (14.5)	15 (14.3)
Upper respiratory tract infection	4 (18.2)	11 (13.3)	15 (14.3)
HZ	4 (18.2)	10 (12.0)	14 (13.3)[‡]
Influenza	3 (13.6)	6 (7.2)	9 (8.6)
Blood creatine phosphokinase increased	3 (13.6)	4 (4.8)	7 (6.7)
Upper respiratory tract inflammation	3 (13.6)	2 (2.4)	5 (4.8)
Hypertension	4 (18.2)	3 (3.6)	7 (6.7)

[†]All patients underwent endoscopy at month 2; induction non-responders were mandated to discontinue if they failed to achieve clinical response by month 2.

[‡]There were also two events of HZ in the tofacitinib 10 mg BID group captured under the MedDRA preferred terms of disseminated HZ and ophthalmic HZ. In total, 16 events of HZ (including the preferred terms of HZ, disseminated HZ, and ophthalmic HZ) occurred in 15 patients, with one patient having two events that occurred at overlapping times (HZ and ophthalmic HZ).

AE, adverse event; BID, twice daily; HZ, herpes zoster; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of patients in the treatment group; *n*, number of unique patients with a particular adverse event; PY, patient-years; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

for Regulatory Activities (version 23.0) preferred term, the most frequent TEAEs were "nasopharyngitis," "colitis ulcerative" (worsening UC), "arthralgia," and "upper respiratory tract infection" (Table 2).

There were no deaths reported in the study population.

Herpes zoster. Overall, 15 patients had HZ (non-serious and serious; 4/22 [18.2%] in the tofacitinib 5 mg BID group and 11/83 [13.3%] in the tofacitinib 10 mg BID group), with IRs similar between the tofacitinib 5 and 10 mg BID groups (Table 3). Of these patients, 7/15 were ≥ 60 years old; 10/15 were from Japan; 5/15 were from Korea, and 7/15 had corticosteroid use at OCTAVE Induction baseline (with 6/15 patients remaining on corticosteroids throughout the study). There was no consistent trend in the IRs of HZ over time in the tofacitinib 5 and 10 mg BID groups (Fig. 1). There was 1/105 (1.0%) patient who had serious HZ and 1/105 (1.0%) patient who had HZ with two adjacent dermatomes; both patients were assigned to the tofacitinib 10 mg BID group. Overall, five patients had adjudicated opportunistic infections, all of which were HZ; 3/105 (2.9%) patients had HZ classified as multidermatomal (two and one patients in the tofacitinib 5 and 10 mg BID groups, respectively), and 2/105 (1.9%) patients had HZ classified as disseminated (both in the tofacitinib 10 mg BID group).

Other adverse events of special interest. IRs for AESI were generally similar between tofacitinib dose groups (Table 3).

Serious infections were reported in 1/22 (4.5%) patients in the tofacitinib 5 mg BID group (tonsillitis) and 3/83 (3.6%) patients in the tofacitinib 10 mg BID group (one patient each with HZ, polyarticular septic arthritis, and infectious enteritis); IRs were similar across the tofacitinib dose groups.

One adjudicated malignancy (excluding NMSC) was reported in a patient in the tofacitinib 10 mg BID group (invasive ductal breast carcinoma in a 43-year-old female), and one patient in the tofacitinib 5 mg BID group had an adjudicated MACE (non-fatal cerebellar hemorrhage in a 55-year-old male). In the East Asia

Table 3 Proportions and IRs of AESI in patients from East Asia in OCTAVE Open

	Tofacitinib 5 mg BID (*N* = 22; 74.6 PY)		Tofacitinib 10 mg BID (*N* = 83; 199.2 PY)		Tofacitinib All (*N* = 105; 273.8 PY)	
	n (%)	IR[†] (95% CI)	*n* (%)	IR[†] (95% CI)	*n* (%)	IR[†] (95% CI)
HZ (non-serious and serious)[‡]	4 (18.2)	5.77 (1.57–14.76)	11 (13.3)	6.19 (3.09–11.08)	15 (14.3)	6.07 (3.40–10.02)
Serious HZ[‡]	0 (0.0)	0.00 (0.00–4.94)	1 (1.2)	0.50 (0.01–2.80)	1 (1.0)	0.37 (0.01–2.04)
Serious infections[‡]	1 (4.5)	1.36 (0.03–7.57)	3 (3.6)	1.51 (0.31–4.41)	4 (3.8)	1.47 (0.40–3.76)
Opportunistic infections[‡,¶,††]	2 (9.1)	2.77 (0.34–10.02)	3 (3.6)	1.58 (0.33–4.61)	5 (4.8)	1.91 (0.62–4.45)
Malignancies (excluding NMSC)[§,¶]	0 (0.0)	0.00 (0.00–4.94)	1 (1.2)	0.50 (0.01–2.80)	1 (1.0)	0.37 (0.01–2.04)
NMSC[§,¶]	0 (0.0)	0.00 (0.00–4.94)	0 (0.0)	0.00 (0.00–1.85)	0 (0.0)	0.00 (0.00–1.35)
MACE[§,¶]	1 (4.5)	1.34 (0.03–7.47)	0 (0.0)	0.00 (0.00–1.85)	1 (1.0)	0.37 (0.01–2.04)
Gastrointestinal perforation	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Deep vein thrombosis	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Pulmonary embolism	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Deaths	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–

[†]IRs were calculated as the number of unique patients with events per 100 PY.
[‡]All events occurred within 28 days after the last dose of study drug.
[§]All events, including those outside the 28-day risk period, were included.
[¶]Adjudicated events.
[††]Excludes tuberculosis and HZ with two adjacent dermatomes.
–, IR not calculated; AESI, adverse events of special interest; BID, twice daily; CI, confidence interval; HZ, herpes zoster; IR, incidence rate; MACE, major adverse cardiovascular events; *N*, number of patients who received at least one dose of study drug; *n*, number of patients with the specified event within the given category; NMSC, non-melanoma skin cancer; PY, patient-years.

study population, there were no patients with NMSC, gastrointestinal perforation, deep vein thrombosis, or pulmonary embolism.

Laboratory parameters of special interest. In OCTAVE Open, observations of laboratory parameters of interest (cholesterol, low-density and high-density lipoprotein cholesterol, triglycerides, creatine kinase, and creatine) were extracted from data generated through month 60 (Fig. 2). No major changes from baseline in laboratory parameters were observed. The proportion of patients with aspartate transaminase (AST) or alanine transaminase (ALT) values ≥ 3 times the upper limit of normal (ULN) was numerically higher in the tofacitinib 5 mg BID group *versus* the tofacitinib 10 mg BID group (Table 4).

Efficacy. The proportion of patients who met these clinical endpoints in the tofacitinib 5 mg BID group remained high throughout the observation period (Fig. 3). A lower proportion of patients in the tofacitinib 10 mg BID group met these clinical endpoints *versus* the tofacitinib 5 mg BID group. In the tofacitinib 10 mg BID group, 22.9%, 77.1%, 63.9%, 55.4%, and 54.2% of patients had a clinical response at baseline and months 2, 12, 24, and 36, respectively, when analyzed by NRI-LOCF. Corresponding values for the tofacitinib 5 mg BID group were 100.0%, 95.5%, 95.5%, 84.6%, and 68.2%.

Discussion

This post-hoc analysis demonstrated the long-term safety and efficacy of tofacitinib 5 or 10 mg BID therapy in patients from East Asia in OCTAVE Open, with generally similar safety and efficacy profiles *versus* the OCTAVE Open global study population.[9]

During OCTAVE Open, the safety profile of tofacitinib 5 and 10 mg BID in patients from East Asia was largely consistent with the results of the global analysis.[9] The frequencies of AEs and SAEs were similar between tofacitinib treatment groups. Consistent with findings from OCTAVE Induction 1 and 2, and OCTAVE Sustain, as well as the OCTAVE Open global study population,[10] nasopharyngitis remained one of the most common TEAEs.

Patients with inflammatory bowel disease (IBD) are at higher risk of HZ *versus* the general population, and the risk is further increased by treatment with immunosuppressive therapies.[11,12] The IR for HZ (non-serious and serious) for all tofacitinib patients reported in this study (IR per 100 PY, 6.07 [95% CI, 3.40–10.02]) was higher than those reported in the general population in Japan (IR per 100 PY, 0.48 [CI not reported])[13] and Korea (IR per 100 PY, 1.04 [CI not reported]).[14] Furthermore, the IR for HZ (non-serious and serious) for all tofacitinib patients was higher than those reported in patients with UC from Korea (IR per 100 PY, 1.93 [1.84–2.02]),[15] in patients with IBD from Japan (IR per 100 PY, 0.74 [0.52–1.02]),[11] and numerically higher than real-world data from patients with UC in the United States who were treated with tofacitinib (IR per 100 PY, 3.29 [1.37–7.90]).[16]

The reason for the higher HZ incidence among patients from East Asia, compared with the global population of patients with UC treated with tofacitinib, remains unclear. In a study of HZ among patients in the global OCTAVE UC clinical program, multivariate analyses identified age and prior TNFi failure as independent risk factors for HZ.[6] The study also found that patients of the Asian race had a higher risk of HZ compared with patients of other races, although this finding was not statistically significant in the multivariate model.[6] A genetic analysis of patients with rheumatoid arthritis and psoriasis treated with tofacitinib identified a rare single nucleotide polymorphism associated with HZ risk that was more prevalent in Japanese patients than Caucasian patients,

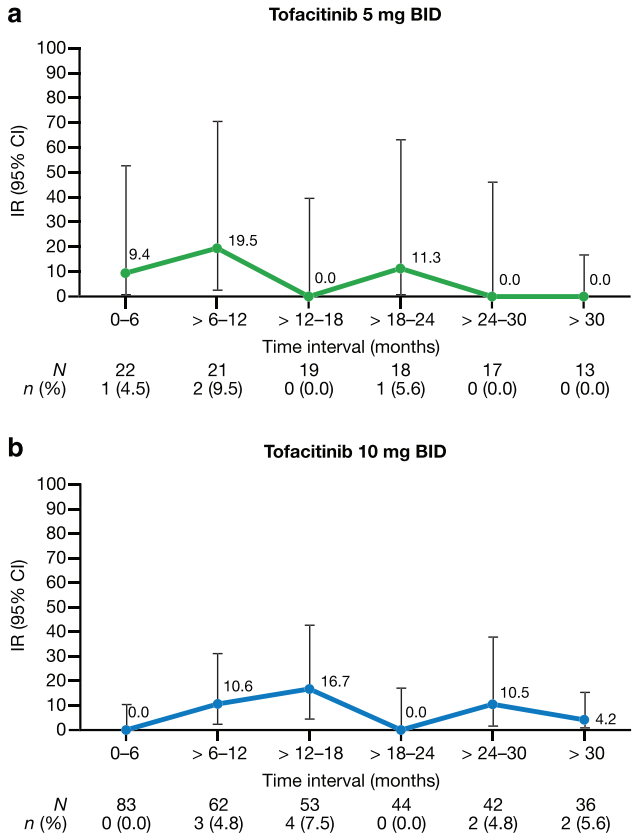

Figure 1 Incidence rate of HZ by time interval in the tofacitinib 5 mg BID (a) and 10 mg BID (b) groups in patients from East Asia in OCTAVE Open. IRs were calculated as the number of unique patients with events per 100 PY. BID, twice daily; CI, confidence interval; HZ, herpes zoster; IR, incidence rate; *N*, number of patients who received at least one dose of study drug; *n*, number of patients with the specified event within the given category; PY, patient-years.

which could have contributed to the increased risk within the population from Japan observed here.[17] Furthermore, two separate reports that analyzed data from phase 2, 3, and open-label, long-term extension studies of tofacitinib in patients with rheumatoid arthritis demonstrated that there was a trend toward higher IRs in patients receiving tofacitinib and prednisone (≤ 10 mg/day prednisone or equivalent), compared with those not taking prednisone, and a trend toward higher IRs among patients who received tofacitinib with corticosteroids and conventional synthetic disease-modifying antirheumatic drugs, compared with tofacitinib monotherapy, respectively.[18,19]

Previous analyses of global data from OCTAVE Induction 1 and 2, and OCTAVE Sustain, indicated that there was an elevated risk of HZ in patients with UC who were treated with tofacitinib.[5,6] An *in vitro* study that investigated the effect of tofacitinib on epithelial cells suggested that the mechanism behind the increased HZ risk associated with tofacitinib may be related to inhibition of antiviral immunity.[20] In the OCTAVE Open global study population, IRs for HZ were numerically similar between tofacitinib dose groups (IR per 100 PY, 2.08 [1.11–3.55] and 3.55 [2.71–4.58] for tofacitinib 5 and 10 mg BID, respectively).[9] This was also true in our analysis; however, it should be noted that IRs were numerically higher among patients from East Asia (IR per 100 PY, 5.77 [1.57–14.76] and 6.19 [3.09–11.08] for tofacitinib 5 and 10 mg BID, respectively) *versus* the global study population. The potential dose-dependency of HZ has been discussed previously;[21] however, the differences in extent of exposure in this study (74.6 PY for tofacitinib 5 mg BID *versus* 199.2 PY for tofacitinib 10 mg BID) and in the OCTAVE Open global study population (643.7 PY for tofacitinib 5 mg BID *versus* 1797.0 PY for tofacitinib 10 mg BID), as well as the differences in study population sizes (particularly the small tofacitinib 5 mg BID group), should be noted when comparing the IRs between doses and studies.

In agreement with previous analyses of HZ in the overall tofacitinib UC clinical program, and similar to the OCTAVE Open global study population, most HZ cases among patients from East Asia were non-serious.[6,9] IRs for HZ did not increase over time.

Corticosteroid use is associated with increased risk of HZ, particularly in patients with IBD.[22] Although corticosteroid tapering was mandatory for patients entering OCTAVE Open, patients unable to tolerate tapering could remain in the study on a dose < 10 mg/day. Here, of the 15 patients who had HZ events, six remained on corticosteroids throughout the study.

Excluding the higher incidence of HZ, the IRs for AESI in the population from East Asia were similar to the global study population. As in the overall tofacitinib UC clinical program, the OCTAVE Open global study population and the overall tofacitinib UC program, serious infections were infrequent in patients from East Asia, with similar IRs reported in the three populations.[9,21] Serious infections were infrequent with tofacitinib treatment in the current study, in keeping with real-world data from various regions.[23,24]

In patients from East Asia, no deaths or venous thromboembolic events, one adjudicated malignancy, and one adjudicated MACE were reported. Continuous monitoring is required to evaluate the long-term safety of tofacitinib in patients with UC from East Asia, and post-marketing surveillance studies are ongoing in Japan and Korea.

In keeping with the findings from the OCTAVE Open global study population, the proportion of patients with abnormal AST or ALT values (≥ 3 × the ULN) was numerically higher in the tofacitinib 5 *versus* 10 mg BID group.[9] While there were no notable differences in baseline disease characteristics or prior therapies between the tofacitinib treatment groups, aside from higher baseline corticosteroid use in the tofacitinib 10 *versus* 5 mg BID group, the body mass index (BMI) of the tofacitinib 5 mg BID group was numerically higher than the tofacitinib 10 mg BID group. This slight difference in BMI could account for the elevated liver enzyme levels observed in patients who received tofacitinib 5 mg BID, as was noted in a study of patients with psoriatic arthritis treated with tofacitinib.[25]

This analysis showed that the proportions of patients in the tofacitinib 5 mg BID group who achieved the efficacy endpoints up to 36 months remained high throughout the observation period. When assessed by NRI-LOCF, a lower proportion of patients in the tofacitinib 10 mg BID group achieved clinical response at month 36 (54.2%) *versus* the tofacitinib 5 mg BID group (68.2%), as in the OCTAVE Open global study population (40.3% and 66.9% at month 36, respectively).[9] Notably, patients

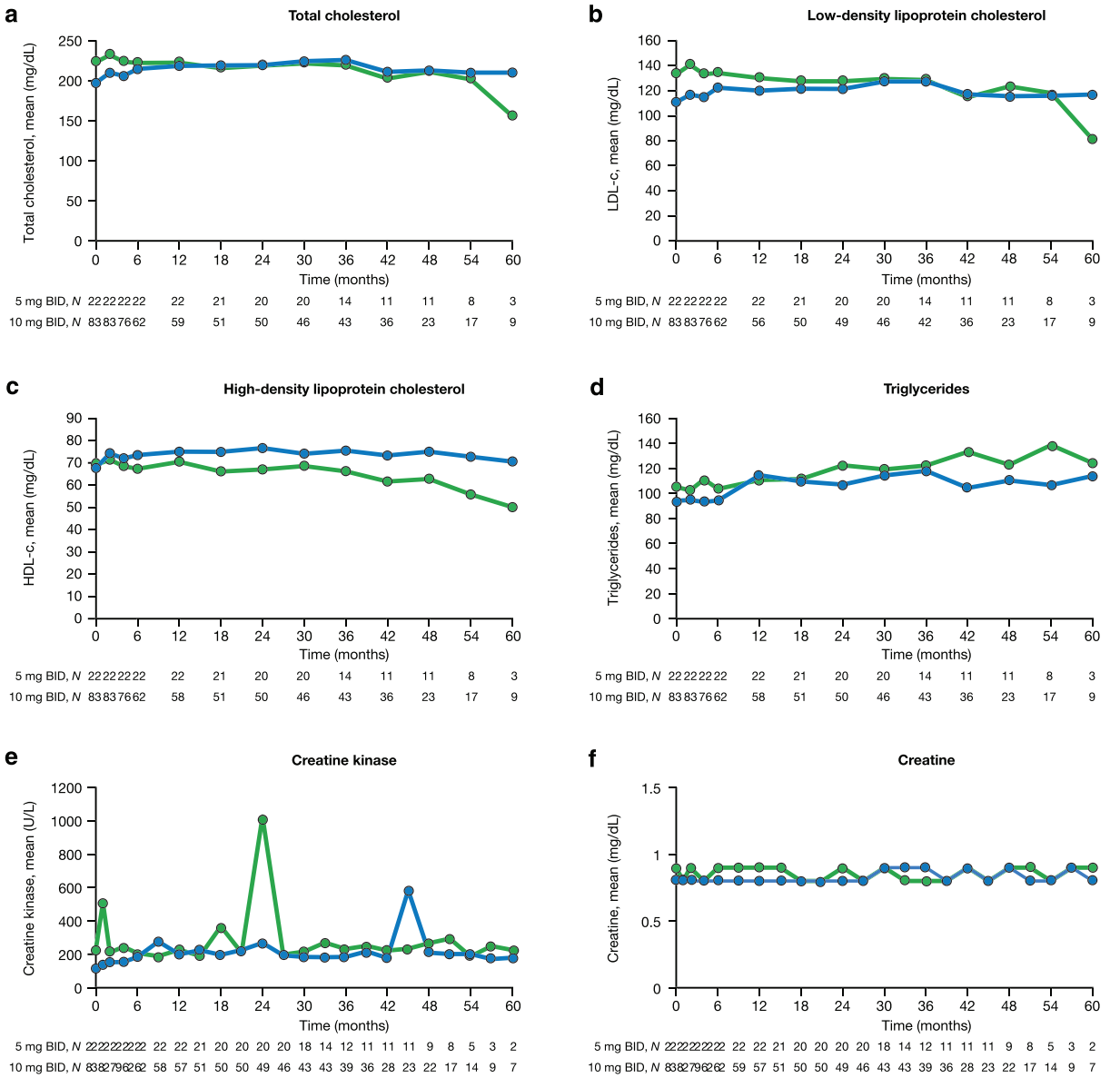

Figure 2 Mean cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, creatine kinase, and creatine levels over time from baseline of OCTAVE Open up to month 60 in patients from East Asia. BID, twice daily; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; *N*, number of patients in the specified category with non-missing data. (a–f) —●—, Tofacitinib 10 mg BID; —●—, Tofacitinib 5 mg BID.

who were assigned to the tofacitinib 10 mg BID group were not in remission at baseline; hence, they were likely a more treatment-refractory population *versus* the tofacitinib 5 mg BID group. This may explain the difference in proportions of patients achieving the efficacy endpoints. Despite the differences between dose groups, exploratory efficacy results for endoscopic improvement and remission support sustained efficacy with tofacitinib 5 and 10 mg BID through to month 36 in patients from East Asia.

Limitations for the OCTAVE Open study were reported previously.[9] Here, the sample size of the cohort from East Asia was small (n = 105) compared with the OCTAVE Open global study population (n = 944), and the ability to detect and compare AEs with low occurrence rates was limited, particularly due to the small number of patients in each treatment group. Our results should, therefore, be interpreted with caution and may not be generalizable to the entire East Asian population. Furthermore, differences in disease activity between patient populations at study enrollment may have impacted study outcomes. Tofacitinib dose assignment was based on baseline remission status and, due to this study design, 79% of patients from East Asia were assigned to tofacitinib 10 mg BID. Due to these differences,

Table 4 Summary of liver function test values as multiples of the upper limit of normal in patients from East Asia in OCTAVE Open

n (%)	Tofacitinib 5 mg BID (*N* = 22)	Tofacitinib 10 mg BID (*N* = 83)
Alanine aminotransferase		
≥ 1 × ULN	9 (40.9)	23 (27.7)
≥ 2 × ULN	3 (13.6)	6 (7.2)
≥ 3 × ULN	2 (9.1)	3 (3.6)
Aspartate aminotransferase		
≥ 1 × ULN	8 (36.4)	25 (30.1)
≥ 2 × ULN	4 (18.2)	4 (4.8)
≥ 3 × ULN	2 (9.1)	0 (0.0)

Liver function test results presented here are regardless of baseline values. BID, twice daily; *N*, number of patients in the treatment group; *n*, number of patients who met the criteria; ULN, upper limit of normal.

and because dose adjustments were allowed during the study, between-group comparisons are limited, and dose-dependency of AEs could not be established. Finally, OCTAVE Open had no placebo or active comparator arm, limiting the direct comparability of tofacitinib to other UC therapies, including other biologics.

In conclusion, in patients from East Asia who enrolled in OCTAVE Open, tofacitinib was efficacious and demonstrated long-term safety profiles that were generally consistent with those of the global study population. Compared with the global study population, the IR of HZ (non-serious and serious) was numerically higher among patients from East Asia. Therefore, patients with UC from East Asia who are receiving tofacitinib treatment may have an increased risk of HZ and should be monitored closely.

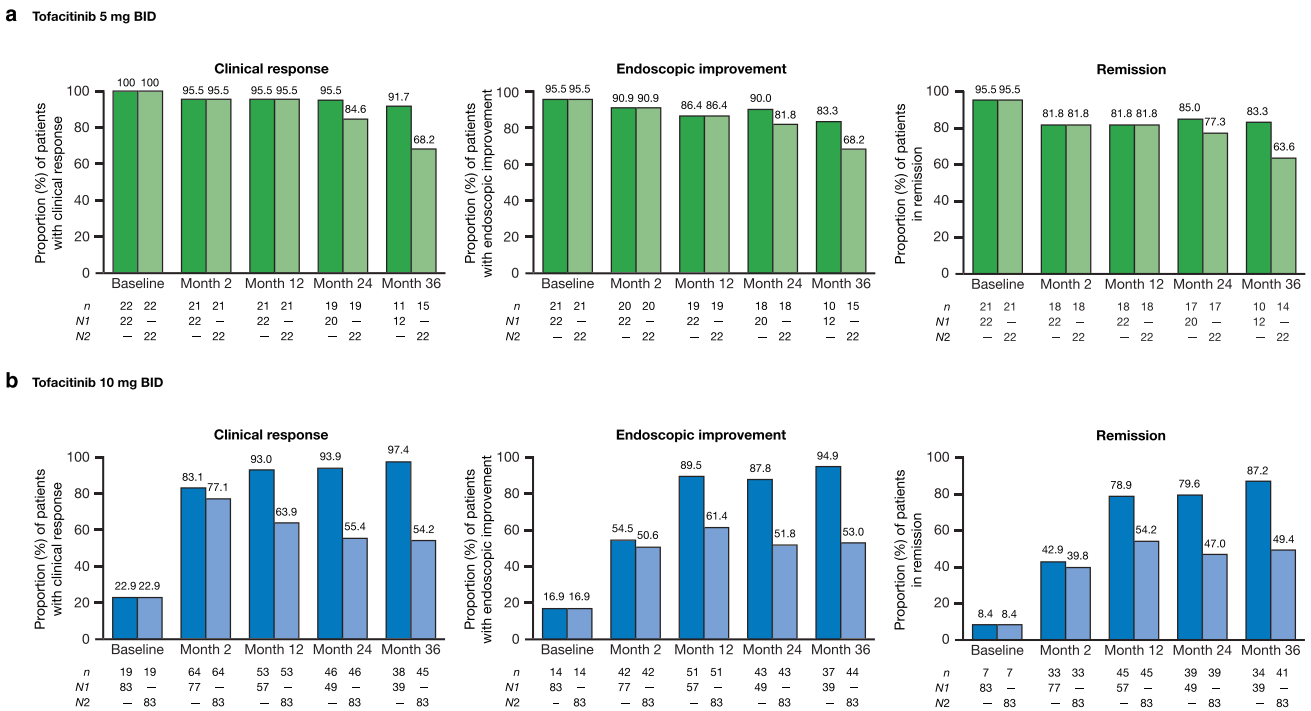

Figure 3 Proportions of patients from East Asia in the tofacitinib 5 mg BID (a) and 10 mg BID (b) groups who achieved clinical response, endoscopic improvement, or remission, observed and with NRI-LOCF, in OCTAVE Open (full analysis set). Data are per local read of endoscopy. Patients in remission at the start of OCTAVE Open were assigned to tofacitinib 5 mg BID; all other patients were assigned to tofacitinib 10 mg BID. A clinical response was defined as a decrease from induction study baseline total Mayo score of ≥ 3 points and ≥ 30%, plus a decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1. Endoscopic improvement (referred to as "mucosal healing" in the OCTAVE Open protocol) was defined as a Mayo endoscopic subscore of 0 or 1. Remission was defined as a total Mayo score of ≤ 2 with no individual subscore > 1, and a rectal bleeding subscore of 0. BID, twice daily; *N1*, number of patients in the specified category with non-missing data; *N2*, number of patients who, based on their enrollment dates, could have reached the specified timepoint by the end of the study; *n*, number of patients with the specified response within the given category; NRI-LOCF, non-responder imputation, applied after a patient discontinued, and last observation carried forward imputation, after a patient advanced to a subsequent study up to the visit they would have reached if they had stayed in the study. No imputation for missing data was applied for ongoing patients, except non-responder imputation for intermittent missing data. (a) ■, Observed; ■, NRI-LOCF. (b) ■, Observed; ■, NRI-LOCF.

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Data availability statement. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Clinical endpoint definitions.