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Original Article

Long-Term Safety of Abrocitinib in Moderate-to-Severe Atopic Dermatitis: Integrated Analysis by Age

Michael J. Cork, PhD, FRCP[a], Mette Deleuran, MD, DMSc[b], Bob Geng, MD[c], Jonathan I. Silverberg, MD, PhD, MPH[d], Eric L. Simpson, MD, FAAD[e], Linda F. Stein Gold, MD[f], Alan D. Irvine, MD, DSc[g], William Romero, MD[h], Hernan Valdez, MD[i], Haiyun Fan, MS[j], and Justine Alderfer, PharmD[j] *Sheffield and Surrey, United Kingdom; Aarhus, Denmark; San Diego, calif; Washington, DC; Portland, OR; Detroit, mich; Dublin, Ireland; New York, NY; and Collegeville, PA*

What is already known about this topic? Abrocitinib has a manageable long-term safety profile that can be optimized using proper dose and patient selection. The long-term safety of abrocitinib in patients of different age groups remains to be elucidated.

What does this article add to our knowledge? Long-term abrocitinib is well tolerated across all age groups. Incidence rates of most treatment-emergent adverse events of special interest were numerically higher in patients aged 65 years or older than in younger age groups, particularly in those treated with 200 mg.

How does this study impact current management guidelines? Adverse events associated with the Janus kinase inhibitor class were infrequent with abrocitinib but more common in older patients. Safety risk may be minimized by starting older patients on the abrocitinib lower dose (100 mg).

BACKGROUND: Abrocitinib has a manageable long-term safety profile for patients with moderate-to-severe atopic dermatitis. Identifying populations at higher risk of adverse events will help optimize dose selection.

OBJECTIVE: To evaluate abrocitinib long-term safety by age.

METHODS: Data (cutoff: September 25, 2021) from JADE clinical trials were pooled in a consistent-dose cohort (patients who received the same abrocitinib dose throughout exposure) or a variable-dose cohort (patients who received abrocitinib 200 mg [12 wk], were randomly assigned later to receive abrocitinib

[a]Sheffield Dermatology Research, Department of Infection, Immunity & Cardiovascular Disease, University of Sheffield and Sheffield Children's Hospital, Sheffield, UK
[b]Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark
[c]Department of Allergy and Immunology, UC San Diego School of Medicine, San Diego, calif
[d]Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC
[e]Department of Dermatology, Oregon Health & Science University, Portland, ore
[f]Department of Dermatology, Henry Ford Health System, Detroit, mich
[g]Clinical Medicine, School of Medicine, Trinity College Dublin, Dublin, Ireland
[h]Pfizer Ltd., Tadworth, Surrey, UK
[i]Pfizer Inc., New York, NY
[j]Pfizer Inc., Collegeville, Pa

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Conflicts of interest: M. J. Cork has been a clinical trial investigator for Pfizer Inc., Atopix, Galapagos, Hyphens, Johnson & Johnson, Kymab, LEO Pharma, L'Oreal/La Roche-Posay, Novartis, Regeneron, and Sanofi Genzyme and an advisory board member, consultant, and/or invited lecturer for Pfizer Inc., AbbVie, Amlar, Astellas, Atopix, Boots, Dermavant, Galapagos, Galderma, Hyphens, Johnson & Johnson, Kymab, LEO Pharma, L'Oreal/La Roche-Posay, Menlo Therapeutics, Novartis, Oxagen, Procter & Gamble, Reckitt Benckiser, Regeneron, and Sanofi Genzyme. M. Deleuran has been a consultant, advisory board member, and/or speaker for Pfizer Inc., AbbVie, Almirall, Arena Pharmaceuticals, ASLAN Pharmaceuticals, Eli Lilly and Company, Incyte Biosciences International Sàrl, Kymab, La Roche-Posay, LEO Pharma, Mustela, Numab Therapeutics AG, Pierre Fabre, Regeneron Pharmaceuticals, and Sanofi Genzyme. B. Geng has worked as a consultant for Pfizer Inc. and Genentech; as a speaker/consultant for CSL Behring, Horizon Therapeutics, Regeneron Pharmaceuticals, and Sanofi Genzyme; and is on advisory boards for Novartis and Takeda. J. I. Silverberg served as an investigator for Celgene, Eli Lilly and Company, F. Hoffmann-La Roche, Menlo Therapeutics, Realm Therapeutics, Regeneron Pharmaceuticals, and Sanofi Genzyme; as a consultant for Pfizer Inc., AbbVie, Anacor, AnaptysBio, Arena Pharmaceuticals, Dermavant, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Glenmark, Incyte, Kiniksa Pharmaceuticals, LEO Pharma, Menlo Therapeutics, Novartis, Realm Therapeutics, Regeneron Pharmaceuticals, and Sanofi Genzyme; and as a speaker for Regeneron Pharmaceuticals and Sanofi Genzyme. E. L. Simpson has received grants from Pfizer Inc., Eli Lilly and Company, Kyowa Kirin, LEO Pharma, Merck, and Regeneron Pharmaceuticals and personal fees from Pfizer Inc., Bausch Health (Valeant), Dermira, Eli Lilly and Company, Galderma, LEO Pharma, Menlo Therapeutics, Novartis, Regeneron Pharmaceuticals, and Sanofi Genzyme. L. F. Stein Gold received grants from Pfizer Inc., Incyte, and LEO Pharma; and has received payment for lectures from Pfizer Inc. and LEO Pharma. A. D. Irvine is/has served as a consultant for Pfizer Inc., AbbVie, Amgen, Arena, Benevolent AI, Eli Lilly and Company, LEO Pharma, Novartis, Regeneron, and Sanofi Genzyme. W. Romero was an employee and shareholder of Pfizer Ltd. at the time this analysis was conducted. H. Valdez was an employee and shareholder of Pfizer Inc. at the time this analysis was conducted. H. Fan and J. Alderfer are employees and shareholders of Pfizer Inc.

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Corresponding author: Justine Alderfer, PharmD, Pfizer Inc., 500 Arcola Rd., Collegeville, PA 19426. E-mail: justine.alderfer@pfizer.com.

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Abbreviations used
AD- Atopic dermatitis
AAD- American Academy of Dermatology
AE- Adverse event
CV- Cardiovascular
CVD- Cardiovascular disease
EMA- European Medicines Agency
HZ- herpes zoster
IR- Incidence rate
JAK- Janus kinase
JAKi- Janus kinase inhibitor
MACE- Major adverse cardiovascular event
NMSC- Nonmelanoma skin cancer
PY- Patient-years
RA- Rheumatoid arthritis
SAE- Serious adverse event
TEAE- Treatment-emergent adverse event
VTE- Venous thromboembolism

200 mg, 100 mg, or placebo [up to 40 wk], and assigned to receive abrocitinib 200 mg or 100 mg in the long-term study). Data were stratified *post hoc* by age at baseline (12 to < 18 y; 18 to < 40 y, 40 to < 65 y, and ≥65 y). Incidence rates of treatment-emergent adverse events (TEAEs) of special interest were assessed.

RESULTS: Analysis included 3,802 patients (exposure: 5,214 patient-years). The incidence rates for serious adverse events, TEAEs leading to study discontinuation, serious infections, herpes zoster, thrombocytopenia, lymphopenia, nonmelanoma skin cancer, malignancies (excluding nonmelanoma skin cancer), major cardiovascular events, and venous thromboembolism were numerically higher in patients aged 65 years or older than in younger patients. Overall, adolescents had the lowest rates for TEAEs of special interest.

CONCLUSIONS: Abrocitinib has a manageable long-term safety profile. TEAEs of special interest were lower in adolescents and higher in the 65-years-old or older age group. Risk of specific TEAEs was numerically higher in patients aged 65 years or older treated with abrocitinib 200 mg and underscores the importance of dose selection in older patients. **(J Allergy Clin Immunol Pract 2025;■:■-■)**

Key words: *JAK 1-selective inhibitor; Age groups; Herpes zoster; Thrombocytopenia; Lymphopenia; Venous thromboembolism; Major adverse cardiovascular events*

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disorder associated with itch, eczematous lesions, and pain[1-3]; its course can be continuous or relapsing-remitting.[4] As new therapies for AD are approved, evaluation of the long-term safety of these treatments is needed.

Abrocitinib, baricitinib, and upadacitinib are oral Janus kinase (JAK) inhibitors (JAKis) approved for the treatment of AD in many countries and regions.[5-7] In 2023, the European Medicines Agency (EMA) adopted a set of safety recommendations for the JAKi class of drugs; they state that JAKis should be used in patients who are 65 years of age or older, are current or past long-time smokers, have malignancy risk factors, or are at an increased risk of major adverse cardiovascular events (MACE) or venous thromboembolism (VTE) only if no suitable alternatives are available.[8] The EMA safety assessment was initiated on the basis of the results of the tofacitinib (JAK 1/3 inhibitor)[9] and baricitinib (JAK 1/2 inhibitor)[10] safety studies in patients with rheumatoid arthritis (RA), which showed an increased risk of serious infections, VTE, MACE, and malignancies with these JAKis versus tumor necrosis factor-α inhibitors in patients with RA.[8] The long-term risk of these safety events in patients with AD receiving JAKis remains to be elucidated, especially considering that patients with AD are often younger and have fewer comorbidities than patients with RA.[3]

Abrocitinib has demonstrated rapid, sustained, and clinically meaningful improvements in the signs and symptoms of AD as monotherapy and in combination with topical medicated therapy across multiple clinical trials.[11-20] An integrated safety analysis of abrocitinib was reported previously, which included pooled clinical trial data from 2,856 adult and adolescent patients, representing 1,614 patient-years (PY) of abrocitinib exposure.[21] Results showed that abrocitinib had short-term side effects that were manageable and a safety profile appropriate for long-term use that can be optimized with proper dose and patient selection.[21] An updated integrated analysis of abrocitinib safety including data from 3,802 patients representing 5,214 PY of exposure has recently been published (data cut-off date: September 25, 2021).[22] Because older age is a risk factor for several safety events of interest with the JAKi class of drugs, such as herpes zoster (HZ) infection, cardiovascular disease (CVD), certain malignancies, and VTE,[23-26] the objective of this analysis of the September 25, 2021 datacut was to assess abrocitinib long-term safety in different age groups and ascertain whether the relationship between age and risk for safety events of interest is also applicable to patients with AD.

METHODS

Long-term safety population

Safety data were pooled from all abrocitinib-treated patients who enrolled in qualifying studies in the JADE clinical program and met the individual study inclusion/exclusion criteria. The data cut-off for this analysis was September 25, 2021; the long-term extension study, JADE EXTEND, is ongoing, and the final data may change. Qualifying studies were the phase 2b study (NCT02780167),[15] phase 3 JADE MONO-1 (NCT03349060),[12] JADE MONO-2 (NCT03575871),[11] JADE TEEN (NCT03796676),[13] JADE COMPARE (NCT03720470),[16] JADE DARE (NCT04345367),[17] and JADE REGIMEN (NCT03627767).[14] Adverse events (AEs) of special interest were assessed in patients stratified *post hoc* at qualifying study baseline into age groups of 12 to younger than 18 years, 18 to younger than 40 years, 40 to younger than 65 years, and 65 years or older. AEs were also assessed in a subset of patients who were 75 years of age or older. All studies were approved by the appropriate institutional review boards/ethics committees at each study site and conducted in compliance with the ethical principles from the Declaration of Helsinki and all International Council for Harmonisation Good Clinical Practice Guidelines. All patients provided informed consent.

Analysis data sets

Data from patients who received 1 or more doses of abrocitinib 200 mg or 100 mg in the JADE clinical trial program were pooled for analysis in 2 separate cohorts: (1) consistent-dose cohort and (2) variable-dose cohort (Figure 1). The consistent-dose cohort included patients who received the same abrocitinib dose during the entire exposure time in the phase 2b study or qualifying phase 3 studies and/or the long-term extension study JADE EXTEND. Patients from the qualifying study JADE REGIMEN were included in the consistent-dose cohort only if they had received abrocitinib 200 mg in the 12-week open-label run-in phase and had not subsequently entered the randomized double-blind phase. Patients in the consistent-dose cohort might have received their first dose of abrocitinib in JADE EXTEND if they previously received placebo in the placebo-controlled qualifying studies and/or dupilumab in JADE COMPARE or JADE DARE. Patients previously randomized to placebo in JADE MONO-1 or MONO-2 were randomly assigned to abrocitinib 200 mg or 100 mg in JADE EXTEND. Patients previously randomized to placebo in JADE COMPARE continued to receive the same abrocitinib dose in JADE EXTEND as the dose randomly allocated for the final 4 weeks in JADE COMPARE. Patients enrolled in the phase 2b monotherapy study did not enroll in JADE EXTEND but were included in the consistent-dose cohort if they had received either abrocitinib 200 mg or 100 mg.

The variable-dose cohort included patients who might have received different doses of abrocitinib (100 mg and 200 mg) throughout exposure in the qualifying study JADE REGIMEN and who had enrolled in JADE EXTEND. Patients in this cohort completed the 12-week open-label period of JADE REGIMEN (abrocitinib 200 mg only) as responders and entered the randomized phase, in which they received abrocitinib 200 mg, abrocitinib 100 mg, or placebo. Some patients subsequently entered the JADE REGIMEN rescue phase (abrocitinib 200 mg) and/or JADE EXTEND (abrocitinib 200 mg or 100 mg).

Assessments included serious adverse events (SAEs), treatment-emergent adverse events (TEAEs) leading to discontinuation, and TEAEs of special interest (infections [serious and opportunistic]; malignancies; cardiovascular [CV] events, including MACE and VTE; and hematological changes). The TEAEs were classified as mild, moderate, or severe per the investigator's judgment. Opportunistic infections, malignancies, and CV events were adjudicated by independent committees based on prespecified criteria.

Statistical analyses

Statistical analyses were conducted on patients who received 1 or more doses of study treatment. Incidence rates (IRs) were calculated for SAEs, TEAEs leading to discontinuation, and TEAEs of special interest and were expressed as numbers of unique patients with events per 100 PY, along with the associated 95% confidence intervals (95% CIs). Exposure time was defined as the duration from the first abrocitinib dose up to the day of the first event for patients who experienced events or up to the end of the risk period for patients who did not experience events. The risk period was defined as the time from the first abrocitinib dose to one of the following: last dose plus 28 days, death, or data cut-off date (for JADE EXTEND only), whichever occurred first. The 95% CIs for IRs were calculated based on the assumption that the actual case count followed a Poisson distribution. No formal statistical analyses were conducted, and all comparisons between IRs or proportions are nominal (using 95% CIs) and for exploratory purposes only. In situations in which point estimates were different, but 95% CIs overlapped, the phrasing "numerically higher" or "numerically lower" was used to describe the relationship between groups.

Results

The consistent-dose cohort included 3,004 patients: 1,981 exposed to abrocitinib 200 mg and 1,023 exposed to abrocitinib 100 mg. Of those 3,004 patients, 944 patients had 96 weeks or greater and 154 had 144 weeks or greater of exposure (Table I). Total exposure in this cohort was 3,680 PY: 2,173 PY for abrocitinib 200 mg and 1,507 PY for abrocitinib 100 mg. The variable-dose cohort included 798 patients (abrocitinib total exposure: 1,534 PY). Of those, 688 (86%), 543 (68%), 328 (41%), and 30 (4%) patients were exposed to abrocitinib for 48 or greater, 96 or greater, 120 or greater, and 144 or greater weeks, respectively.

Demographics and baseline disease characteristics

Demographics and baseline characteristics were generally similar between the consistent- and variable-dose cohorts (Table II). A greater proportion of patients in the variable-dose cohort was exposed to prior systemic therapy than those in the consistent-dose cohort (Table II). In the consistent-dose cohort, 490 patients (16%) were aged 12 to younger than 18 years, 1,573 (52%) were 18 to younger than 40 years, 795 (26%) were 40 to younger than 65 years, and 146 (5%) were 65 years or older; a similar age distribution was seen in the variable-dose cohort (Table II). The oldest patient in this analysis was 84 years old at baseline.

Serious adverse events, treatment-emergent adverse events leading to study discontinuation, and deaths in subgroups by age

In the consistent-dose cohort, IRs for SAEs and TEAEs leading to discontinuation were generally numerically higher in the abrocitinib 200-mg group compared with the abrocitinib 100-mg group with overlapping 95% CIs (Figure 2). Although 95% CIs were wide in the subgroup of patients aged 65 years or older, IRs were numerically higher compared with younger age groups (Figure 2). Similar trends were seen in the subset of patients aged 75 years or older in the consistent-dose cohort (n = 29; Table E1; available in this article's Online Repository at www.jaci-inpractice.org) and the variable-dose cohort (n = 3; Table E2; available in this article's Online Repository at www.jaci-inpractice.org).

Seven patients died during the exposure period: 1 of cardiac failure (male, 42 y, abrocitinib 200 mg), 3 of COVID-19 (female, 69 y, abrocitinib 200 mg; male, 71 y, abrocitinib 200 mg; female, 65 y, abrocitinib 100 mg), 1 of septic shock (male, 75 y, abrocitinib 200 mg), 1 of cardiorespiratory arrest (female, 62 y, abrocitinib 200 mg), and 1 of sudden death (female, 73 y, abrocitinib 100 mg). In the previous integrated safety analysis, 1 event of gastric adenocarcinoma was also reported as death.[21] This event occurred in a 78-year-old female patient early in treatment with abrocitinib 200 mg. The symptoms were present before taking the study medication, and the patient died 242 days after the last dose of the study treatment. Therefore, this case of adenocarcinoma was reclassified as an SAE.

TEAEs of special interest in subgroups stratified by age

Serious infections. The IRs for serious infections in the consistent-dose cohort were generally higher in the abrocitinib 200-mg arm than in the abrocitinib 100-mg arm, and were numerically higher in patients aged 65 years or older treated with abrocitinib

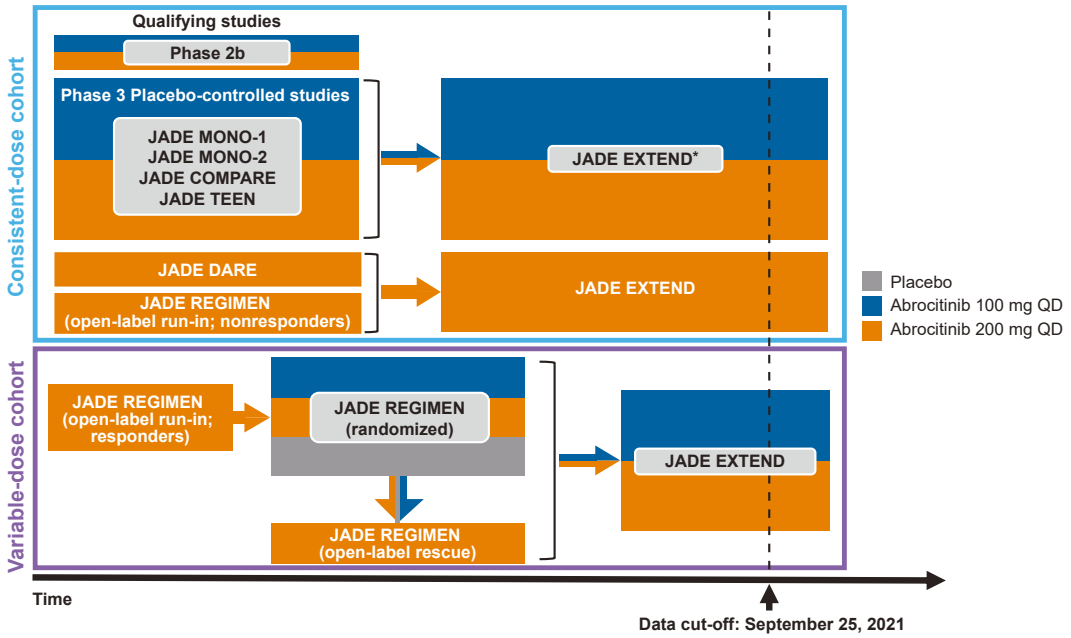

FIGURE 1. Safety design and cohorts. *Includes patients who received their first dose of abrocitinib (200 or 100 mg) in JADE EXTEND after receiving placebo in a phase 3 placebo-controlled trial or dupilumab in JADE COMPARE or JADE DARE, and patients who first received abrocitinib in a qualifying phase 3 trial. JADE EXTEND is ongoing. *QD,* Once daily.

TABLE I. Treatment exposure in the consistent-dose cohort

Treatment exposure	Abrocitinib 100 mg QD n = 1,023	Abrocitinib 200 mg QD n = 1,981	All abrocitinib n = 3,004
Duration of treatment, d			
Median (Q1, Q3)	642.0 (178.0, 782.0)	297.0 (116.0, 688.0)	347.0 (131.5, 740.0)
Range	1–1,251	1–1,369	1–1,369
Cumulative exposure (wk), n (%)			
≥48	685 (67)	864 (44)	1,549 (52)
≥96	423 (41)	521 (26)	944 (31)
≥120	189 (18)	242 (12)	431 (14)
≥144	68 (7)	86 (4)	154 (5)

Q1, quartile 1; *Q3,* quartile 3; *QD,* once daily.

200 mg or 100 mg compared with other age groups; however, 95% CIs were overlapping (Figure 3, *A*). One event of adjudicated tuberculosis, classified as serious disseminated tuberculosis, was observed in a 70-year-old female patient in the abrocitinib 200-mg arm; there were no events of adjudicated tuberculosis in the variable-dose cohort. Most adjudicated opportunistic infections were nonserious multidermatomal HZ; however, 2 extracutaneous events were observed: 1 serious disseminated varicella zoster virus infection in a 52-year-old female patient treated with abrocitinib 100 mg in the consistent-dose cohort and 1 case of serious HZ meningitis in a 28-year-old female patient in the variable-dose cohort (patient received 200 mg in the 12-wk open-label period of JADE REGIMEN, placebo in the maintenance period of JADE REGIMEN, and 100 mg in JADE EXTEND). In the consistent-dose cohort, IRs for all HZ infections were generally numerically higher with overlapping 95% CIs in the abrocitinib 200-mg group compared with the abrocitinib 100-mg group, and in patients aged 65 years or older than in the younger age groups (Figure 3, *B*). The IRs for all eczema herpeticum in the consistent-dose cohort were numerically lower in the abrocitinib 200-mg arm than in the abrocitinib 100-mg arm, and in the 65 years or older age group than in the younger age groups across doses; however, 95% CIs were overlapping (Figure 3, *C*).

Thrombocytopenia and lymphopenia. In the consistent-dose cohort, no thrombocytopenia (platelet count $< 75 \times 10^3$/mm^3) or lymphopenia (absolute lymphocyte count $< 0.5 \times 10^3$/mm^3) events were observed in the abrocitinib 100-mg group, regardless of age (Figure 4 and Table E1). Among patients treated with abrocitinib 200 mg in the consistent-dose cohort, the IR for thrombocytopenia in the 65 years or older age group was generally numerically higher than in the younger age groups with largely overlapping 95% CIs (Figure 4, *A*). The IR for lymphopenia in patients treated with abrocitinib 200 mg in the consistent-dose cohort was higher in patients aged 65 years or older than in the younger age groups (Figure 4, *B*).

Malignancies. The IRs for adjudicated nonmelanoma skin cancer (NMSC) in the consistent-dose cohort did not show a

TABLE II. Demographics and baseline disease characteristics in the consistent- and variable-dose cohorts

Demographics and baseline disease characteristics	Consistent-dose cohort N = 3,004		Variable-dose cohort N = 798
	Abrocitinib 100 mg QD n = 1,023	Abrocitinib 200 mg QD n = 1,981	
Age (y), median (IQR)	31.0 (21.0–44.0)	29.0 (21.0–43.0)	29.0 (20.0–41.0)
Age group (y), n (%)			
12 to < 18	201 (20)	289 (15)	145 (18)
18 to < 40	494 (48)	1,079 (54)	437 (55)
40 to < 65	277 (27)	518 (26)	186 (23)
≥65	51 (5)	95 (5)	30 (4)
Female, n (%)	464 (45)	920 (46)	359 (45)
Race, n (%)			
American Indian or Alaska Native	7 (0.7)	12 (0.6)	7 (0.9)
Asian	228 (22.3)	423 (21.4)	124 (15.5)
Black or African American	59 (5.8)	139 (7.0)	33 (4.1)
Multiracial	5 (0.5)	23 (1.2)	10 (1.3)
Native Hawaiian or other Pacific Islander	1 (0.1)	6 (0.3)	0 (0.0)
Not reported	4 (0.4)	19 (1.0)	3 (0.4)
Other	1 (0.1)	0 (0.0)	0 (0.0)
White	718 (70.2)	1,359 (68.6)	621 (77.8)
IGA score, %			
3 (moderate)	63	59	64
4 (severe)	37	41	36
Prior systemic therapy, n (%)	431 (42)	957 (48)	475 (60)
Smoking status, n (%)*			
Yes	190 (19)	380 (19)	127 (16)
No†	828 (81)	1,592 (80)	665 (83)

IGA, Investigator's Global Assessment; *IQR,* interquartile range; *QD*, once daily
*Smoking history data were missing for some patients.
†Former smokers were included in the "No" category.

numerical increase in the abrocitinib 200-mg arm relative to the abrocitinib 100-mg arm but were numerically higher with overlapping 95% CIs among patients aged 65 years or older than among patients in the other 3 age groups, regardless of the abrocitinib dose (Figure 5, *A*). All events of NMSC occurred in current or former smokers. In the consistent-dose cohort, IRs for other adjudicated malignancies (excluding NMSC) also did not show a consistent numerical increase across each age group in the abrocitinib 200-mg arm relative to the abrocitinib 100-mg arm; however, numerically higher IRs with overlapping 95% CIs were generally observed among patients aged 65 years or older than in the other 3 age groups (Figure 5, *B*).

MACE. The IRs for adjudicated MACE in the consistent-dose cohort were less than 1 per 100 PY in all age groups, regardless of the abrocitinib dose, except in the 65 years or older age group treated with abrocitinib 100 mg, in which the IR was 2.64 per 100 PY (Table III). Of the 10 MACE observed in the consistent-dose cohort, 9 occurred in the 2 older age groups: 7 in the 40 to younger than 65 years age group and 2 in the 65 years or older age group (Table III); the number of MACE were observed evenly across treatment arms (5 events each in the abrocitinib 200-mg and 100-mg groups, respectively).

VTE. The IRs for adjudicated VTE (all nonfatal events) in the consistent-dose cohort were less than 1 per 100 PY in all age groups, regardless of the abrocitinib dose, except in the oldest age group (65 years or older), in which IRs for adjudicated VTE were 2.64 per 100 PY (abrocitinib 100 mg) and 1.04 per 100 PY (abrocitinib 200 mg; Table III). In total, there were 7 events of adjudicated VTE, including 5 in the abrocitinib 200-mg arm and 2 in the abrocitinib 100-mg arm. Five of the 7 events were reported in a previous integrated safety analysis.[21]

Similar trends were observed in the subset of patients aged 75 years or older (Table E1) and in the variable-dose cohort (Table E2).

Long-term safety in adolescents. Overall, IRs for TEAEs of special interest in the consistent-dose cohort were lowest in adolescents, except for all eczema herpeticum, which was lowest in the 65 years or older age group, and all HZ infections in patients treated with the 100-mg dose, which was lowest in the 18 to younger than 40 years age group (Figures 3–5).

DISCUSSION

Overall, patients aged 65 years or older had numerically higher IRs with overlapping 95% CIs for SAEs, TEAEs leading to study discontinuation, serious infections, all HZ infections, thrombocytopenia, lymphopenia, adjudicated NMSC, adjudicated malignancies (except NMSC), MACE, and VTE than younger patients. These data can be contextualized with the analysis of abrocitinib efficacy across 4 abrocitinib studies (phase 2b, JADE MONO-1, JADE MONO-2, and JADE COMPARE), which were stratified into age groups of 18 to 40 years, 41 to 50 years, and 51 years or older.[27] Results of that analysis suggested that the

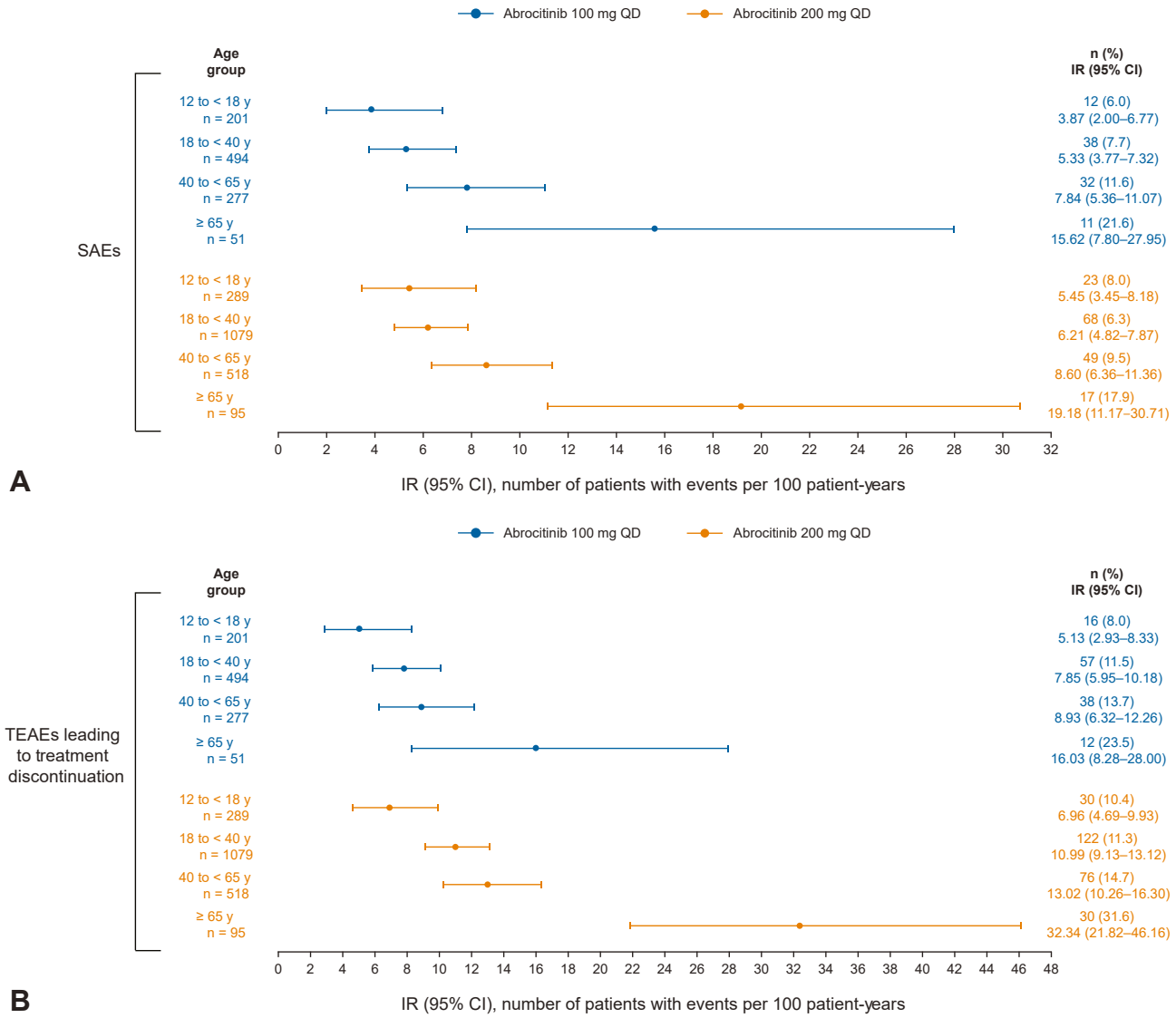

FIGURE 2. IRs for (**A**) SAEs and (**B**) TEAEs resulting in permanent discontinuation from the study by age group in the consistent-dose cohort.

efficacy of abrocitinib after 12 or 16 weeks of treatment was dose-dependent across age groups and was comparable between patients aged 51 years or older and patients in the other 2 age groups.[27]

JAKis have been associated with an increased risk of serious infections with age.[28,29] In the current analysis, IRs for serious infections were numerically higher (with overlapping CIs) in patients aged 65 years or older (IR/100 PY [95% CI]: abrocitinib 200 mg, 6.27 [2.30−13.65]; abrocitinib 100 mg, 3.97 [0.82−11.59]) compared with all other age groups, regardless of abrocitinib dose. According to the American Academy of Dermatology (AAD) guidelines, AD in adults is associated with an elevated risk of skin infection (moderate certainty evidence).[30] Serious infections, including respiratory, systemic, or multiorgan infections, are more likely to occur in adults with AD than in adults without AD, and the prevalence of serious infections increases with age.[31] However, in a recent integrated safety analysis of abrocitinib in patients with moderate-to-severe AD with up to 4 years of exposure, a Cox regression analysis did not identify patient age as a significant risk factor for serious infection.[22]

HZ is the best-characterized infectious complication of JAKi; several steps in the *Varicella zoste*r virus life cycle rely on JAK-dependent signaling.[32] In the current analysis, IRs for HZ infections with abrocitinib 200 mg were numerically higher in patients aged 65 years or older than in younger age groups. These findings are consistent with those of a multivariate analysis presented in a previously published integrated safety analysis (data cut-off: April 22, 2020), in which older age (≥65 y), abrocitinib dose of 200 mg, and severe disease at baseline were associated with a higher risk of HZ infection[21]; in an updated integrated analysis (data cut-off: September 25, 2021), older age (≥65 y), abrocitinib dose of 200 mg, confirmed absolute lymphocyte count less than 1.0 ($10^3/mm^3$) prior to the event, and prior medical history of HZ were among factors associated with a higher risk of HZ infection.[22] Epidemiological studies suggest that older age is a risk factor for HZ infection in the general

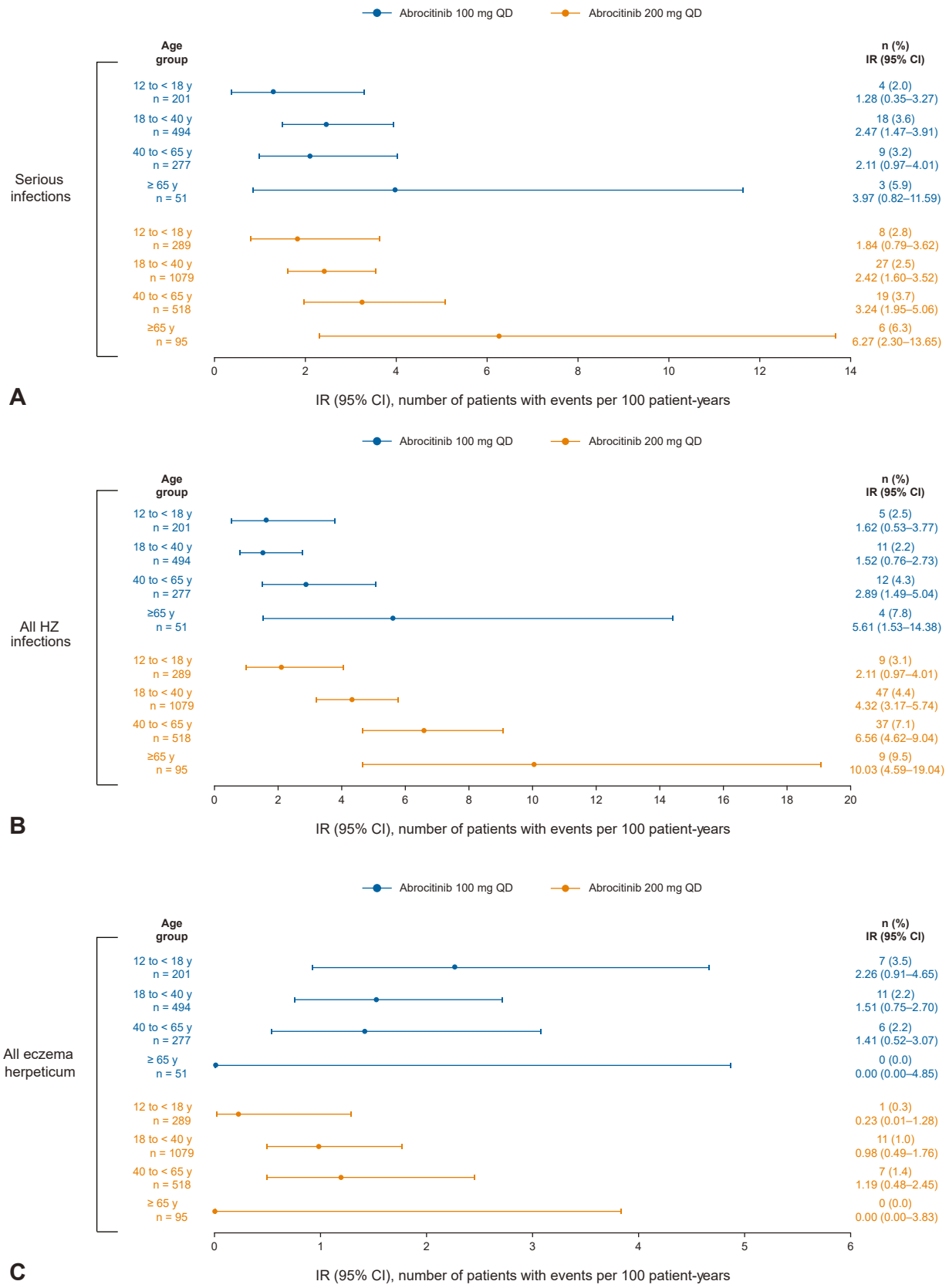

FIGURE 3. IRs for (**A**) serious infection, (**B**) all HZ infections, and **(C)** all eczema herpeticum by age group in the consistent-dose cohort.

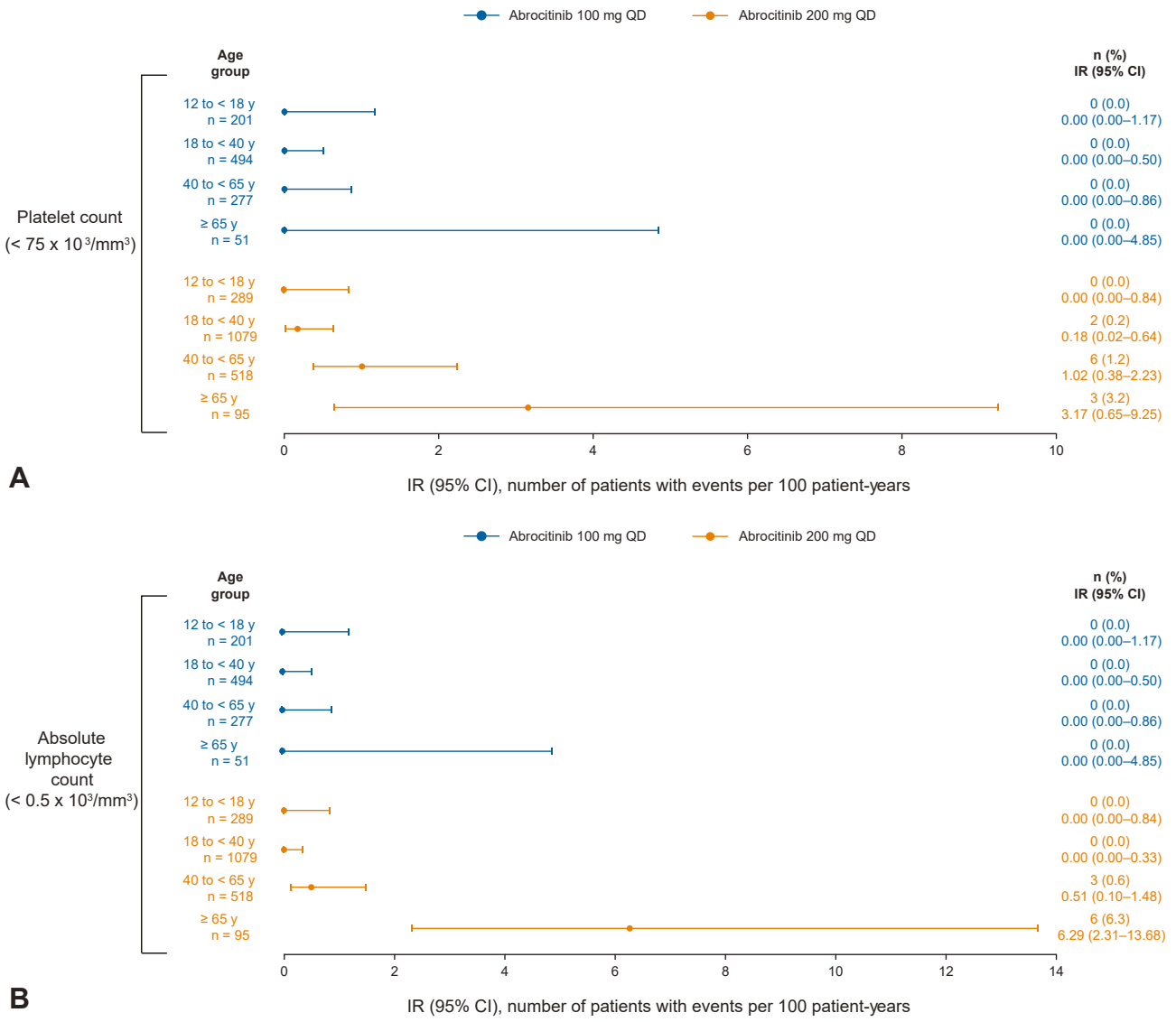

FIGURE 4. IRs for (**A**) platelet count $< 75 \times 10^3/mm^3$ and (**B**) absolute lymphocyte count $< 0.5 \times 10^3/mm^3$ by age group in the consistent-dose cohort.

population. The IR for HZ in the Asia-Pacific region, Europe, and North America is estimated to be 0.3 to 0.5 per 100 PY but varies with age, increasing to 0.6 to 0.8 per 100 PY in the 60-year-old age group and 0.8 to 1.2 per 100 PY in the 80-year-old age group.[24] These estimates are lower than the IRs for all HZ infections observed in abrocitinib-treated patients with AD aged 65 years or older in the current analysis (IR per 100 PY [95% CI]: abrocitinib 200 mg, 10.03 [4.59−19.04]; abrocitinib 100 mg, 5.61 [1.53−14.38]). However, our findings are in line with a population-based cohort study using data from The Health Improvement Network, which estimated the IR per 1,000 PY for HZ in U.K. adults (aged ≥ 18 y) with AD to range from 5.27 to 7.79 (95% CI 5.17−8.24).[33] Completion of all age-appropriate vaccinations and vaccinations of immunocompromised patients as recommended by current immunization guidelines, including those for HZ, is advised.[5,34]

Eczema herpeticum is a disseminated cutaneous infection caused by the herpes simplex virus associated with life-threatening complications.[35] In the current study, the IR (95% CI) for eczema herpeticum was numerically higher in the abrocitinib 100-mg arm versus the 200-mg arm in the 12 to younger than 18 years age group (2.26 [0.91−4.65] vs 0.23 [0.01−1.28]), 18 to younger than 40 years age group (1.51 [0.75−2.70] vs 0.98 [0.49−1.76]), and 40 to younger than 65 years age group (1.41 [0.52−3.07] vs 1.19 [0.48−2.45]). These findings mirror the inverse-dose relationship observed in 2 previous integrated safety analyses, and support the relationship between increased skin barrier integrity and decreased herpes simplex dissemination with abrocitinib 200 mg.[21,22]

The IRs (95% CI) for thrombocytopenia and lymphopenia were numerically higher with abrocitinib 200 mg in the 65 years or older age group than in the 12 to younger than 18 years age group (thrombocytopenia: 12 to ≥ 18 years age group, 0.00 [0.00−0.84] vs 65 years or older age group, 3.17 [0.65−9.25]; lymphopenia: 0.00 [0.00−0.84] vs 6.29 [2.31−13.68]). This is consistent with findings from previous studies that showed that

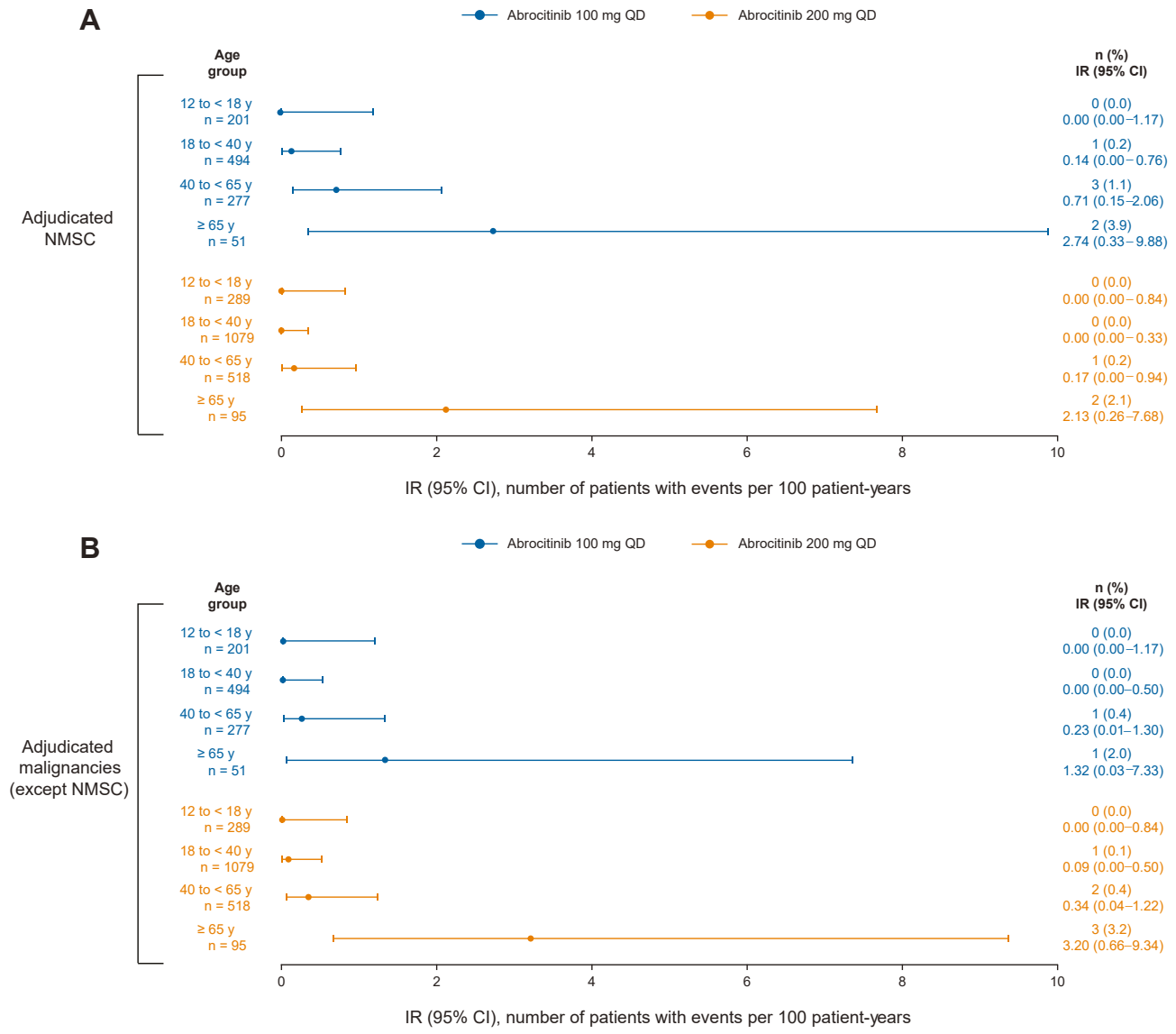

FIGURE 5. IRs for (**A**) adjudicated NMSC and (**B**) adjudicated malignancies (except NMSC) by age group in the consistent-dose cohort.

platelet counts[36,37] and immune response[38-40] in the general population decline with age.

The IRs for adjudicated NMSC were numerically higher with overlapping 95% CIs among patients aged 65 years or older than among other age groups, regardless of abrocitinib dose, and all cases occurred in current or former smokers. Similarly, IRs for other adjudicated malignancies were numerically higher with overlapping 95% CIs among patients aged 65 years or older than among other age groups, regardless of abrocitinib dose. In the general population, the incidence of most malignancies increases with age,[41] which is consistent with the findings of the current analysis. A systematic analysis estimated the global IR (95% CI) of NMSC in 2017 was 7,664 per 100,000 PY (5,251−10,570]).[42] In 2020, in the United States, the rates per 100,000 people for all types of cancer were 59 in the 25- to 29-years age group, 1,183 in the 60- to 64 years age group, and 2,240 in the 80- to 84-years age group.[41] The IRs (95% CI) for adjudicated NMSCs observed in patients aged 65 years or older treated with abrocitinib 200 mg (2.13 per 100 PY [0.26−7.68]) and abrocitinib 100 mg (2.74 per 100 PY [0.33−9.88]) were comparable with a retrospective cohort study of patients with moderate-to-severe AD in the Kaiser Permanente Northern California health care system, in which IR (95% CI) for NMSC ranged from 18.0 per 1,000 PY (13.9−23.2) to 23.6 per 1,000 PY (12.4−45.0) in patients aged 65 years or older.[43]

Most adjudicated MACE occurred in the 2 older age groups (40 to < 65 y: 100 mg, n = 2; 200 mg, n = 5; ≥ 65 y: 100 mg, n = 2; no events occurred in the 200-mg arm), with the IRs for these events being the highest in the 65 years or older age group treated with abrocitinib 100 mg. Consistent with what is shown in the literature,[25,44] MACE risk increased with age. In the general U.K. population, between 1998 and 2017, the IR for stroke was 0.1 per 100 PY for all ages, 0.2 per 100 PY for people between the ages of 60 and 64 years, and increased to 1.0 per 100 PY for people between the ages of 90 and 94 years.[25] In addition, the AAD guidelines note that, in adults, AD may be

TABLE III. IRs* of adjudicated MACE and adjudicated VTE in the consistent-dose cohort*

n (%) and IR (95% CI)	Abrocitinib 100 mg QD n = 1,023	Abrocitinib 200 mg QD n = 1,981
Adjudicated MACE		
12 to <18 y		
n (%)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−1.17)	0.00 (0.00−0.84)
18 to <40 y		
n (%)	1 (0.2)	0 (0.0)
IR (95% CI)	0.14 (0.00−0.76)	0.00 (0.00−0.33)
40 to <65 y		
n (%)	2 (0.7)	5 (1.0)
IR (95% CI)	0.47 (0.06−1.68)	0.84 (0.27−1.97)
≥65 y		
n (%)	2 (3.9)	0 (0.0)
IR (95% CI)	2.64 (0.32−9.52)	0.00 (0.00−3.83)
Adjudicated nonfatal VTE		
12 to < 18 y		
n (%)	0 (0.0)	1 (0.3)
IR (95% CI)	0.00 (0.00−1.17)	0.23 (0.01−1.28)
18 to < 40 y		
n (%)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−0.50)	0.00 (0.00−0.33)
40 to < 65 y		
n (%)	0 (0.0)	3 (0.6)
IR (95% CI)	0.00 (0.00−0.86)	0.51 (0.10−1.48)
≥65 y		
n (%)	2 (3.9)	1 (1.1)
IR (95% CI)	2.64 (0.32−9.53)	1.04 (0.03−5.79)

IR, incidence rate; *MACE*, major adverse cardiovascular event; *PY*, patient-years; *QD*, once daily; *VTE*, venous thromboembolism.
*IR (95% CI) was defined as the number of patients with events per 100 PY.

associated with CV death (low-certainty evidence; small magnitude of association), myocardial infarction (low-certainty evidence), or stroke (very low-certainty evidence).[30] A retrospective cohort study of patients with moderate-to-severe AD in the Kaiser Permanente Northern California health care system found that the IR (95% CI) for MACE was 2.6 (2.1−3.2) for the full population, 2.9 (2.1−4.0) for patients aged 40 to 64 years, and increased to 14.1 (10.6−18.6) per 1,000 PY for patients aged 65 years or older.[45] These estimates are lower than the current analysis (with overlapping CIs), in which the IR (95% CI) for MACE was 0.84 (0.27−1.97) and 0.47 (0.06−1.68) per 100 PY in patients aged 40 to younger than 65 years treated with abrocitinib 200 mg and 100 mg; in patients aged 65 years or older, IRs were 0.00 (0.00−3.83) and 2.64 (0.32−9.52) per 100 PY.

As of the data cut-off date, most adjudicated VTE events included in the current analysis occurred in patients treated with abrocitinib 200 mg. Rates for these events were highest in the oldest age group (≥65 y; abrocitinib 200 mg, 1.04 per 100 PY [0.03−5.79]; abrocitinib 100 mg, 2.64 per 100 PY [0.32−9.53]), consistent with the age-related VTE risk in the general population (IR 222−984 per 100,000 PY for people aged ≥ 65 y) and patients with moderate-to-severe AD in the Kaiser Permanente Northern California health care system (IR 6.6 per 1,000 PY [95% CI 4.5−9.8]).[26,45] Major risk factors for VTE among the general population include superficial vein thrombosis, hospitalization due to acute illness or surgery, fracture, using oral contraception, and hormone therapy.[46] According to the AAD guidelines, AD in adults is probably associated with thromboembolic disease (moderate-certainty evidence; small magnitude of association).[30] Comorbidities and use of medications known or suspected to increase the risk of VTE are factors that may contribute to the increased risk of VTE among patients with moderate-to-severe AD.[47] Because the clinical implications of the association between AD and CVD are unclear, the AAD recommends that patients with AD should follow the same CV screening or treatment guidelines used for the general population.[30]

This *post hoc* integrated safety analysis explored age as a risk factor for TEAEs of special interest. The sample sizes of the 65 years and older and 75 years and older age groups were relatively small, resulting in large CIs and limiting interpretation of results from these age groups. Despite these limitations, the data suggest a higher risk of certain TEAEs in the oldest patients, consistent with findings from other studies with oral JAKi.[9,48] Studies with longer follow-up are necessary to elucidate the relationship between safety of abrocitinib and age in more detail, as well as whether current or former smokers and people with a history of malignancy, MACE, or VTE who receive abrocitinib are at increased risk for TEAEs of special interest. Patients with AD tend to be in a younger age group with fewer comorbidities than patients with other chronic inflammatory conditions such as RA.[3,49,50] Overall, rates of TEAEs of special interest in the current *post hoc* analysis were lower in adolescents, and the results suggest that patients aged 65 years or older may require closer monitoring during abrocitinib treatment and appropriate dose selection. While the current integrated safety analysis supports the long-term safety of abrocitinib, additional investigations using longer follow-up and larger data sets are necessary to provide more accuracy for the safety event rates and any treatment effects with abrocitinib in older populations at increased risk of severe outcomes of infections, CVD, malignancies, and VTE.

In summary, abrocitinib has a manageable long-term safety profile across all age groups. The AEs associated with the JAK class were infrequent overall, but more common in older age groups, particularly in patients aged 65 years or older. The IRs of most AEs were generally higher with abrocitinib 200 mg across age groups, except for eczema herpeticum, which was more common in the abrocitinib 100-mg arm. Risk may be minimized in older patients by administering abrocitinib at the lower 100-mg dose.

Acknowledgments

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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 deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

CLINICAL TRIAL REGISTRATION

The studies described in this analysis are registered at clinicaltrials.gov: NCT02780167 (phase 2b trial), NCT03349060 (JADE MONO-1), NCT03575871 (JADE MONO-2), NCT03720470 (JADE COMPARE), NCT04345367 (JADE DARE), NCT03796676 (JADE TEEN), NCT03627767 (JADE REGIMEN), NCT03422822 (JADE EXTEND).

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ONLINE REPOSITORY

TABLE E1. IR* for safety events and AEs of special interest in patients aged ≥ 75 y in the consistent-dose cohort

	≥75-y age subset in the consistent-dose cohort N = 29	
n (%) and IR (95% CI)	Abrocitinib 100 mg QD n = 10	Abrocitinib 200 mg QD n = 19
SAEs		
n (%)	2 (20.0)	4 (21.1)
IR (95% CI)	12.23 (1.48−44.19)	29.40 (8.01−75.27)
TEAEs leading to treatment discontinuation		
n (%)	2 (20.0)	9 (47.4)
IR (95% CI)	11.16 (1.35−40.31)	68.97 (31.54−130.93)
Serious infections		
n (%)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−20.40)	0.00 (0.00−26.13)
All HZ infections		
n (%)	1 (10.0)	1 (5.3)
IR (95% CI)	6.25 (0.16−34.83)	7.48 (0.19−41.67)
All eczema herpeticum		
n (%)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−20.40)	0.00 (0.00−26.13)
Thrombocytopenia (platelet count $< 75 \times 10^3/mm^3$)		
n (%)	0 (0.0)	1 (5.3)
IR (95% CI)	0.00 (0.00−20.40)	7.13 (0.18−39.71)
Lymphopenia (absolute lymphocyte count $< 0.5 \times 10^3/mm^3$)		
n (%)	0 (0.0)	2 (10.5)
IR (95% CI)	0.00 (0.00−20.40)	14.37 (1.74−51.90)
Adjudicated NMSC		
n (%)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−20.40)	0.00 (0.00−26.13)
Adjudicated malignancies (except NMSC)		
n (%)	0 (0.0)	1 (5.3)
IR (95% CI)	0.00 (0.00−20.40)	7.13 (0.18−39.75)
Adjudicated MACE		
n (%)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−20.40)	0.00 (0.00−26.13)
Adjudicated nonfatal VTE		
n (%)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−20.40)	0.00 (0.00−26.13)

AE, Adverse event; *HZ,* herpes zoster; *IR,* incidence rate; *MACE,* major adverse cardiovascular event; *NMSC,* nonmelanoma skin cancer; *QD,* once daily; *SAE,* serious adverse event; *TEAE,* treatment-emergent adverse event; *VTE,* venous thromboembolism.

*IR (95% CI) was defined as the number of patients with events per 100 patient-years.

TABLE E2. IR* for safety events and TEAEs of special interest in the variable-dose cohort

	Variable-dose cohort N = 798				
n (%) and IR (95% CI)	12 to < 18 y n = 145	18 to < 40 y *n* = 437	40 to < 65 y n = 186	≥ 65 y n = 30	≥75 y n = 3
SAEs					
n (%)	9 (6.2)	33 (7.6)	18 (9.7)	1 (3.3)	0 (0.0)
IR (95% CI)	3.18 (1.46−6.04)	3.94 (2.71−5.54)	5.17 (3.06−8.17)	1.71 (0.04−9.53)	0.00 (0.00−98.13)
TEAEs leading to treatment discontinuation					
n (%)	16 (11.0)	44 (10.1)	29 (15.6)	2 (6.7)	1 (33.3)
IR (95% CI)	5.66 (3.23−9.19)	5.17 (3.75−6.94)	8.21 (5.50−11.79)	3.32 (0.40−11.99)	27.69 (0.70−154.29)
Serious infections					
n (%)	3 (2.1)	19 (4.3)	7 (3.8)	0 (0.0)	0 (0.0)
IR (95% CI)	1.05 (0.22−3.07)	2.23 (1.35-3.49)	1.97 (0.79−4.07)	0.00 (0.00−6.10)	0.00 (0.00−98.13)
All HZ infections					
n (%)	6 (4.1)	24 (5.5)	15 (8.1)	3 (10.0)	0 (0.0)
IR (95% CI)	2.17 (0.80−4.72)	2.89 (1.85−4.30)	4.37 (2.44−7.20)	5.03 (1.04−14.69)	0.00 (0.00−98.13)
All eczema herpeticum					
n (%)	0 (0.0)	9 (2.1)	2 (1.1)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−1.29)	1.06 (0.49−2.02)	0.56 (0.07−2.03)	0.00 (0.00−6.10)	0.00 (0.00−98.13)
Thrombocytopenia (platelet count $< 75 \times 10^3/mm^3$)					
n (%)	0 (0.0)	1 (0.2)	3 (1.6)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−1.29)	0.12 (0.00−0.65)	0.85 (0.18−2.49)	0.00 (0.00−6.10)	0.00 (0.00−98.13)
Lymphopenia (absolute lymphocyte count $< 0.5 \times 10^3/mm^3$)					
n (%)	0 (0.0)	4 (0.9)	1 (0.5)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−1.29)	0.47 (0.13−1.20)	0.28 (0.01−1.56)	0.00 (0.00−6.10)	0.00 (0.00−98.13)
Adjudicated NMSC					
n (%)	0 (0.0)	0 (0.0)	1 (0.5)	3 (10.0)	1 (33.3)
IR (95% CI)	0.00 (0.00−1.29)	0.00 (0.00−0.43)	0.28 (0.01−1.57)	5.46 (1.13−15.96)	27.69 (0.70−154.29)
Adjudicated malignancies (except NMSC)					
n (%)	0 (0.0)	0 (0.0)	1 (0.5)	1 (3.3)	1 (33.3)
IR (95% CI)	0.00 (0.00−1.29)	0.00 (0.00−0.43)	0.28 (0.01−1.56)	1.66 (0.04−9.23)	27.69 (0.70−154.29)
Adjudicated MACE					
n (%)	0 (0.0)	1 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−1.29)	0.12 (0.00−0.65)	0.28 (0.01−1.56)	0.00 (0.00−6.10)	0.00 (0.00−98.13)
Adjudicated nonfatal VTE					
n (%)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)
IR (95% CI)	0.00 (0.00−1.29)	0.00 (0.00−0.43)	0.56 (0.07−2.03)	0.00 (0.00−6.10)	0.00 (0.00−98.13)

*IR (95% CI) was defined as the number of patients with events per 100 patient-years.