



# The Safety Profile of Upadacitinib in Patients with Rheumatoid Arthritis in Japan

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## Abstract

**Introduction** Upadacitinib is a Janus kinase inhibitor with demonstrated efficacy in patients with rheumatoid arthritis (RA).

**Objective** The aim of this study was to assess the long-term safety of upadacitinib in patients with active RA from Japan compared with global clinical trial populations.

**Methods** Pooled data in patients enrolled from Japan (the ‘Japanese population’; SELECT-SUNRISE, SELECT-EARLY, and SELECT-MONOTHERAPY) were compared with that from global (Japan and ex-Japan) upadacitinib clinical trial populations and summarized descriptively.

**Results** The Japanese population (mean age 57.0 years; mean RA duration 6.1 years) received upadacitinib 7.5 mg ( $n = 121$ ), 15 mg ( $n = 126$ ), and 30 mg ( $n = 124$ ) once daily, while the global population (mean age 54.8 years; mean RA duration 9.1 years) received upadacitinib 6 mg twice daily/15 mg once daily ( $n = 2883$ ) and 12 mg twice daily/30 mg once daily ( $n = 1375$ ). Most patients were female (79.3%). The exposure-adjusted incidence rates (EAIRs) of serious adverse events in the Japanese population were 11.5, 12.2, and 21.2 per 100 patient-years (PY) with upadacitinib 7.5, 15, and 30 mg, respectively. Herpes zoster rates were higher in the Japanese population (7.8, 12.4, and 16.7 per 100 PY with 7.5, 15, and 30 mg, respectively) versus global populations (3.7 and 7.0 per 100 PY with 15 and 30 mg, respectively). Prior herpes zoster was a significant risk factor for herpes zoster.

**Conclusions** The safety profile of upadacitinib was generally similar between Japanese and global RA populations, except for higher EAIRs for serious adverse events and infections, including herpes zoster, in the Japanese population.

**Trial Registration Numbers** SELECT-EARLY: NCT02706873; SELECT-NEXT: NCT02675426; SELECT-COMPARE: NCT02629159; SELECT-MONOTHERAPY: NCT02706951; SELECT-BEYOND: NCT02706847; SELECT-SUNRISE: NCT02720523; BALANCE I: NCT01960855; BALANCE II: NCT02066389.

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## 1 Introduction

The Janus kinase (JAK) family are important mediators of types I and II cytokine receptor signaling pathways involved in normal cellular processes as well as in the pathogenesis of rheumatoid arthritis (RA) and other immune-mediated inflammatory diseases [1–3]. Upadacitinib (ABT-494) is an oral JAK inhibitor engineered for greater selectivity for JAK1 versus JAK2, JAK3, and TYK2 based on in vitro analysis [4]. Upadacitinib has demonstrated clinical and functional efficacy in diverse RA populations, both in combination with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and as monotherapy [5–10]. Adverse events of special interest (AESIs) with upadacitinib include serious infections, opportunistic infections, herpes

## Key Points

Upadacitinib is an oral Janus kinase inhibitor that has been approved for the treatment of rheumatoid arthritis (RA) at a dose of 15 mg once daily in the European Union and United States, and at doses of 7.5 and 15 mg once daily in Japan.

Compared with the global RA clinical trial population, a higher incidence of serious infections, opportunistic infections, herpes zoster, and creatine phosphokinase elevations was observed in the Japanese population; this increased risk of herpes zoster should be considered when assessing the benefit–risk of prescribing upadacitinib.

In the Japanese population, the safety profiles of upadacitinib 15 mg and 7.5 mg doses were generally similar, except for numerically lower rates of opportunistic infections, herpes zoster, and creatine phosphokinase elevations with the 7.5 mg dose compared with the 15 mg dose, although no statistical comparisons were conducted.

zoster, malignancies, major adverse cardiovascular events (MACE), and venous thromboembolism (VTE).

Differences may exist in the safety profiles of JAK inhibitors in patients from Asia compared with global patients with RA [11–15]. For example, a higher rate of infections, particularly herpes zoster, has previously been observed in patients treated with JAK inhibitors enrolled from clinical sites in Asia than patients enrolled from other regions [14, 15]. It is therefore necessary to determine the long-term safety profile of upadacitinib in Asia to identify any region-specific safety signals. The purpose of this analysis was to assess the long-term safety of upadacitinib in patients with RA enrolled from Japan and compare this with the global (both Japan and ex-Japan) RA clinical trial population.

## 2 Methods

### 2.1 Studies and Patients

The Japanese population was defined as patients with RA who were enrolled in Japan from three ongoing, multicenter, randomized, double-blind trials of upadacitinib: two methotrexate-controlled phase III studies that included subsets of patients from Japan (SELECT-EARLY [9] and SELECT-MONOTHERAPY [8]) and one placebo-controlled phase IIb/III study conducted exclusively in Japan (SELECT-SUNRISE [16]). The safety of upadacitinib in these trials

was compared with the global population (including patients from Japan and outside Japan), which included six phase III trials (SELECT-EARLY [9], SELECT-MONOTHERAPY [8], SELECT-SUNRISE [16], SELECT-NEXT [5], SELECT-BEYOND [7], and SELECT-COMPARE [6]) and two phase II dose-ranging studies (BALANCE I [17] and BALANCE II [18]). Details of all the trials included in this analysis have been published previously and are summarized in Table 1. Patients who completed the randomized, controlled periods of each study had the option to enter a long-term extension study, in which all patients received blinded or open-label treatment with upadacitinib.

All studies were conducted according to the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations and guidelines governing clinical study conduct, and the Declaration of Helsinki. Study-related documents were reviewed and approved by independent Ethics Committees and Institutional Review Boards. All patients provided written informed consent.

### 2.2 Analysis

Exposure-adjusted incidence rates (EAIRs) of adverse events (AEs) and AESIs per 100 patient-years (PY) were assessed. All AEs were treatment-emergent, defined as an onset date on or after the first dose of upadacitinib and up to 30 days after the last dose of upadacitinib. In patients who switched from upadacitinib to adalimumab in SELECT-COMPARE [6], AEs were censored at the switch date. The severity of AEs was evaluated using the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Common Toxicity Criteria v2.0.

There was no statistical testing between treatment groups or between the Japanese and global populations, therefore all comparisons were summarized descriptively. In the global population, twice-daily dosing of upadacitinib 6 and 12 mg in phase II studies was considered nearly equivalent to the once-daily dosing of upadacitinib 15 and 30 mg in phase III studies, respectively, based on pharmacokinetic analyses [19].

Univariable Cox proportional hazards regression models were used to evaluate risk factors for serious infections and herpes zoster in the Japanese and global RA populations. Time to first infection was used as a response variable, with covariates as fixed factors. Multivariable Cox proportional hazards regression models with stepwise selection were used to evaluate risk factors for serious infections and herpes zoster. Hazard ratios with 95% confidence intervals (CIs) were reported.

**Table 1** Overview of the upadacitinib RA clinical development program

Study	BALANCE I [17]	BALANCE II [18]	SELECT- SUNRISE <sup>a</sup> [16]	SELECT- EARLY <sup>b</sup> [9]	SELECT- NEXT [5]	SELECT- MONO- THERAPY <sup>b</sup> [8]	SELECT- COMPARE [6]	SELECT- BEYOND [7]
Phase	I Ib	I Ib	IIb/III	III	III	III	III	III
Populations	TNFi-IR/Int	MTX-IR	csDMARD- IR	MTX-naïve	csDMARD- IR	MTX-IR	MTX-IR	bDMARD-IR
Number of patients randomized	276	300	197	947 <sup>b</sup>	661	648 <sup>b</sup>	1629	498
Background therapy	MTX	MTX	csDMARDs	–	csDMARDs	–	MTX	csDMARDs
Upadacitinib dose	3 mg twice daily <sup>c</sup> 6 mg twice daily 12 mg twice daily 18 mg twice daily <sup>c</sup>	3 mg twice daily <sup>c</sup> 6 mg twice daily 12 mg twice daily 18 mg twice daily <sup>c</sup> 24 mg once daily <sup>c</sup>	7.5 mg once daily 15 mg once daily 30 mg once daily	7.5 mg once daily <sup>a</sup> 15 mg once daily 30 mg once daily	15 mg once daily 30 mg once daily	15 mg once daily 30 mg once daily	15 mg once daily	15 mg once daily 30 mg once daily
Comparator	Placebo	Placebo	Placebo	MTX	Placebo	MTX	Placebo Adalimumab	Placebo

*bDMARD* biologic disease-modifying antirheumatic drug, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *Int* intolerance, *IR* inadequate response/responders, *MTX* methotrexate, *RA* rheumatoid arthritis, *TNFi* tumor necrosis factor inhibitor

<sup>a</sup>Japan only

<sup>b</sup>SELECT-EARLY and SELECT-MONOTHERAPY included 138 and 61 patients, respectively, from Japan

<sup>c</sup>Patients receiving these doses were not included in the pooled RA global population for this integrated safety analysis

### 3 Results

#### 3.1 Patients

Across the three trials, a total of 371 patients with RA were enrolled from Japan and received upadacitinib 7.5 mg once daily ( $n = 121$ ), 15 mg once daily ( $n = 126$ ), or 30 mg once daily ( $n = 124$ ). Median duration of exposure in the Japanese population was 604, 611, and 585 days in the 7.5, 15, and 30 mg groups, respectively. In the global RA population, a total of 2883 patients received upadacitinib 6 mg twice daily/15 mg once daily and 1375 patients received upadacitinib 12 mg twice daily/30 mg once daily. For this population, median duration of exposure was 491 days in the 6 mg twice daily/15 mg once daily group and 505 days in the 12 mg twice daily/30 mg once daily group.

Baseline demographics were generally well-balanced across treatment groups for both the Japanese and global RA populations (Table 2). Similar to the global population, most patients from the Japanese population were female and aged between 40 and 64 years. Compared with the global population, the Japanese population had a shorter RA duration but had similar levels of disease activity (which was

measured using Disease Activity Score in 28 joints based on C-reactive protein). Fewer patients in the Japanese population were receiving any csDMARDs at baseline compared with the global 6 mg twice daily/15 mg once daily group. Methotrexate use was less frequent and at a lower mean dose (approved dose in Japan: 6–16 mg/week [20]) in the Japanese versus global populations, and patients in the Japanese population were also receiving lower doses of oral glucocorticoids at baseline. Weight and body mass index (BMI) were lower in patients in the Japanese population compared with the global population, whereas use of statins, elevated high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were more common in the global population. A history of herpes zoster was more common in the Japanese population compared with the global population, while prior herpes zoster vaccination was less common.

#### 3.2 Overall Safety

The EAIRs of AEs, AEs leading to discontinuation of study drug, and serious AEs in the Japanese population were higher in patients receiving upadacitinib 30 mg compared with the 7.5 and 15 mg doses (Table 3). EAIRs for these

**Table 2** Baseline characteristics in the upadacitinib Japanese and global RA populations

Characteristic	Japanese RA population			Global RA population	
	Upadacitinib 7.5 mg once daily [n = 121]	Upadacitinib 15 mg once daily [n = 126]	Upadacitinib 30 mg once daily [n = 124]	Upadacitinib 6 mg twice daily/ 15 mg once daily [n = 2883]	Upadacitinib 12 mg twice daily/ 30 mg once daily [n = 1375]
Female [n (%)]	84 (69.4)	92 (73.0)	96 (77.4)	2296 (79.6)	1090 (79.3)
Race, Asian [n (%)]	121 (100.0)	126 (100.0)	124 (100.0)	245 (8.5)	169 (12.3)
Age, years [mean (SD)]	57.2 (13.1)	56.7 (11.8)	57.1 (11.6)	54.2 (12.1)	55.5 (11.9)
Weight, kg [mean (SD)]	57.3 (11.5)	58.4 (9.9)	56.6 (12.1)	77.1 (19.6)	77.4 (20.7)
BMI, kg/m <sup>2</sup> [mean (SD)]	22.5 (3.4)	23.1 (3.6)	22.8 (4.5)	28.9 (6.7) <sup>a</sup>	28.9 (6.9) <sup>b</sup>
Duration of RA since diagnosis, years					
Mean (SD)	6.0 (7.9)	6.7 (9.0)	5.5 (6.1)	9.4 (8.6) <sup>c</sup>	8.9 (8.9) <sup>d</sup>
Median (range)	2.5 (0.2–38.8)	3.0 (0.2–54.2)	2.8 (0.3–25.5)	6.8 (0.2–60.1) <sup>c</sup>	5.7 (0.1–51.7) <sup>d</sup>
DAS28-CRP at baseline [mean (SD)]	5.3 (0.9)	5.2 (1.0)	5.2 (1.0)	5.8 (1.0) <sup>e</sup>	5.7 (1.0) <sup>b</sup>
Concomitant csDMARDs at baseline [n (%)]					
None	56 (46.7)	62 (49.6)	58 (46.8)	831 (28.8)	742 (54.0)
MTX alone	34 (28.3)	36 (28.8)	46 (37.1)	1814 (62.9)	430 (31.3)
MTX + other csDMARDs	17 (14.2)	15 (12.0)	12 (9.7)	118 (4.1)	93 (6.8)
csDMARDs other than MTX	13 (10.8)	12 (9.6)	8 (6.5)	119 (4.1)	110 (8.0)
Missing	1 (0.8)	1 (0.8)	0	1 (< 0.1)	0
MTX dose at baseline <sup>f</sup> [mean (SD)]	9.8 (3.0)	8.7 (2.5)	9.8 (3.1)	16.7 (4.3)	16.3 (4.8)
GCs at baseline <sup>g</sup> [n (%)]	59 (48.8)	70 (55.6)	57 (46.0)	1576 (54.7)	655 (47.6)
Oral GC dose at baseline <sup>h</sup> [mean (SD)]	3.5 (1.5)	3.7 (1.9)	3.7 (1.9)	6.1 (2.5)	6.2 (3.5)
History of herpes zoster [n (%)]	21 (17.4)	11 (8.7)	19 (15.3)	126 (4.4)	106 (7.7)
History of herpes zoster vaccination [n (%)]	1 (0.8)	0	1 (0.8)	102 (3.5)	80 (5.8)
History of VTE [n (%)]	6 (5.0)	4 (3.2)	4 (3.2)	145 (5.0)	70 (5.1)
History of CV events [n (%)]	2 (1.7)	0	0	66 (2.3)	30 (2.2)
CV risk factors at baseline [n (%)]					
Medical history of hypertension	44 (36.4)	35 (27.8)	35 (28.2)	1131 (39.2)	535 (38.9)
Diabetes	11 (9.1)	16 (12.7)	6 (4.8)	387 (13.4)	188 (13.7)
Current or former tobacco/nicotine use	63 (52.1)	69 (54.8)	57 (46.0)	1110 (38.5)	584 (42.5)
Elevated LDL-C	19 (15.7)	23 (18.3)	30 (24.2)	801 (27.8)	382 (27.9)
Lowered HDL-C	45 (37.2)	40 (31.7)	46 (37.1)	1641 (56.9)	791 (57.5)
Statin use	11 (9.1)	10 (7.9)	4 (3.2)	339 (11.8)	184 (13.4)

BMI body mass index, csDMARD conventional synthetic disease-modifying antirheumatic drug, CV cardiovascular, DAS28-CRP disease activity score with 28 joints based on C-reactive protein, GC glucocorticoid, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, MTX methotrexate, RA rheumatoid arthritis, SD standard deviation, VTE venous thromboembolism

<sup>a</sup>n = 2878

<sup>b</sup>n = 1368

<sup>c</sup>n = 2872

<sup>d</sup>n = 1373

<sup>e</sup>n = 2867

<sup>f</sup>n = 51, n = 51, n = 58, n = 1931, n = 523

<sup>g</sup>Including both oral and non-oral GCs

<sup>h</sup>n = 57, n = 67, n = 55, n = 1567, n = 649. The prednisone equivalent dose is shown

events in the 7.5 and 15 mg groups were comparable. In comparison with the global population, incidence rates for

AEs and serious AEs were higher in the Japanese population at equivalent upadacitinib doses across the two populations.

Mortality rates were low across all groups. There were two deaths in the Japanese population, both of which occurred with upadacitinib 30 mg treatment. This included a 78-year-old woman with a history of hypertension and hyperlipidemia who died suddenly after 36 days of treatment, and a 64-year-old woman with no known risk factors who died of pneumothorax respiratory failure after 384 days of treatment.

### 3.3 Adverse Events of Special Interest

Infections were the most common AESI in both Japanese and global populations. EAIRs for infection, serious infection, and opportunistic infection were higher in the Japanese population compared with the global population, and higher with upadacitinib 30 mg versus 15 mg and 7.5 mg (Table 4). In univariable analyses, age  $\geq$  65 years, concomitant use of non-methotrexate csDMARDs, and smoking (also significant according to multivariable analyses) were risk factors for serious infection in the global population (Electronic Supplementary Tables 1 and 2). No significant risk factors for serious infection were found in the Japanese population due to the small sample size. Common serious infections in the Japanese population included herpes zoster, pneumonia and, in the 30 mg group only, *Pneumocystis jirovecii* pneumonia. EAIRs of active tuberculosis were low in the Japanese population and comparable with the global population.

EAIRs for herpes zoster in the Japanese population were 7.8, 12.4, and 16.7 per 100 PY in the 7.5, 15, and 30 mg groups, respectively, compared with 3.7 and 7.0 per 100 PY in the global 6 mg twice daily/15 mg once daily and 12 mg twice daily/30 mg once daily groups. Most cases of herpes zoster in the Japanese population involved a single dermatome; unilateral herpes zoster involving multiple dermatomes was reported in one patient in the 7.5 mg group, three patients in the 15 mg group, and eight patients in the 30 mg group. Disseminated herpes zoster was reported in four patients in the 15 mg group and four patients in the 30 mg group. Ophthalmic herpes zoster was reported in one patient in the 7.5 mg group and one patient in the 30 mg group. Two patients in the 7.5 mg group, one patient in the 15 mg group, and five patients in the 30 mg group discontinued treatment due to herpes zoster.

History of herpes zoster was a significant risk factor for herpes zoster, based on univariable (Table 5) and multivariable (Electronic Supplementary Table 3) Cox analyses, in both the Japanese and global populations. Other significant risk factors in the univariable analysis included age  $\geq$  65 years in the Japanese population, and body weight  $<$  60 kg (vs. 60 to  $<$  100 or  $\geq$  100 kg), BMI  $<$  18.5 or 18.5 to  $<$  25 kg/m<sup>2</sup> (vs.  $\geq$  30 kg/m<sup>2</sup>), and methotrexate + other csDMARDs or csDMARDs other than methotrexate (vs. methotrexate alone) in the global population. EAIRs of

**Table 3** Incidence and exposure-adjusted incidence rates of AEs in the upadacitinib Japanese and global RA populations

AE <sup>a</sup>	Japanese RA population			Global RA population		
	Upadacitinib 7.5 mg once daily [n = 121]	Upadacitinib 15 mg once daily [n = 126]	Upadacitinib 30 mg once daily [n = 124]	Upadacitinib 6 mg twice daily/15 mg once daily [n = 2883]	Upadacitinib 12 mg twice daily/30 mg once daily [n = 1375]	
	n (%)	n (%)	n (%)	n (%)	n (%)	n/100 PY (95% CI)
Any AE	120 (99.2)	124 (98.4)	124 (100.0)	2260 (78.4)	1175 (85.5)	230.8 (217.7–244.3)
Serious AE	22 (18.2)	24 (19.0)	36 (29.0)	334 (11.6)	231 (16.8)	14.7 (12.9–16.7)
AE leading to discontinuation of study drug	13 (10.7)	11 (8.7)	26 (21.0)	211 (7.3)	172 (12.5)	10.3 (8.8–11.9)
Death	0	0	2 (1.6)	18 (0.6)	16 (1.2)	1.0 (0.5–1.5)
						n/100 PY (95% CI)
						498.0 (415.0–594.8)
						21.2 (14.8–29.3)
						14.1 (9.2–20.6)
						1.1 (0.1–3.9)
						0.5 (0.3–0.8)

AE adverse event, CI confidence interval, PY patient-years, RA rheumatoid arthritis

<sup>a</sup>Any AE with an onset date on or after the first dose of upadacitinib and no more than 30 days after the last dose of upadacitinib if subject discontinued study drug prematurely

**Table 4** Incidence and exposure-adjusted incidence rates of AESIs in the upadacitinib Japanese and global RA populations

AESIs <sup>a</sup>	Japanese RA population			Global RA population		
	Upadacitinib 7.5 mg once daily [n = 121]	Upadacitinib 15 mg once daily [n = 126]	Upadacitinib 30 mg once daily [n = 124]	Upadacitinib 15 mg once daily [n = 2883]	Upadacitinib 6 mg twice daily/ 30 mg once daily [n = 1375]	
	n (%)	n/100 PY (95% CI)	n (%)	n/100 PY (95% CI)	n (%)	n/100 PY (95% CI)
Infection	93 (76.9)	117.0 (94.4–143.3)	103 (81.7)	116.8 (95.3–141.6)	106 (85.5)	156.1 (127.8–188.7)
Serious infection	10 (8.3)	4.9 (2.4–9.0)	10 (7.9)	4.8 (2.3–8.9)	19 (15.3)	10.6 (6.4–16.5)
Opportunistic infection	2 (1.7)	1.0 (0.1–3.5)	5 (4.0)	2.4 (0.8–5.5)	15 (12.1)	8.5 (4.7–13.9)
Herpes zoster	15 (12.4)	7.8 (4.3–12.8)	24 (19.0)	12.4 (7.9–18.4)	28 (22.6)	16.7 (11.1–24.2)
Active/latent tuberculosis	0	0	1 (0.8)	0.5 (0.0–2.6)	2 (1.6)	1.1 (0.1–3.9)
NMSC	0	0	0	0	0	0
Malignancy other than NMSC	1 (0.8)	0.5 (0.0–2.7)	2 (1.6)	0.9 (0.1–3.4)	3 (2.4)	1.6 (0.3–4.7)
Lymphoma	0	0	0	0	1 (0.8)	0.5 (0.0–3.0)
Hepatic disorders	13 (10.7)	6.8 (3.6–11.6)	16 (12.7)	8.2 (4.7–13.3)	11 (8.9)	6.3 (3.1–11.2)
Gastrointestinal perforation	0	0	1 (0.8)	0.5 (0.0–2.6)	1 (0.8)	0.5 (0.0–3.0)
Anemia	4 (3.3)	2.0 (0.5–5.1)	4 (3.2)	1.9 (0.5–4.9)	18 (14.5)	10.3 (6.1–16.3)
Neutropenia	5 (4.1)	2.5 (0.8–5.9)	3 (2.4)	1.4 (0.3–4.2)	13 (10.5)	7.7 (4.1–13.1)
Lymphopenia	7 (5.8)	3.5 (1.4–7.2)	9 (7.1)	4.4 (2.0–8.3)	9 (7.3)	5.0 (2.3–9.5)
CPK elevation	9 (7.4)	4.6 (2.1–8.7)	17 (13.5)	8.8 (5.1–14.0)	24 (19.4)	14.7 (9.4–21.8)
Renal dysfunction	1 (0.8)	0.5 (0.0–2.7)	1 (0.8)	0.5 (0.0–2.6)	4 (3.2)	2.2 (0.6–5.5)
Adjudicated MACE <sup>b</sup>	1 (0.8)	0.5 (0.0–2.7)	0	0	2 (1.6)	1.1 (0.1–3.9)
Adjudicated VTE <sup>c</sup>	0	0	1 (0.8)	0.5 (0.0–2.6)	1 (0.8)	0.5 (0.0–3.0)
Pulmonary embolism	0	0	0	0	0	0
Deep vein thrombosis	0	0	1 (0.8)	0.5 (0.0–2.6)	1 (0.8)	0.5 (0.0–3.0)

AESI adverse event of special interest, CI confidence interval, CPK creatine phosphokinase, MACE major adverse cardiovascular events, MedDRA Medical Dictionary for Regulatory Activities, NMSC non-melanoma skin cancer, PY patient-years, RA rheumatoid arthritis, VTE venous thromboembolism

<sup>a</sup>AESIs were identified by a Standardized MedDRA query or Company MedDRA query with an onset date on or after the first dose of upadacitinib and no more than 30 days after the last dose of upadacitinib

<sup>b</sup>Defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

<sup>c</sup>Including pulmonary embolism or deep vein thrombosis



malignancy, MACE, VTE, and hepatic disorder were similar between the Japanese and global populations. Of the VTEs in the Japanese population, one patient in the upadacitinib 30 mg group and one patient in the upadacitinib 15 mg group each had a deep vein thrombosis. The patient in the 30 mg group was a current smoker and the patient in the 15 mg group experienced a VTE following a total knee arthroplasty. No events of non-melanoma skin cancer were reported in the Japanese population (Table 4).

### 3.4 Laboratory Abnormalities

EAIRs of laboratory-related AESIs were similar in the Japanese and global populations (Table 4), except for higher rates of creatine phosphokinase (CPK) elevation in the Japanese population. In the Japanese population, EAIRs of anemia, neutropenia, and CPK elevation were higher in the upadacitinib 30 mg group compared with the upadacitinib 7.5 and 15 mg groups. Grade 3 or 4 decreases in hemoglobin, neutrophils, and lymphocytes, and Grade 3 or 4 increases in CPK, were similar in the upadacitinib 7.5 and 15 mg groups, but higher in the upadacitinib 30 mg group (Table 6).

Overall, mean hemoglobin levels from baseline through 84 weeks were lower in the Japanese population compared with the global population. Despite lower baseline mean hemoglobin levels in the Japanese population, Grade 3 or 4 decreases in hemoglobin were less common with the 7.5 and 15 mg groups in the Japanese population compared with the 15 mg group in the global population. There were slight increases in mean hemoglobin levels with upadacitinib 7.5 and 15 mg (with numerically greater increases with 7.5 mg) in the Japanese population, which were maintained over time (Electronic Supplementary Fig. 1). Upadacitinib 30 mg was associated with decreases in mean hemoglobin levels in the Japanese and global populations, which were within the normal range of hemoglobin levels in females.

Grade 3 or 4 increases in hepatic enzymes were similar in the upadacitinib 15 and 30 mg groups, but numerically less frequent in the upadacitinib 7.5 mg group.

## 4 Discussion

Among patients enrolled in the upadacitinib clinical RA program, the overall safety profile of upadacitinib was generally similar in the Japanese population compared with the global population. However, incidence rates for serious AEs, infections (including serious infections, opportunistic infections, and herpes zoster), and CPK elevations, were higher in the Japanese population than in the global population at equivalent upadacitinib doses. Consistent with the global population, infections were the most common AESI observed in the Japanese population with upadacitinib. Malignancies,

MACE, and VTE were uncommon with upadacitinib in the Japanese population, and both patients who experienced VTE while receiving upadacitinib had risk factors for VTE.

In Japan, upadacitinib 7.5 mg and 15 mg are both approved for the treatment of RA in patients with inadequate response to existing treatments. The 15 mg dose was associated with greater efficacy compared with the 7.5 mg dose, particularly for more stringent endpoints such as 70% improvement in American College of Rheumatology criteria and Clinical Disease Activity Index remission at 84 weeks, in the SELECT-SUNRISE study [16]. The results of this integrated safety analysis suggested that the safety profiles of the 7.5 and 15 mg doses were generally similar, with both doses associated with numerically lower EAIRs of AEs, serious AEs, AEs leading to discontinuation, and most AESIs compared with the 30 mg dose, which is currently not approved in Japan or in other countries. However, a degree of dose dependency was observed for opportunistic infections, herpes zoster, and CPK elevations for both the Japanese and global RA populations, but no statistical comparisons were conducted. Despite this, the consequences of a dose reduction from upadacitinib 15 mg once daily to 7.5 mg once daily for safety reasons are not clear.

Infections, including serious infections and opportunistic infections, were more common in the Japanese population than in the global population. No risk factors for serious infections were found in the Japanese population due to the small sample size. However, age  $\geq 65$  years, use of csDMARDs other than methotrexate, and current tobacco/nicotine use were identified as risk factors for serious infections in the global population. A previous report has also shown that smoking is associated with a higher risk of pulmonary infections in patients from Japan receiving immunosuppressant therapies [21]. A numerically greater proportion of patients in the Japanese population were aged  $\geq 65$  years (29% vs. 21%), had lower body weight ( $< 60$  kg: 63% vs. 18%), had lower BMI ( $< 25$  kg/m<sup>2</sup>: 78% vs. 31%), or had current or former tobacco or nicotine use (51% vs. 40%), compared with the global population. These factors may have contributed to the higher incidence of serious infections observed in the Japanese population in this analysis, although further research is required to confirm this.

The higher frequency of herpes zoster in patients in the Japanese population compared with the global clinical trial population is in agreement with previous studies that have shown higher incidence rates of herpes zoster in patients enrolled from Japan and Korea who were treated with baricitinib and tofacitinib compared with other geographic regions [11–15]. The reasons why herpes zoster occurs to a greater extent in populations in Asia than in other regional populations is currently unknown, although it has been suggested that genetic predisposition, regional differences in reporting, and other cultural or medical factors could be involved [13,

**Table 5** Risk factors for herpes zoster in the upadacitinib Japanese and global RA populations based on univariable Cox analysis

	Japanese RA population		Global RA population	
	<i>N</i>	Hazard ratio (95% CI)	<i>N</i>	Hazard ratio (95% CI)
Age, years				
≥ 65	108	<b>1.95 (1.03–3.70)</b>	898	<b>1.78 (1.23–2.57)</b>
50 to < 65	164	1.12 (0.60–2.11)	2050	<b>1.51 (1.10–2.08)</b>
< 50	99	Ref	1310	Ref
Sex				
Male	99	0.83 (0.47–1.46)	872	1.11 (0.82–1.51)
Female	272	Ref	3386	Ref
Weight, kg				
≥ 100	1	0	543	<b>0.50 (0.30–0.82)</b>
60 to < 100	135	0.93 (0.57–1.54)	2929	<b>0.67 (0.50–0.89)</b>
< 60	235	Ref	786	Ref
BMI, kg/m <sup>2</sup>				
< 18.5	30	0.79 (0.26–2.34)	85	<b>2.94 (1.50–5.74)</b>
18.5 to < 25	260	0.57 (0.24–1.33)	1234	<b>1.95 (1.41–2.68)</b>
25 to < 30	60	0.53 (0.19–1.47)	1348	1.30 (0.92–1.83)
≥ 30	21	Ref	1579	Ref
EGFR at screening, mL/min/1.73 m <sup>2</sup>				
30 to < 60	3	0	202	0.97 (0.51–1.84)
60 to < 90	83	1.05 (0.59–1.86)	1747	1.02 (0.78–1.33)
> 90	285	Ref	2307	Ref
History of herpes zoster				
Yes	51	<b>6.28 (3.87–10.19)</b>	232	<b>18.20 (14.06–23.55)</b>
No	320	Ref	3998	Ref
History of herpes zoster vaccination				
Yes	2	<b>12.27 (1.63–92.18)</b>	182	1.08 (0.59–1.98)
No	341	Ref	3772	Ref
Concomitant csDMARDs at baseline				
None	176	1.04 (0.59–1.84)	1573	1.02 (0.77–1.36)
MTX + other csDMARDs	44	1.04 (0.48–2.24)	211	<b>1.72 (1.08–2.75)</b>
csDMARDs other than MTX	33	1.03 (0.44–2.40)	229	<b>1.64 (1.03–2.62)</b>
MTX alone	116	Ref	2244	Ref
Concomitant GCs at baseline				
Yes	186	0.65 (0.40–1.05)	2231	0.86 (0.67–1.11)
No	185	Ref	2027	Ref
Diabetes mellitus at baseline				
Yes	33	1.16 (0.53–2.54)	575	0.99 (0.66–1.48)
No	338	Ref	3655	Ref
History of tobacco/nicotine use				
Current user	76	0.55 (0.26–1.14)	828	1.19 (0.85–1.66)
Former user	113	0.85 (0.50–1.46)	866	<b>1.49 (1.10–2.02)</b>
Never	181	Ref	2559	Ref

Statistically significant interactions of treatment by risk factors are denoted in bold

*BMI* body mass index, *CI* confidence interval, *csDMARD* conventional synthetic disease-modifying anti-rheumatic drug, *EGFR* estimated glomerular filtration rate, *GC* glucocorticoid, *MTX* methotrexate, *RA* rheumatoid arthritis, *Ref* Reference

15]. In this analysis, upadacitinib 15 mg appeared to be associated with a numerically higher incidence of herpes zoster in the Japanese population compared with that of other JAK

inhibitors reported in the literature [13–15, 22]. However, any cross-study comparisons should be interpreted with caution due to differences in study design (including potential



**Table 6** Grade 3 or 4 laboratory abnormalities in the upadacitinib Japanese and global RA populations

Laboratory parameters	Japanese RA population			Global RA population	
	Upadacitinib 7.5 mg once daily [n = 121]	Upadacitinib 15 mg once daily [n = 126]	Upadacitinib 30 mg once daily [n = 124]	Upadacitinib 6 mg twice daily/ 15 mg once daily [n = 2883]	Upadacitinib 12 mg twice daily/ 30 mg once daily [n = 1375]
<b>Hemoglobin (g/L)</b>					
Grade 3 (70 to < 80 or decreased 21 to < 30)	2 (1.7)	2 (1.6)	16 (12.9)	169 (5.9) <sup>a</sup>	160 (11.7) <sup>b</sup>
Grade 4 (< 70 or decreased ≥ 30)	1 (0.8)	0	9 (7.3)	51 (1.8) <sup>a</sup>	59 (4.3) <sup>b</sup>
<b>Neutrophils (× 10<sup>9</sup>/L)</b>					
Grade 3 (0.5 to < 1.0)	2 (1.7)	1 (0.8)	4 (3.2)	29 (1.0) <sup>c</sup>	34 (2.5) <sup>d</sup>
Grade 4 (< 0.5)	1 (0.8)	0	0	7 (0.2) <sup>c</sup>	3 (0.2) <sup>d</sup>
<b>Lymphocytes (× 10<sup>9</sup>/L)</b>					
Grade 3 (0.5 to < 1.0)	48 (39.7)	40 (31.7)	56 (45.2)	572 (20.0) <sup>c</sup>	333 (24.4) <sup>d</sup>
Grade 4 (< 0.5)	6 (5.0)	2 (1.6)	6 (4.8)	45 (1.6) <sup>c</sup>	39 (2.9) <sup>d</sup>
<b>CPK (U/L)</b>					
Grade 3 (> 5.0 to 10.0 × ULN)	3 (2.5)	3 (2.4)	5 (4.0)	48 (1.7) <sup>e</sup>	29 (2.1) <sup>f</sup>
Grade 4 (> 10.0 × ULN)	1 (0.8)	1 (0.8)	4 (3.2)	15 (0.5) <sup>e</sup>	16 (1.2) <sup>f</sup>
<b>Creatinine (μmol/L)</b>					
Grade 3 (> 3.0 to 6.0 × ULN)	0	0	0	1 (< 0.1) <sup>c</sup>	1 (< 0.1) <sup>g</sup>
Grade 4 (> 6.0 × ULN)	0	1 (0.8)	0	2 (< 0.1) <sup>c</sup>	0 <sup>g</sup>
<b>Alanine aminotransferase (U/L)</b>					
Grade 3 (> 3.0 to 8.0 × ULN)	1 (0.8)	3 (2.4)	5 (4.0)	89 (3.1) <sup>h</sup>	48 (3.5) <sup>i</sup>
Grade 4 (> 8.0 × ULN)	0	1 (0.8)	1 (0.8)	12 (0.4) <sup>h</sup>	7 (0.5) <sup>i</sup>
<b>Aspartate aminotrans- ferase (U/L)</b>					
Grade 3 (> 3.0 to 8.0 × ULN)	1 (0.8)	2 (1.6)	2 (1.6)	55 (1.9) <sup>e</sup>	22 (1.6) <sup>i</sup>
Grade 4 (> 8.0 × ULN)	0	1 (0.8)	0	8 (0.3) <sup>e</sup>	5 (0.4) <sup>i</sup>

Data are expressed as *n* (%)

CPK creatine phosphokinase, RA rheumatoid arthritis, ULN upper limit of normal

<sup>a</sup>*n* = 2858

<sup>b</sup>*n* = 1364

<sup>c</sup>*n* = 2857

<sup>d</sup>*n* = 1363

<sup>e</sup>*n* = 2855

<sup>f</sup>*n* = 1367

<sup>g</sup>*n* = 1368

<sup>h</sup>*n* = 2856

<sup>i</sup>*n* = 1366

differences in the calculation of herpes zoster rates), patient populations, and baseline characteristics, especially those

associated with significantly greater risk of herpes zoster such as age and history of herpes zoster.

History of herpes zoster was numerically more common in the Japanese population and was an independent risk factor for herpes zoster while receiving upadacitinib. Herpes zoster vaccination did not appear to reduce the risk of herpes zoster in the global population. However, as we do not have detailed information regarding the types and dates of the vaccination, it is difficult to assess the benefits of vaccination in this patient population. Furthermore, the benefits of herpes zoster vaccination in the Japanese population could not be assessed as only two patients were vaccinated. More information about the impact of herpes zoster vaccination on the risk of herpes zoster among patients receiving upadacitinib or other JAK inhibitors is necessary to inform future clinical practice. The increased risk of herpes zoster associated with JAK inhibitors, including upadacitinib, should be considered and explained to the patient before prescription, particularly to those who have a history of herpes zoster.

In addition to geographic region, the risk of AESIs may also vary with race or ethnicity. For example, in the general population, Asian Americans had a higher risk of herpes zoster [23] and a lower risk of VTE [24] compared with non-Asian Americans. In the current analysis, all patients in the Japanese population were Asian by race, and most were from a Japanese ethnic background. It was however not an objective to investigate the effect of race or ethnicity on the safety profile of upadacitinib in patients with RA. Thus, the current results should be interpreted as the safety profile of patients enrolled in clinical trials from Japan.

The current analysis has several limitations. As an analysis of long-term follow-up data, this analysis was conducted without a placebo comparison. However, data from placebo-controlled periods of the studies included in this analysis have indicated a favorable benefit–risk balance for upadacitinib 15 mg once daily compared with placebo [25]. Overall conclusions from placebo-controlled data were generally consistent with the current analysis. Moreover, comparisons across the three upadacitinib doses and between the Japanese and global populations should be interpreted with caution as no statistical comparisons were performed. Another limitation is the small sample size of the Japanese population evaluated in this study, especially when compared with the global population. The median exposure to upadacitinib in this analysis was up to 600 days, which may not be long enough to accurately assess the incidence of rare events. Furthermore, patients from Japan were enrolled in a limited set of clinical trials (three of eight clinical trials in the upadacitinib phase II/III program).

## 5 Conclusions

Upadacitinib at equivalent doses generally had a similar safety profile in the Japanese and global populations enrolled in the RA clinical program, with the exception of higher rates of serious infections, opportunistic infections, herpes zoster, and CPK elevations in the Japanese population. In the majority of patients enrolled in Japan from the three clinical trials included in the current analysis, the safety profiles of upadacitinib 15 mg and 7.5 mg were generally similar, except for numerically lower EAIRs of opportunistic infections, herpes zoster, and CPK elevations with the 7.5 mg dose compared with the 15 mg dose, although no statistical comparisons were conducted. It is important that rheumatologists consider the risk of herpes zoster in their benefit–risk assessment prior to prescribing JAK inhibitors. Further postmarketing research will continue to clarify the safety of upadacitinib in patients with RA in Japan, especially regarding the risk of infections, in real-world settings.

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**Ethics Approval** All studies were conducted according to the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations and guidelines governing clinical study conduct, and the Declaration of Helsinki. Study-related documents were reviewed and approved by independent Ethics Committees and Institutional Review Boards.

**Consent to Participate** All patients provided written informed consent.

**Consent for Publication** Not applicable.

**Availability of Data and Material** These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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