Herpes Zoster and Herpes Simplex Infections in Patients From Japan and Korea With Moderate-to-Severe Atopic Dermatitis Following Treatment With Abrocitinib in the JADE Clinical Programme

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INTRODUCTION

- Patients with atopic dermatitis (AD) are susceptible to viral skin infections including eczema herpeticum, a disseminated herpes simplex (HS) virus infection[1,2]
- Treatment with Janus kinase (JAK) inhibitors is associated with an increased risk of herpes zoster (HZ) infection in patients with AD[3,4]
- Abrocitinib, an oral, once-daily, JAK1-selective inhibitor is approved for the treatment of adults and adolescents with moderate-to-severe AD[5-7]
  - Findings from randomised global clinical trials in the JADE clinical programme have shown a dose-dependent increase in the incidence of HZ and HS infections in patients treated with abrocitinib[8,9]
- A higher incidence of HZ infections has also been observed among patients treated with JAK inhibitors from Asian regions including Japan and Korea, in comparison to patients from non-Asian regions[10,11]

OBJECTIVE

- To assess events of HZ and HS infections in a subpopulation of patients from Japan and Korea from the JADE global clinical trial programme who received abrocitinib for moderate-to-severe AD

METHODS

Study Design and Patients

- This was a post hoc integrated subgroup analysis of abrocitinib clinical trial data by geographic region, including: (1) Japan and Korea, (2) other Asian regions, (3) overall Asian region, and (4) global clinical trial population (previously published)[8,9]
  - Other Asian regions included patients from China, Israel, and Taiwan
- The analysis included patients aged ≥12 years who received oral abrocitinib 200 mg or 100 mg once daily (QD) as monotherapy or in combination with topical therapy in the phase 2b trial (NCT02780167); phase 3 trials JADE MONO-1 (NCT03349060), MONO-2 (NCT03575871), COMPARE (NCT03720470), REGIMEN (NCT03627767), and TEEN (NCT03796676); and the long-term extension JADE EXTEND (NCT03422822; data cutoff: 24 July, 2020) (**Supplementary Figure S1,** accessed via QR code)

Assessments

- The following outcomes were assessed
  - Incidence of HZ and HS infections
  - Proportions of patients with HZ and HS infection events, stratified by disease severity
  - Mean absolute lymphocyte counts (ALCs) for patients with and without HZ and HS infections
    - Data collected before or on the first occurrence HZ or HS infection was included
  - Hazard ratios (HRs) of the risk factors of HZ and HS infections

Statistical Analysis

- Analyses were performed in the safety analysis set, consisting of all eligible patients from applicable pooled studies who received at least 1 dose of abrocitinib
- Time to first occurrence of HZ or HS infection was evaluated using a Kaplan-Meier time-to-event analysis
- Median of mean ALCs among patients with and without HZ and HS infections was calculated
- Cox regression analysis for HZ and HS infections including multiple potential risk factors was conducted

RESULTS

Patient Population

- Of a total of 3128 patients in the global clinical trial population, 452 were enrolled from Asia (abrocitinib 100 mg, n=143; abrocitinib 200 mg, n=309); of these, 135 were from Japan (100 mg, n=62; 200 mg, n=73), 63 were from Korea (100 mg, n=34; 200 mg, n=29), and 254 were from other Asian regions (100 mg, n=47; 200 mg, n=207) (data cutoff: 24 July, 2020)

Incidence of HZ and HS Infections

- Overall, HZ infection events were reported in 2.3% of the global clinical trial population, 4.0% of the overall Asian region cohort, and 3.5% of patients from Japan and Korea (**Table 1**)
- Overall, the proportions of patients with HS infection events were 6.2% in the global clinical trial population, 7.1% in the overall Asian region cohort, and 9.6% in patients from Japan and Korea (**Table 1**)
- Among patients with HS or HZ infection events, greater proportions from Japan and Korea than those from the overall Asian region and the global clinical trial population had mild HZ infections (71.4% vs 55.6% and 31.9%, respectively) and mild HS infections (94.7% vs 87.5% and 71.8%, respectively) (**Supplementary Figure S2,** accessed via QR code)
- Medians of mean ALCs were generally within normal ranges and were similar between patients with or without HZ or HS infections in the global clinical trial population (with HZ: 1.57; without HZ: 1.79; with HS: 1.70; without HS: 1.79), the overall Asian region (with HZ: 1.53; without HZ: 1.66; with HS: 1.47; without HS: 1.66), and Japan and Korea (with HZ: 1.56; without HZ: 1.60; with HS: 1.43; without HS: 1.61)

Table 1. Incidence of HZ and HS Infections by Geographic Region

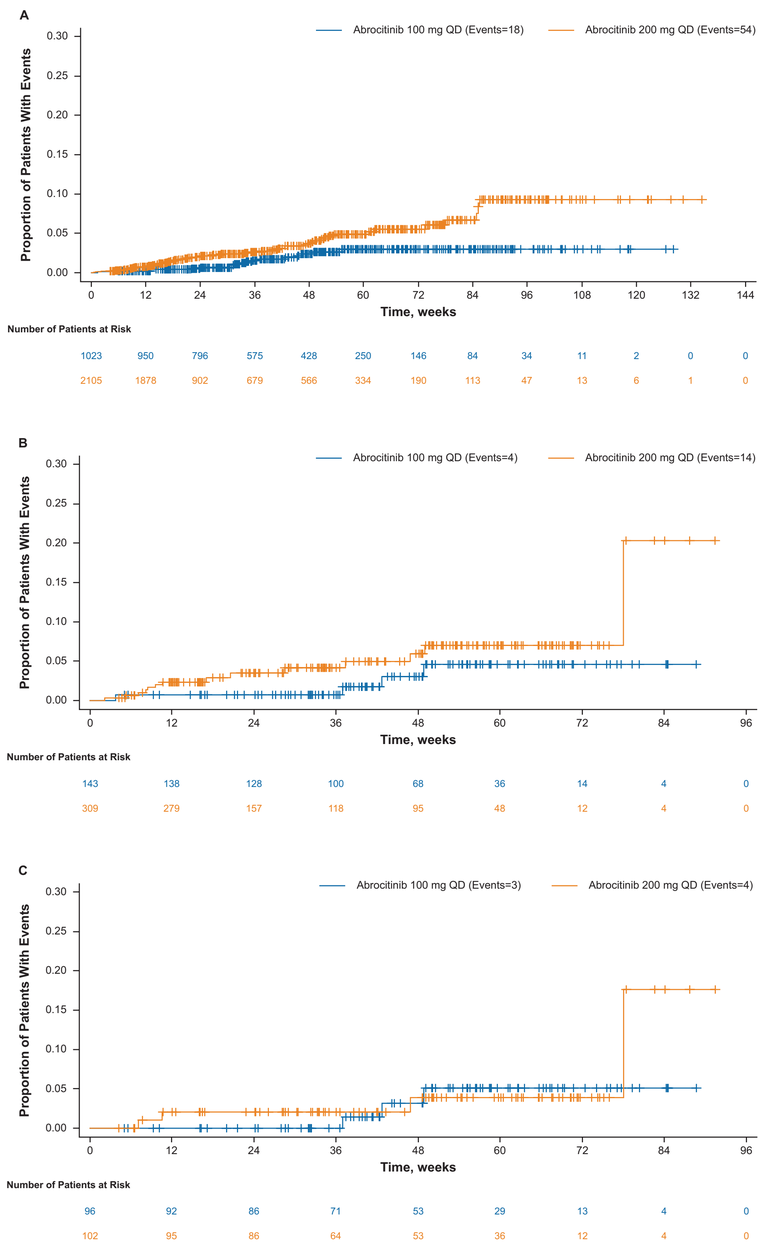
		All Abrocitinib	
		HZ Infections	HS Infections
Global clinical trial population	N (PY)	3128 (2122.65)	3128 (2052.29)
	Patients with event, n (%)	72 (2.3)	195 (6.2)
	IRs (95% CI)	3.39 (2.65-4.27)	9.5 (8.21-10.93)
Asian region	N (PY)	452 (317.79)	452 (305.03)
	Patients with event, n (%)	18 (4.0)	32 (7.1)
	IRs (95% CI)	5.66 (3.36-8.95)	10.49 (7.18-14.81)
Japan and Korea	N (PY)	198 (180.93)	198 (169.74)
	Patients with event, n (%)	7 (3.5)	19 (9.6)
	IRs (95% CI)	3.87 (1.56-7.97)	11.19 (6.74-17.48)

HZ, herpes zoster; HS, herpes simplex, IR, incidence rate; PY, person-years.

Time-to-Event Analysis of HZ and HS Infections

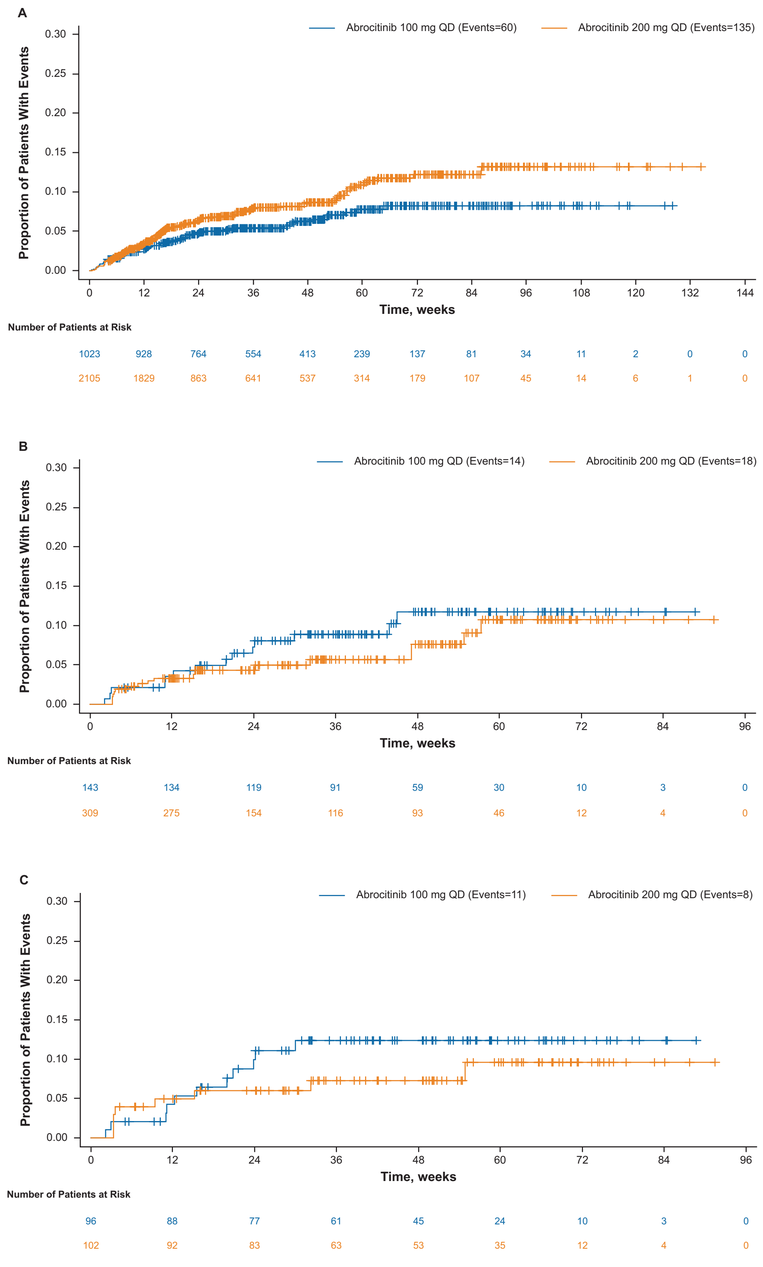
- Kaplan-Meier estimates of HZ and HS infection events (data cutoff, 24 July 2020) were similar across all subgroups (**Figures 1 and 2**)
- At Week 48 the probability of being HZ or HS infection event-free was comparable among patients from Japan and Korea (HZ: 0.964 [95% CI, 0.914-0.985]; HS: 0.902 [95% CI, 0.848-0.937]), the overall Asian region (HZ: 0.952 [95% CI, 0.918-0.972]; HS: 0.907 [95% CI, 0.866-0.936]), and the global clinical trial population (HZ: 0.968 [95% CI, 0.958-0.976]; HS: 0.923 [95% CI, 0.910-0.934]) (**Figures 1 and 2**)
  - The risk of HZ and HS infection events generally increased with dose; however, the risk of HS infection events in the overall Asian region population and patients from Japan and Korea was higher among patients treated with abrocitinib 100 mg compared with abrocitinib 200 mg
  - Median time to HS and HZ infection events were not evaluable across all populations because too few events were observed

Figure 1. Time to Event for HZ Infections in Patients From (A) the Global Clinical Trial Population, (B) the Overall Asian Region, and (C) Japan and Korea



HZ, herpes zoster; QD, once daily.

Figure 2. Time to Event for HS Infections in Patients From (A) the Global Clinical Trial Population, (B) the Overall Asian Region, and (C) Japan and Korea



HS, herpes simplex; QD, once daily.

Risk Factors for HZ and HS Infections

- The risk of HZ infections was numerically higher in patients from Asia who received abrocitinib 200 mg versus abrocitinib 100 mg (**Table 2**)
- The risk of HZ and HS infections was numerically higher in patients from Asia with severe AD than moderate AD and in patients from Japan than those from Korea or other regions in Asia (**Table 2**)
- The risk of HS infections was numerically higher in patients from Asia with a body mass index (BMI) of <25 kg/m^2 vs ≥25 kg/m^2 and baseline estimated glomerular filtration rate (eGFR) of ≥90 mL/min vs <90 mL/min (**Table 2**)

Table 2. Hazard Ratios (95% CI) of Fixed Effects for Identifying Risk Factors Associated With Time to All Treatment-Emergent HZ and HS Infections in Patients From Asia With Moderate-to-Severe AD

	Hazard Ratio (95% CI)	
	HZ Infections	HS Infections
Abrocitinib dose 200 mg QD vs 100 mg QD	1.30 (0.34-4.95)	0.63 (0.28-1.42)
Baseline age, years ≥18 vs <18	1.63 (0.20-13.34)	0.66 (0.17-2.54)
Baseline disease severity Severe vs moderate	2.51 (0.89-7.07)	1.19 (0.57-2.49)
Sex Female vs male	1.08 (0.39-2.96)	0.83 (0.38-1.80)
BMI, kg/m^2 ≥25 vs <25	0.93 (0.33-2.63)	0.38 (0.15-0.95)
Asian region Japan vs Korea Japan vs other Asian regions[a] Korea vs other Asian regions[a]	 3.77 (0.41-34.72) 2.23 (0.38-13.29) 0.59 (0.04-7.92)	 1.44 (0.48-4.29) 1.35 (0.45-4.04) 0.94 (0.25-3.53)
Prior systemic therapy No vs yes	0.60 (0.22-1.60)	1.23 (0.57-2.66)
Baseline eGFR, mL/min <90 vs ≥90	0.54 (0.15-1.97)	0.45 (0.16-1.21)
Confirmed ALC prior to event ≥1.0 vs <1.0 (10^3/mm^3)	0.95 (0.12-7.52)	1.09 (0.25-4.77)

AD, atopic dermatitis; ALC, absolute lymphocyte count; BMI, body mass index; eGFR, estimated glomerular filtration rate; HS, herpes simplex, HZ, herpes zoster; QD, once daily.
Hazard ratios and associated confidence intervals were estimated using a Cox regression model including fixed effects of treatment; study (parent); categorical variables of baseline age, baseline disease severity, sex, BMI, Asian region, prior systemic therapy, baseline eGFR; and a time-dependent variable of confirmed absolute lymphocyte count prior to the event (≥1.0 or <1.0 [10^3/mm^3]).
[a]Other Asian regions included China (n=188), Israel (n=8), and Taiwan (n=58).

CONCLUSIONS

- The risk of HZ or HS infection events was similar in patients from Japan and Korea, the overall Asian population, and the global clinical trial populations
- In the overall Asian population, the risk of HZ infection was numerically higher in patients who received a higher dose of abrocitinib, and the risk of both HZ and HS infection was numerically higher in patients who had severe AD, resided in Japan, had a baseline BMI <25 kg/m^2, or had a baseline eGFR ≥90 mL/min; most HZ and HS infections were mild
- Medians of mean ALCs were similar among patients with or without HZ or HS infections

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