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Atopic Dermatitis, Urticaria and Skin Disease

Integrated Efficacy and Safety Analysis of Abrocitinib in Adolescents With Moderate-to-Severe Atopic Dermatitis

Amy S. Paller[1] | Lawrence F. Eichenfield[2] | Alan D. Irvine[3] | Carsten Flohr[4] | Andreas Wollenberg[5,6,7] | Sébastien Barbarot[8] | Christine Bangert[9] | Jonathan M. Spergel[10,11] | Andrew Selfridge[12] | Pinaki Biswas[12] | Haiyun Fan[13] | Justine Alderfer[13] | Melissa Watkins[12] | Herwig Koppensteiner[14]

[1]Northwestern University Feinberg School of Medicine and the Ann and Robert H. Lurie Children's Hospital, Chicago, Illinois, USA | [2]University of California San Diego and Rady Children's Hospital-San Diego, San Diego, California, USA | [3]Clinical Medicine, School of Medicine, Trinity College Dublin, Dublin, Ireland | [4]St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, King's College London, London, UK | [5]University Hospital Augsburg, Augsburg, Germany | [6]Ludwig Maximilian University, Munich, Germany | [7]Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany | [8]Department of Dermatology, CHU Nantes-Hôtel Dieu, Nantes, France | [9]Department of Dermatology, Medical University of Vienna, Vienna, Austria | [10]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA | [11]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA | [12]Pfizer Inc., New York, New York, USA | [13]Pfizer Inc., Collegeville, Pennsylvania, USA | [14]Pfizer Corporation Austria GmbH, Vienna, Austria

Correspondence: Herwig Koppensteiner (herwig.koppensteiner@pfizer.com)

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ABSTRACT

Background: Abrocitinib has demonstrated long-term efficacy (48 weeks) and safety (~4 years) in adults and adolescents with moderate-to-severe atopic dermatitis (AD). This analysis evaluated abrocitinib efficacy in adolescents through 112 weeks, and safety of up to 4.6 years of exposure.

Methods: Data were from adolescents in JADE MONO-1 (NCT03349060), MONO-2 (NCT03575871), TEEN (NCT03796676), REGIMEN (NCT03627767; safety analysis only), and the ongoing phase 3 extension trial, EXTEND (NCT03422822; data cutoff: September 5, 2022). Efficacy assessments included proportions of patients achieving an Investigator's Global Assessment score of 0 or 1 (IGA 0/1) and ≥ 75%/≥ 90% improvement in Eczema Area and Severity Index (EASI-75/-90). Treatment-emergent adverse events (TEAEs) and AEs of special interest were reported as incidence rate/100 patient-years. A substudy of JADE TEEN assessed immune response to vaccination.

Results: Efficacy was assessed in 170 and 187 patients in the abrocitinib 200-mg and 100-mg arms, respectively; median exposure was 971.0 and 899.0 days. At Week 112, comparable proportions of patients treated with abrocitinib (200, 100 mg) achieved EASI-75 (85%, 83%), EASI-90 (62%, 60%), and IGA 0/1 (57%, 57%). Safety was assessed in 289 and 201 patients in the abrocitinib 200- and 100-mg arms, respectively; median exposure was 882.0 and 863.0 days. Incidence rates were numerically higher with abrocitinib 200 mg versus 100 mg, with overlapping confidence intervals for serious TEAEs (IR [95% CI]; 5.47 [3.69–7.80] vs. 3.45 [1.89–5.80]) and TEAEs leading to discontinuation (6.78 [4.80–9.31] vs. 5.39 [3.38–8.16]).

Conclusions: Efficacy and safety results support long-term abrocitinib use in adolescent patients.

Trail Registration: ClinicalTrials.gov Identifiers NCT03349060, NCT03575871, NCT03796676, NCT03627767, NCT03422822.

1 | Introduction

Atopic dermatitis (AD) is a common inflammatory skin condition with a continuous or relapsing–remitting disease course [1, 2]. Onset usually occurs in infancy and may persist beyond childhood, with a prevalence of 15% in adolescents [1, 3, 4]. The impact of AD can be multifaceted, with itching, lesions, stigma, and low self-esteem contributing to impaired quality of life [1].

AD typically requires ongoing management. Maintenance of therapeutic response and a manageable safety profile are important goals of long-term AD treatment [5]. Abrocitinib, an oral, once-daily, Janus kinase (JAK) 1-selective inhibitor, demonstrated short-term (12-week) and long-term (48-week) efficacy in patients with moderate-to-severe AD in phase 3 clinical trials [6–10]. An integrated safety analysis including data from up to 4 years (5213.9 patient-years [PY]) of exposure in 3802 patients with moderate-to-severe AD showed a manageable safety profile appropriate for long-term abrocitinib use [11].

Here, we evaluated the efficacy of up to 112 weeks of abrocitinib treatment and the long-term safety in adolescents with up to 4.6 years of exposure.

2 | Methods

2.1 | Efficacy and Safety Populations

Data were assessed from adolescents (12 to <18 years) with moderate-to-severe AD who met individual trial inclusion/exclusion criteria for and were enrolled in phase 3 JADE MONO-1 (NCT03349060) [6], MONO-2 (NCT03575871) [7], TEEN (NCT03796676) [8], and REGIMEN (NCT03627767) [9], and the phase 3 extension trial EXTEND (NCT03422822) [10]. Patients could enroll in JADE EXTEND following completion of the full treatment period in a qualifying phase 3 trial or in REGIMEN (full open-label run-in, randomized maintenance, or rescue treatment period). Patients received concomitant medicated topical therapies in JADE TEEN and REGIMEN (rescue period only); medicated topical therapies were permitted in JADE EXTEND per physician's discretion.

The short-term safety population included patients from the 12-week qualifying trials JADE MONO-1, MONO-2, and TEEN. The long-term efficacy population and safety population included patients from JADE MONO-1, MONO-2, TEEN, REGIMEN (safety only), and EXTEND (data cutoff date: September 5, 2022; JADE EXTEND is an ongoing trial; final data may change).

All patients provided written informed consent. Trials were conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. All local regulatory requirements were followed. This research was approved by the appropriate institutional review boards or ethics committees at each site.

2.2 | Analysis Data Sets

Efficacy was assessed in the full analysis set, including all patients who were randomly assigned to and received at least one dose of abrocitinib (100 mg/200 mg; Figure 1). Efficacy data were analyzed up to Week 112.

Short-term safety data were pooled into the placebo-controlled short-term cohort, which included patients who received abrocitinib (100 mg/200 mg) or placebo in the 12-week qualifying trials (Figure 1). Long-term safety data were pooled into two cohorts (Figure 1). The consistent-dose cohort included patients who received the same abrocitinib dose (100 mg/200 mg) during the entire exposure time in the qualifying JADE trials and/or EXTEND; patients from JADE REGIMEN were included only if they had received abrocitinib 200 mg in the 12-week open-label run-in phase and had not subsequently entered the randomized maintenance phase. The variable-dose cohort included patients who entered the randomized maintenance phase and therefore could receive different doses of abrocitinib (100 and 200 mg) throughout exposure in JADE REGIMEN, and who subsequently enrolled in EXTEND where they received a consistent abrocitinib dose (100 mg/200 mg).

2.3 | Assessments

Efficacy endpoints were proportions of patients achieving Investigator's Global Assessment score of 0 (clear) or 1 (almost clear) with ≥2-grade improvement from baseline (IGA 0/1), ≥75%/≥90%/100% improvement from baseline in Eczema Area and Severity Index (EASI-75/-90/-100), and ≥4-point improvement from baseline in Peak Pruritus Numerical Rating Scale (PP-NRS4; with permission from Regeneron Pharmaceuticals Inc., and Sanofi).

Safety endpoints were proportions of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, severe TEAEs, TEAEs leading to discontinuation, and most frequently reported TEAEs (classified by MedDRA term). Incidence rates (IRs) were reported for serious TEAEs, severe TEAEs, TEAEs leading to discontinuation, and TEAEs of special interest (infections [serious and opportunistic], malignancies, cardiovascular events including major adverse cardiovascular events [MACE] and venous thromboembolism [VTE], hematologic changes, and fractures; herpes simplex infection, herpes zoster infection, and fracture events were identified by custom MedDRA queries [CMQ]). Deviation in growth curves was also evaluated over the long term.

2.4 | Statistical Analyses

Efficacy was reported using all observed data at each time point without imputation for missing values. Estimates and 95% confidence intervals (CIs) for differences between treatment groups for responder-based endpoints were calculated based on the Cochran–Mantel–Haenszel weighted average difference stratified by factors of study, baseline disease severity, and age category using normal approximation of binomial proportions. To assess the impact of missing data,

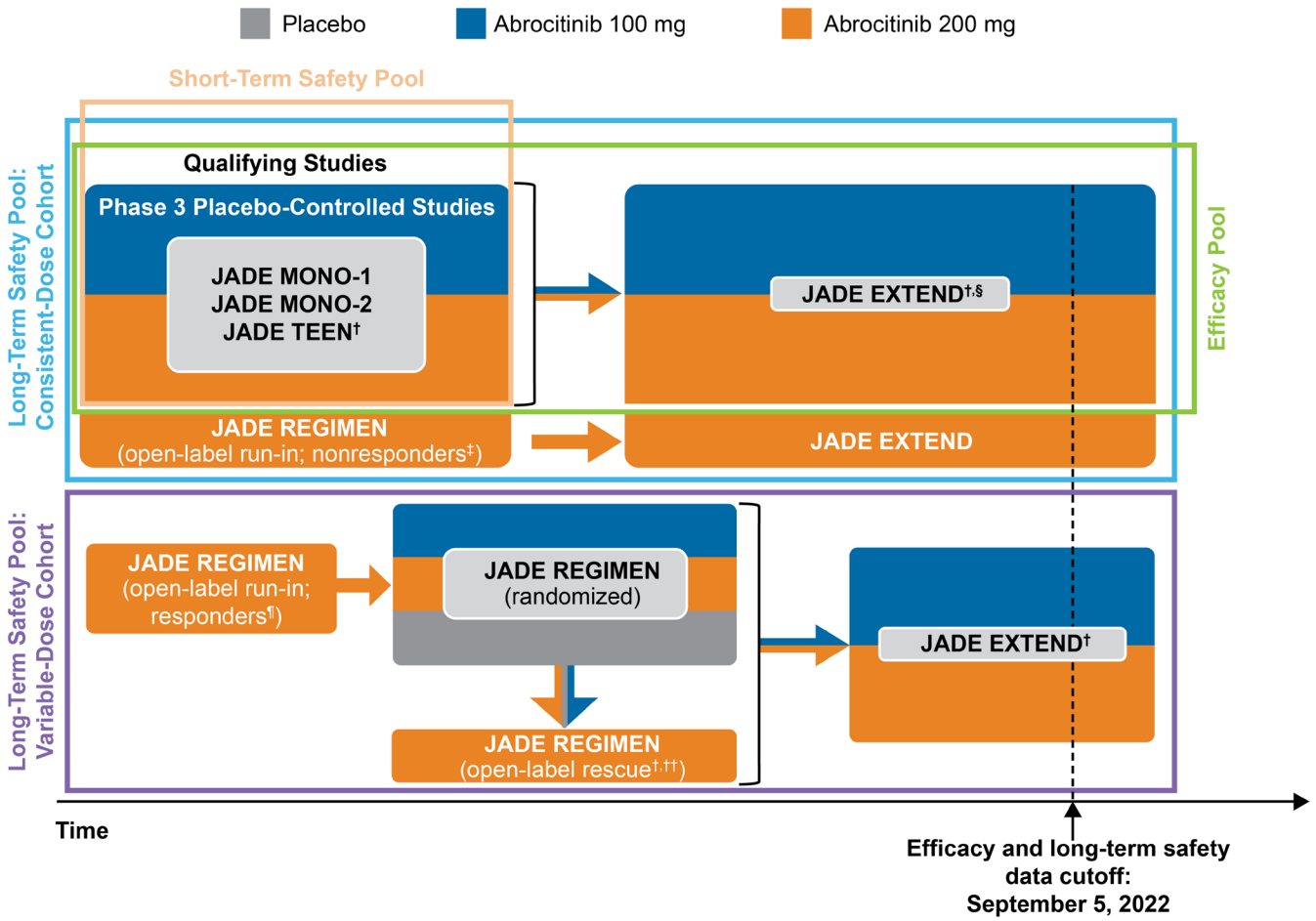


FIGURE 1 | Schematic of efficacy and safety patient cohorts. †Patients received concomitant topical medicated therapy (topical corticosteroids, calcineurin inhibitors, and/or crisaborole); patients who received medicated or nonmedicated topical treatments in parent studies were permitted to use these throughout the study. ‡Patients who did not achieve an IGA score of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline and ≥75% improvement from baseline in EASI after 12 weeks of treatment with abrocitinib 200 mg. §Patients may have received their first dose of abrocitinib (100 mg/200 mg) in JADE EXTEND after receiving placebo in a phase 3 placebo-controlled trial. ¶Patients in the open-label run-in phase who were considered responders (IGA score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline and ≥75% improvement from baseline in EASI) after 12 weeks of treatment with abrocitinib 200 mg were randomly assigned to treatment with abrocitinib 200 mg, abrocitinib 100 mg, or placebo. ††Patients who experienced a flare (≥50% loss of Week 12 EASI response and new IGA score ≥2) during the maintenance period of JADE REGIMEN entered a 12-week open-label rescue period. EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment.

responder-based endpoints were evaluated using the last-observation-carried-forward (LOCF) method, with missing data imputed as the last observed value. Continuous data were analyzed using a mixed-effects model with repeated measures containing fixed factors of treatment, week, treatment-by-week interaction, study, baseline disease severity, age category, and unstructured or compound symmetry as covariance matrix.

For safety analyses, data were reported as *n* (%) and/or IR. IRs were expressed as the number of unique patients with events per 100 PY. Exposure time for IR analysis was defined as the duration from the first abrocitinib dose to the first event for patients with events, or to the end of the risk period for patients without events. The risk period for IR analysis was defined as the time from the first abrocitinib dose to the last dose plus 28 days, death, or data cutoff date (for JADE EXTEND only), whichever occurred first. CIs for IRs were calculated based on the assumption that the actual case count followed a Poisson distribution. Height standard deviation score (SDS) was standardized to the US population by age and sex.

2.5 | Phase 3 Adolescent Vaccine Immunogenicity Substudy

The vaccine immunogenicity substudy population included eligible patients in JADE TEEN who enrolled to receive a single dose of Tdap vaccine. Study design and statistical analysis are further described in the Supplemental Methodology in Appendix .

2.6 | Phase 3 Adolescent MRI Substudy

The magnetic resonance image (MRI) substudy population included adolescents from JADE EXTEND who enrolled to undergo annual knee MRI procedures. Initial findings are reported

in this preplanned interim analysis. Study design and statistical analysis are further described in the Supplemental Methodology in Appendix S1.

3 | Results

3.1 | Patient Demographics and Baseline Disease Characteristics

The long-term efficacy population included 357 patients (170 and 187 in the abrocitinib 200-mg and 100-mg arms, respectively). The placebo-controlled short-term safety population comprised 409 patients, including 142, 146, and 121 in the abrocitinib 200-mg, 100-mg, and placebo arms, respectively. The long-term safety population comprised 635 patients, including 490 in the consistent-dose cohort (abrocitinib 200 mg, $n = 289$; 100 mg, $n = 201$) and 145 in the variable-dose cohort. Baseline characteristics were generally similar across treatment arms and populations (Tables S1–S3).

In the consistent-dose cohort of the long-term safety population, 251 patients had ≥ 120 weeks and 32 had ≥ 192 weeks of exposure to abrocitinib (Table S4). Median (Q1, Q3) exposure duration was 882.0 (199.0, 1068.0) days and 863.0 (329.0, 1035.0) days in the abrocitinib 200- and 100-mg arms, respectively. Treatment duration ranged from 7 to 1670 days across arms. Total exposure duration in the consistent-dose cohort was 964.0 PY: 559.5 PY and 404.5 PY in the abrocitinib 200-mg and 100-mg arms, respectively. Total abrocitinib exposure duration in the variable-dose cohort was 362.1 PY; 93 patients had ≥ 120 weeks and 8 had ≥ 192 weeks of exposure (Table S4). Details of the duration of exposure to abrocitinib in the long-term efficacy population can be found in the Supplemental Results in Appendix S1.

In the vaccine immunogenicity substudy, the safety analysis set included 25 patients: 6, 9, and 10 in the abrocitinib 200-mg, 100-mg, and placebo arms, respectively (Figure S1). The immunogenicity analysis set included 4, 8, and 10 patients who received abrocitinib 200 mg, 100 mg, and placebo, respectively.

The adolescent MRI substudy enrolled 58 patients (Figure S2); 23 (40%) were aged 12 to < 15 years when they received their first dose of abrocitinib prior to entering the substudy. Median (range) duration of abrocitinib exposure at the initial MRI scan was 32.6 (27.7–53.6) months.

3.2 | Long-Term Efficacy

At Week 2, a substantial proportion of patients reached EASI-75 with abrocitinib at either dose; the proportion of patients achieving EASI-75 at Week 4 was greater with abrocitinib 200 mg than with 100 mg (Figure 2A). At Week 112, ≥ 83% of patients achieved EASI-75 with either abrocitinib dose (Figure 2A). Similarly, a numerically greater proportion of patients achieved the high threshold efficacy responses of IGA 0/1, EASI-90, and EASI-100 with abrocitinib 200 mg than with 100 mg as early as Week 4, with overlapping CIs (Figure 2B–D). At Week 112, IGA 0/1 was achieved by 57% and EASI-90 was achieved by ≥ 60% of patients in each dose group, and EASI-100 was achieved by 30% and 19% of patients who received abrocitinib 200 and 100 mg, respectively (Figure 2B–D). PP-NRS4 response rates were numerically higher at Week 2 through Week 112 with abrocitinib 200 mg than with 100 mg (Figure 3). Results were similar for LOCF analysis.

3.3 | Short-Term Safety

3.3.1 | Safety Summary

In the short-term safety population, more patients reported TEAEs with abrocitinib 200 mg (68%) than with 100 mg (60%) and placebo (52%) during 12 weeks of treatment (Table 1). Serious TEAEs, severe TEAEs, and TEAEs leading to study discontinuation were infrequent (≤ 3%) across treatment groups (Table 1). Nausea was the most frequent TEAE reported with abrocitinib and was dose-related; in most cases, nausea was mild and resolved spontaneously with no change or interruption to treatment. Acne occurred more frequently with a higher abrocitinib dose (placebo, $n = 1$ [0.8%]; abrocitinib 100 mg, $n = 3$ [2.1%]; abrocitinib 200 mg, $n = 6$ [4.2%]). Herpes simplex infections (CMQ) occurred in seven patients treated with abrocitinib 200 mg and in one patient treated with 100 mg. Herpes zoster (HZ) infections (CMQ) were reported in one patient in each abrocitinib treatment group. Serious infection (peritonsillitis) was reported in one patient in the abrocitinib 200-mg treatment arm. No herpes simplex, HZ, or serious infections were reported in the placebo group.

3.4 | Long-Term Safety

3.4.1 | Serious TEAEs, Severe TEAEs, TEAEs Leading to Study Discontinuation, and Deaths

In the consistent-dose cohort, IRs for serious TEAEs and TEAEs leading to discontinuation were numerically higher (with overlapping CIs) with abrocitinib 200 mg than with 100 mg (Figure 4A). IRs for severe TEAEs were similar between the two treatment arms (Figure 4A). In the variable-dose cohort, IRs for serious TEAEs, severe TEAEs, and TEAEs leading to discontinuation were similar to those seen with abrocitinib 100 mg in the consistent-dose cohort (Table S5). No events of thrombocytopenia, rhabdomyolysis, or rhabdomyolysis/myopathy were reported, and no deaths occurred during the exposure period in either cohort. Two events of lymphopenia were reported in the variable-dose cohort.

3.4.2 | TEAEs of Special Interest

In the consistent-dose cohort, IRs for serious infections, all HZ infections, and adjudicated opportunistic HZ infections were numerically higher (with overlapping CIs) with abrocitinib 200 mg than with 100 mg (Figure 4B). Serious infections were reported in 14 patients in the consistent-dose cohort (Figure 4B), including an adjudicated event of pulmonary tuberculosis (TB) in a 17-year-old Asian female patient from China in the abrocitinib 200-mg arm, also with reported serious TEAEs of pneumonia and TB pleurisy. This patient had no prior history of TB and

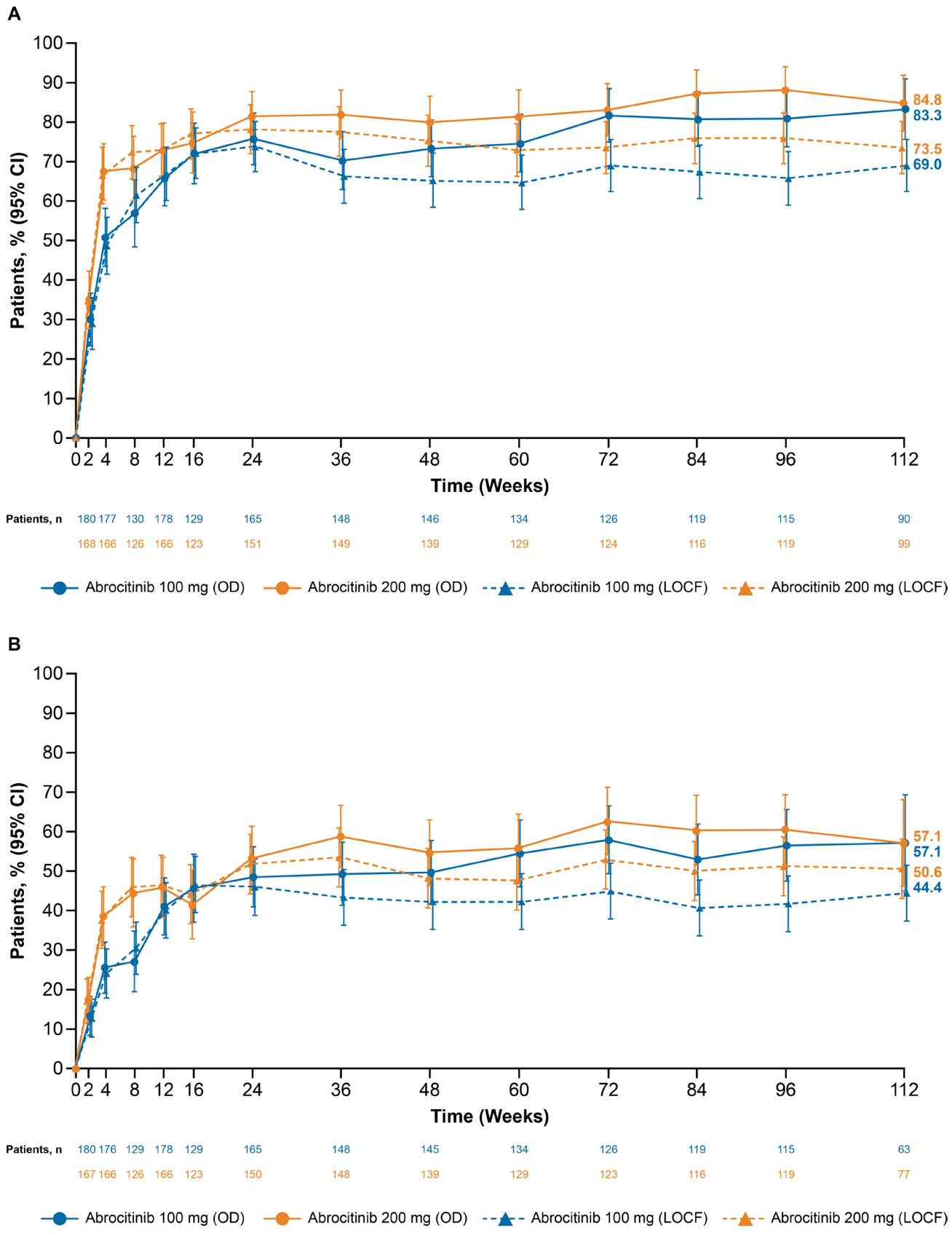
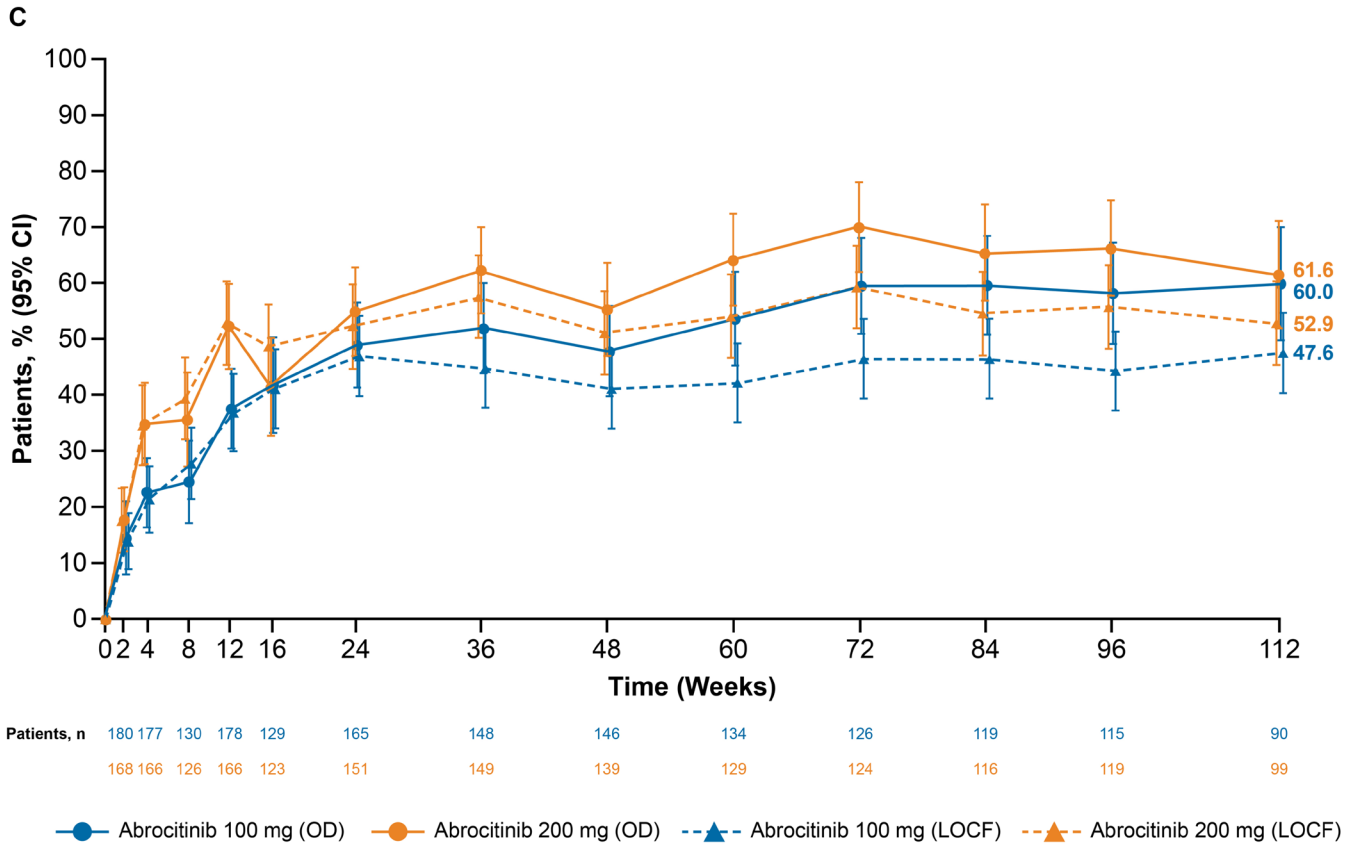


FIGURE 2 | Proportion of patients who achieved (A) EASI-75, (B) IGA 0/1[†], (C) EASI-90, and (D) EASI-100 responses. As-observed data are without any imputation for missing values. Using the LOCF method, missing data were imputed as the last observed value. [†]IGA 0/1 response is defined as an IGA score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline. EASI, Eczema Area and Severity Index; EASI-75, ≥75% improvement from baseline in EASI; EASI-90, ≥90% improvement from baseline in EASI; EASI-100, 100% improvement from baseline in EASI; IGA, Investigator's Global Assessment; LOCF, last observation carried forward; OD, observed data.



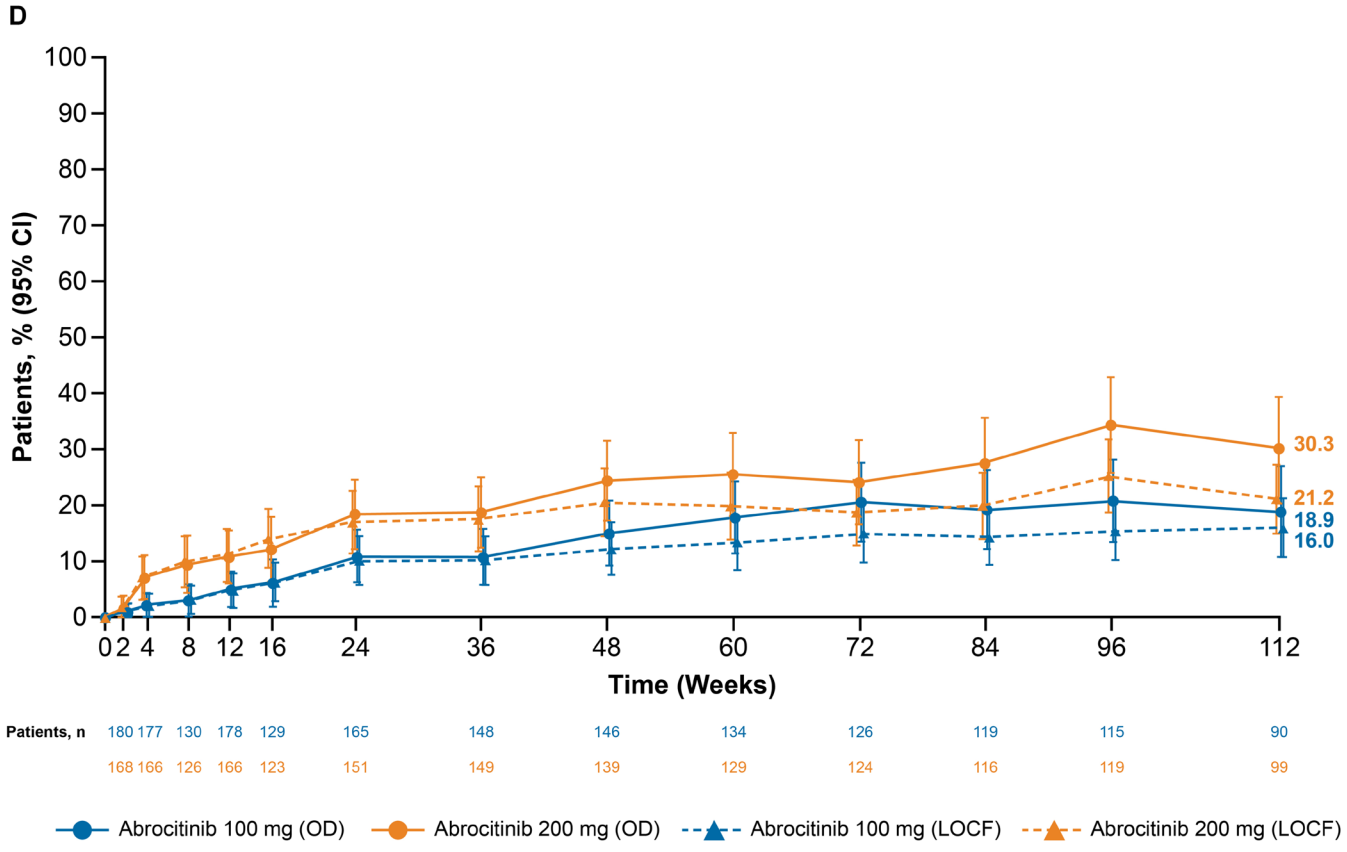


FIGURE 2 | (Continued)

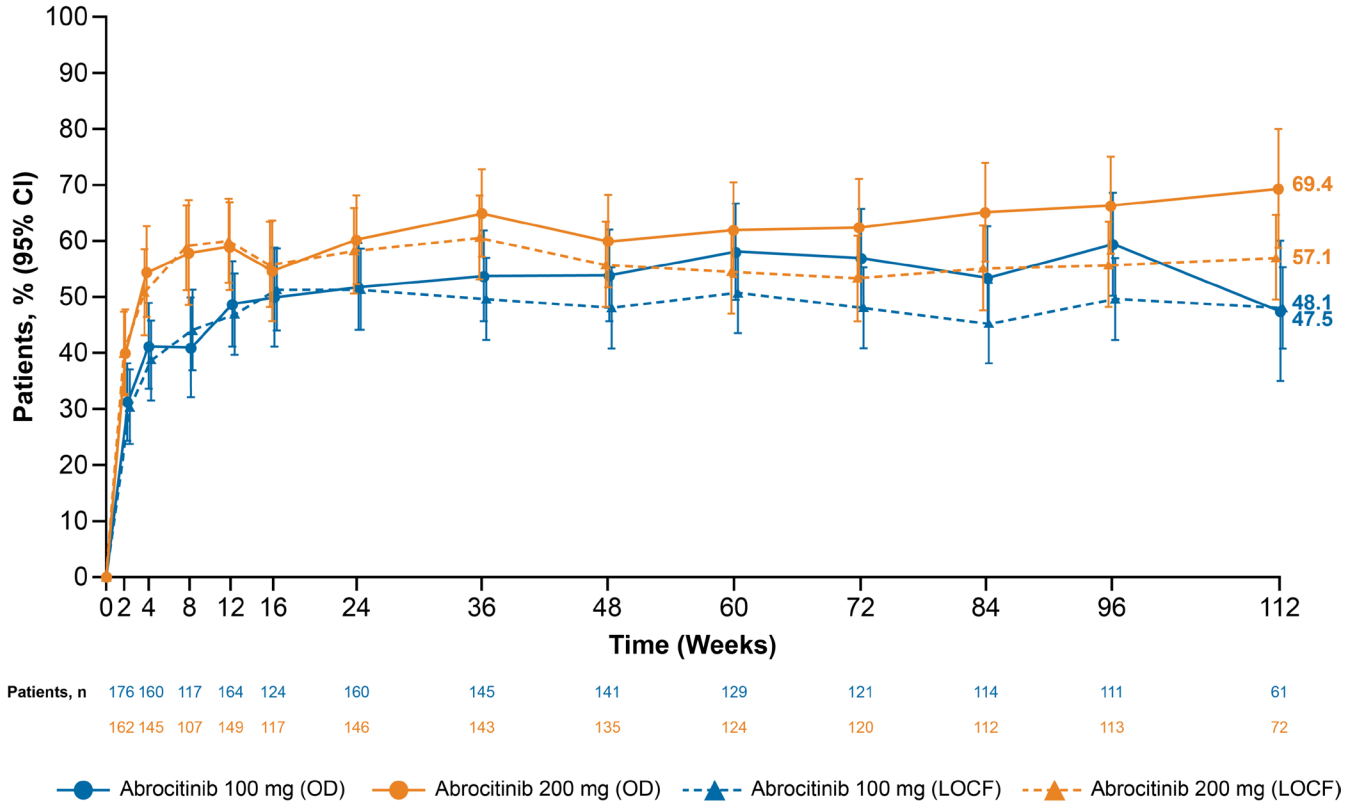


FIGURE 3 | Proportion of patients who achieved PP-NRS4 response. As-observed data are without any imputation for missing values. Using the LOCF method, missing data were imputed as the last observed value. LOCF, last observation carried forward; OD, observed data; PP-NRS, Peak Pruritus Numerical Rating Scale; PP-NRS4, ≥4-point improvement from baseline in PP-NRS.

no recent history of TB exposure and recovered with antibiotics. Other adjudicated opportunistic infections were HZ (one case in the abrocitinib 100-mg arm and three cases in the 200-mg arm). Serious eczema herpeticum was reported in two patients, both in the abrocitinib 100-mg arm.

One occurrence of MACE was reported in the consistent-dose cohort abrocitinib 100-mg arm, in a 16-year-old Asian male patient with ongoing AD, gout, and hyperuricemia (treated with febuxostat). The patient had a serious adverse event of abnormal hepatic function during the study, and an incidental finding of a small lacunar white matter degeneration on the right ventricle was adjudicated as an ischemic stroke based on MRI, despite no report of clinical syndrome concerning stroke; there was no suspicion of cerebrovascular accident, and the event was not considered serious. No MACE occurred in the abrocitinib 200-mg arm or the variable-dose cohort.

One nonfatal event of pulmonary embolism (PE) was reported in a 16-year-old Black/African American male patient with multiple risk factors for PE (including morbid obesity and an extensive family history of PE, including an 18-year-old brother with PE) in the abrocitinib 200-mg arm and has been described in a previous data analysis [11]. No VTE events occurred in the abrocitinib 100-mg arm or the variable-dose cohort, and no events of deep vein thrombosis were reported. No adjudicated malignancies (excluding nonmelanoma skin cancer [NMSC]) or adjudicated NMSC occurred with abrocitinib 200 and 100 mg (Figure 4B). Similar rates for TEAEs of special interest were observed in the variable-dose cohort (Table S5).

Although not examined in this analysis, nausea occurred more frequently with abrocitinib 200 mg ($n = 54$ [18.7%]) vs. 100 mg ($n = 16$ [8.0%]), while events of acne were comparable across treatment arms (200 mg, $n = 22$ [7.6%]; 100 mg, $n = 16$ [8.0%]) up to 1 year of treatment in a previously reported datacut [12].

3.5 | Deviation in Growth Curves and Occurrence of Fractures

Median change from baseline in SDS for height was 0 at all time points through 48 months in the consistent-dose cohort and 36 months in the variable-dose cohort, regardless of abrocitinib dose (Figure S3). IRs for fractures were 1.24/100 PY (95% CI, 0.50–2.56) and 0.74/100 PY (0.15–2.15) with abrocitinib 200 mg and 100 mg in the consistent-dose cohort, respectively, and 0.82/100 PY (0.17–2.41) in the variable-dose cohort. According to the investigators' assessment, fractures were considered unrelated to abrocitinib treatment. The pattern of fractures was not suggestive of bone toxicity or fragility. There were no events of osteonecrosis or gait disorders.

3.6 | Vaccine Immunogenicity Substudy

In samples from a total of 22 patients, immunoglobulin G (IgG) concentrations against Tdap vaccine antigens were increased at 4 weeks postvaccination, regardless of treatment arm (Figure 5). Abrocitinib had no apparent effect on the geometric mean fold increase in antibody concentrations to the six Tdap vaccine

TABLE 1 | Safety summary of the adolescent placebo-controlled short-term safety population.

n (%)	Placebo (*n* = 121)[a]	Abrocitinib 100 mg (*n* = 146)	Abrocitinib 200 mg (*n* = 142)
Patients with ≥ 1 TEAEs	63 (52.1)	88 (60.3)	96 (67.6)
Patients with serious TEAEs	2 (1.7)	1 (0.7)	4 (2.8)
Patients with severe TEAEs	4 (3.3)	3 (2.1)	4 (2.8)
Patients who discontinued the study due to TEAEs	4 (3.3)[b]	2 (1.4)[c]	3 (2.1)[d]
Most frequently reported TEAEs[e] (≥ 5% of patients in any treatment arm), *n* (%)			
Nausea	2 (1.7)	11 (7.5)	26 (18.3)
Nasopharyngitis	12 (9.9)	19 (13.0)	13 (9.2)
Upper respiratory tract infection	13 (10.7)	12 (8.2)	15 (10.6)
Headache	7 (5.8)	9 (6.2)	13 (9.2)
Atopic dermatitis	5 (4.1)	10 (6.8)	2 (1.4)
Vomiting	0 (0.0)	5 (3.4)	9 (6.3)
Folliculitis	1 (0.8)	8 (5.5)	2 (1.4)
TEAEs of special interest in adolescent patients, *n* (%)			
Acne	1 (0.8)	3 (2.1)	6 (4.2)
Herpes zoster (CMQ)	0 (0.0)	1 (0.7)	1 (0.7)
Fracture (CMQ)	1 (0.8)	0 (0.0)	0 (0.0)

Abbreviations: CMQ, custom MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
[a]Included one patient from JADE TEEN who was aged ≥ 18 years at the time of randomization.
[b]TEAEs resulting in permanent discontinuation were atopic dermatitis (*n* = 2), upper respiratory tract infection (*n* = 1), and wound abscess (*n* = 1).
[c]TEAEs resulting in permanent discontinuation were atopic dermatitis and gastrointestinal infection, each occurring once.
[d]TEAEs resulting in permanent discontinuation were abdominal pain, gastroesophageal reflux disease, headache, nausea, and vomiting, each occurring once (patients could report more than one TEAE leading to discontinuation).
[e]TEAEs reported as preferred terms based on MedDRA.

antigens. The proportion of patients with ≥ 4-fold increase in IgG against Tdap vaccine antigens was similar for patients treated with placebo or abrocitinib (Table S6).

3.7 | Bone Safety Data in Adolescents: MRI Substudy

No potential bone safety findings were identified by central readers or the adjudication committee (Table S7). Other findings typically associated with sports or trauma in adolescents occurred in nine patients (16%; Table S7). Altered soft tissue fat signal was the most common outcome of other findings. One patient (2%) had an incidental finding of a popliteal cyst present on MRI central read.

4 | Discussion

In this integrated efficacy and safety analysis, abrocitinib improved skin lesions and itch in adolescents with moderate-to-severe AD treated for up to 112 weeks and was well tolerated. Substantial proportions of adolescents achieved EASI-75 and PP-NRS4 with abrocitinib as early as Week 2, and improvements were sustained long term. Additionally, more patients achieved high-threshold efficacy endpoints through 112 weeks with abrocitinib 200 mg than with 100 mg. Trends were similar irrespective of the imputation approach.

During the first 12 weeks, the proportion of patients with TEAEs was higher with abrocitinib 200 mg than with placebo; the numbers of patients with severe TEAEs and TEAEs leading to study discontinuation were low across all treatment groups, but proportions were slightly higher with placebo than with either abrocitinib dose. Common short-term dose-related TEAEs in adolescents were nausea, headache, and vomiting. In the long-term safety analysis in the consistent-dose cohort, IRs for serious TEAEs and TEAEs leading to discontinuation were numerically higher with abrocitinib 200 mg than with 100 mg, while IRs for severe TEAEs were similar between abrocitinib doses; CIs were largely overlapping.

In the short-term safety cohort, herpes simplex was reported as a frequent dose-related infection, consistent with published reports [11]. In the long-term consistent-dose cohort, IRs for serious infections, all HZ infections, and adjudicated opportunistic HZ infections were numerically higher (with overlapping CIs) with abrocitinib 200 mg than with 100 mg; IRs/100 PY (95% CI) for HZ infections were 2.17 (1.12–3.79) and 1.47 (0.54–3.21) in the abrocitinib 200- and 100-mg arms, respectively, and were

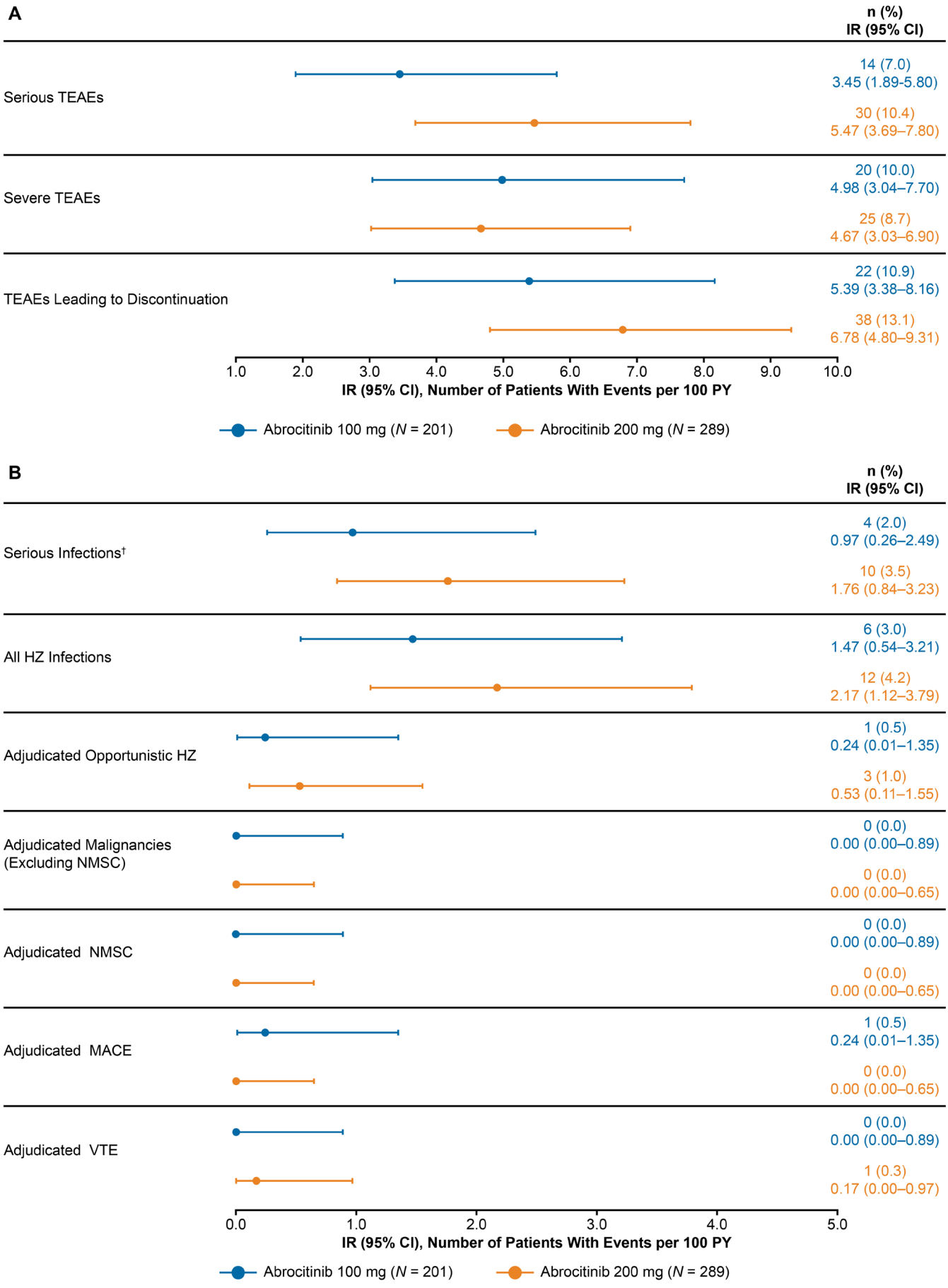


FIGURE 4 | Legend on next page.

FIGURE 4 | IRs for (A) serious TEAEs, severe TEAEs, TEAEs leading to study discontinuation, and (B) TEAEs of special interest in the consistent-dose cohort. †Serious infections included: bacterial arthritis, *Clostridium difficile* infection, COVID-19, COVID-19 pneumonia, eczema herpeticum, infectious mononucleosis, muscle abscess, osteomyelitis, peritonsillitis, pharyngitis, pneumonia, pulmonary tuberculosis, skin infection, staphylococcal sepsis, tuberculous pleurisy, and upper respiratory tract infection. HZ, herpes zoster, IR, incidence rate; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PY, patient-years; TEAE, treatment-emergent adverse event; VTE, venous thromboembolism.

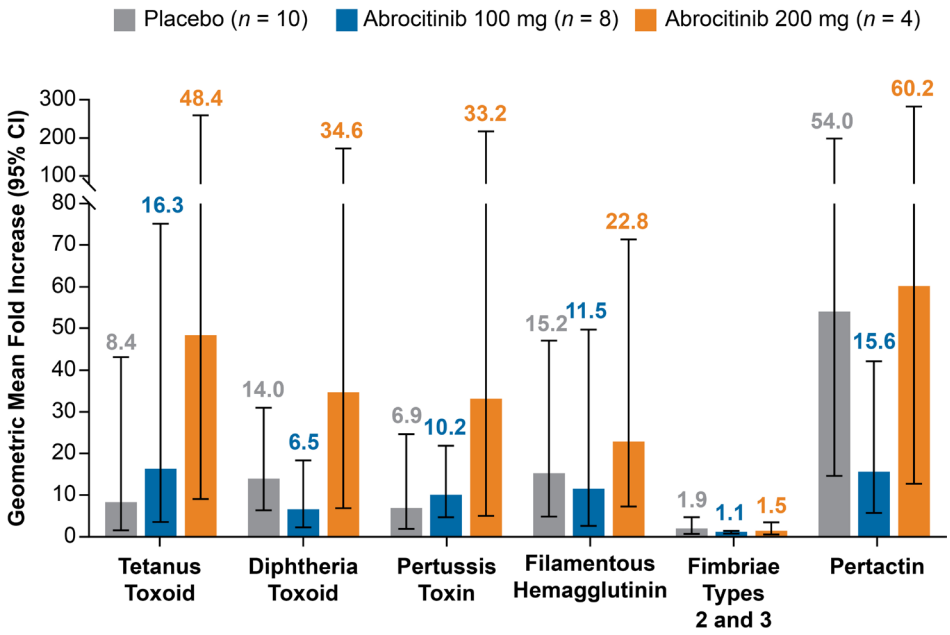


FIGURE 5 | Geometric mean fold increase from baseline in IgG against specific Tdap vaccine antigens at 4 weeks post-vaccination. Statistical significance for the differences between treatment arms was not assessed.

numerically higher in adults aged 18 to < 65 years treated with abrocitinib (200 mg, 4.71 [3.89–5.66]; 100 mg, 2.82 [2.02–3.82]; Pfizer Inc., data on file). The IR of HZ in the general population is low (estimated in a systematic review at 3–5/1000 PY) compared with patients with AD (estimated in a UK population-based cohort study using The Health Improvement Network (THIN) database at 2.1–3.4/1000 PY [age < 18 years] and 5.3–7.8/1000 PY [age ≥ 18 years]) [13, 14]. Aside from one TB event in the consistent-dose cohort, all other opportunistic infections were HZ (IR/100 PY [95% CI]: abrocitinib 200 mg, 0.53 [0.11–1.55]; 100 mg, 0.24 [0.01–1.35]).

An asymptomatic MACE occurred in one patient in the abrocitinib 100-mg arm in whom a right maxillary sinus submucosal cyst was detected. A brain/skull MRI incidentally found lacunar white matter degeneration; the finding was adjudicated as an ischemic stroke based on an MRI report, despite a lack of clinical evidence of stroke, and the event was not considered serious. No other MACE occurred in the current analysis. In the consistent-dose cohort, one event of VTE (PE) occurred in a patient with morbid obesity and an extensive family history of VTE in the abrocitinib 200-mg arm (IR/100 PY [95% CI], 0.17 [0.00–0.97]); no VTE events were reported in the 100-mg arm. A Danish health care registry–based cohort study reported the IR for VTE was 0.02/100 PY (95% CI 0.00–0.08) in adolescents with AD [15]. In a retrospective cohort study in the Kaiser Permanente Northern California healthcare system, the IR/1000 PY for VTE was 0.5 (95% CI 0.2–1.6) in adolescents with moderate-to-severe AD [16]. Further, in a UK population-based cohort study using the THIN database, the IR/1000 PY for DVT ranged from 0.05–0.16 (95% CI, 0.04–0.28) and for PE ranged from 0.02–0.03 (0.1–0.11) in patients aged < 18 years with AD [17]. No adjudicated malignancies were reported among abrocitinib-treated adolescents in the current analysis, consistent with data from a 2020 report indicating the occurrence of malignancies in US adolescents was rare (16–24/100,000 patients) [18].

No apparent effects on growth or bone development were seen in abrocitinib-treated adolescents. Fracture rates are high in adolescents due to a lag between bone mineralization and expansion, alongside increased physical activity compared with adults [19]. Previous population-based studies suggest fracture risk is higher in patients with severe versus mild AD, independent of corticosteroid use [20, 21]. In the Danish registry study, the IR for fractures was 2.72/100 PY (95% CI, 2.42–3.07) in adolescents with AD (Pfizer Inc., data on file). A retrospective cohort study using the THIN database found the crude IR for fractures was 1.34/100 PY (95% CI 1.30–1.38) in adolescents with AD (Pfizer Inc., data on file). In the current analysis, IRs for fractures were lower than in these database studies and were not considered related to abrocitinib treatment. No bone safety findings were observed in initial knee MRI scans of 58 abrocitinib-treated adolescents, and altered soft tissue fat signal findings were within the accepted range (Pfizer Inc., data on file). These interim results indicate no evidence of clinically relevant bone safety concerns in abrocitinib-treated adolescents.

Vaccination against diphtheria, tetanus, and pertussis is widely recommended [22]. Following a 5-dose DTaP vaccination series at ages 2, 4, 6, and 15–18 months and 4–6 years, a single Tdap dose is recommended at age 11–12 [22]. DTaP/Tdap vaccination coverage is high in US children and adolescents, surpassing 90% in 2019 [23]. These data support Tdap as a valid indicator of immunogenicity in the adolescent population. In the current substudy, there were no appreciable differences in concentrations of the six Tdap vaccine antibodies (tetanus, diphtheria, and pertussis toxins, and filamentous hemagglutinin, fimbriae types 2 and 3, and pertactin [pertussis cell surface proteins]) in adolescents receiving abrocitinib versus placebo. Despite the limited sample size of the substudy, the results suggest adequate immune responses to Tdap vaccination.

In clinical practice, topical therapies are the primary treatment option for patients with AD. Systemic therapies, including JAK inhibitors, are added in cases of more severe or refractory disease. If remission can be maintained with topical therapies alone, the discontinuation of systemic therapies may be discussed in a shared decision-making process. For patients who require long-term treatment with abrocitinib for control of AD, the use of the lowest effective dose is recommended to minimize the risk of adverse events [24, 25]. In JADE REGIMEN, the probability of flaring after discontinuation of abrocitinib was 80% for adolescent patients who achieved IGA 0/1 and EASI-75 before discontinuation [26]. Medicated topical therapies were permitted in JADE EXTEND per the physician's discretion; therefore, patients in this study were treated with either abrocitinib monotherapy or received concomitant medicated topical therapies.

4.1 | Limitations and Strengths

JADE EXTEND did not contain a placebo control arm, precluding long-term comparison between placebo and abrocitinib treatment. As JADE EXTEND is an ongoing trial, final data may change. Longer and larger studies may be required to better monitor the long-term safety of consistent-dose and variable-dose abrocitinib treatment. Sample sizes in the immunogenicity substudy were not sufficient to clearly detect significant differences, limiting the interpretation of results. Additional real-world studies are needed. This efficacy analysis was strengthened by the use of data both as observed and LOCF, whereby missing data were imputed as the last observed value; high efficacy response rates were observed using either algorithm.

5 | Conclusions

The results of this analysis of adolescents with moderate-to-severe AD treated with abrocitinib 200 mg or 100 mg demonstrate that efficacy was maintained for up to 112 weeks with both abrocitinib doses. Data from patients treated for up to 4.6 years support the acceptable long-term safety profile of abrocitinib, with no new safety signals observed. No evidence of growth or bone development impairment was found, and Tdap immunogenicity was not impacted by abrocitinib treatment.

Author Contributions

A.S., P.B., H.F., J.A., M.W., and H.K. designed the study. P.B. and H.F. acquired the data. P.B., H.F., J.A., M.W., and H.K. analyzed the data. A.S.P., L.F.E., A.D.I., C.F., A.W., S.B., C.B., J.M.S., A.S., P.B., H.F., J.A., M.W., and H.K. interpreted the data, drafted and critically revised the manuscript, and gave final approval of the version to be published.

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Conflicts of Interest

A. S. Paller has served as a study investigator for AbbVie, Applied Pharma Research, Dermavant, Eli Lilly and Company, Incyte, Janssen, Krystal Biotech, Regeneron Pharmaceuticals, Timber, and UCB; has served as a consultant for AbbVie, Abeona Therapeutics, Apogee Therapeutics, Arcutis Biotherapeutics, ASLAN Pharma, BioCryst Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Incyte, Johnson & Johnson, Krystal Biotech, LEO Pharma, Mitsubishi Tanabe, Nektar, Primus, Procter & Gamble, Regeneron Pharmaceuticals, Sanofi Genzyme, Seanergy, TWi Biotech, and UCB; and has served on the Data Safety Monitoring Board for AbbVie, Abeona Therapeutics, and Galderma. L. F. Eichenfield has served as a scientific adviser, consultant, and/or clinical study investigator for Pfizer Inc., AbbVie, Almirall, Amgen, Arena, ASLAN Pharmaceuticals, Dermavant, Eli Lilly and Company, Forté, Galderma, Glenmark, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Otsuka, Regeneron Pharmaceuticals, and Sanofi Genzyme. A. D. Irvine has served as a consultant for Pfizer Inc., AbbVie, Amgen, Arena, Benevolent AI, Eli Lilly and Company, LEO Pharma, Novartis, Regeneron Pharmaceuticals, and Sanofi Genzyme; and has received honoraria for participation in the speakers' bureau for Pfizer Inc., AbbVie, Eli Lilly and Company, LEO Pharma, Novartis, Regeneron Pharmaceuticals, and Sanofi Genzyme. C. Flohr is chief investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a principal investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/); leads the EU Trans-Foods consortium; department has received funding from Pfizer Inc. and Sanofi Genzyme for skin microbiome work; and has received compensation from the *British Journal of Dermatology* (reviewer and section editor) and EuroGuiDerm (guidelines lead) as well as from Almirall, Bioderma, and Sanofi Genzyme for educational activities. A. Wollenberg has been an advisor, speaker, or investigator for Pfizer Inc., Aileens, Almirall, Beiersdorf, Bioderma, Bristol Myers Squibb, Chugai, Eli Lilly and Company, Galapagos, Galderma, GSK, Hans Karrer, Hexal, Janssen, LEO Pharma, L'Oreal, Maruho, MedImmune, MSD, Novartis, Pierre Fabré, Regeneron, Santen, Sanofi-Genzyme, Serono, and UCB. S. Barbarot is an investigator or speaker for Pfizer Inc., AbbVie, Alexion, Almirall, AstraZeneca, Eli Lilly and Company, Galderma, Janssen, LEO Pharma, Novartis, Sanofi Genzyme, and UCB. C. Bangert has been a clinical trial investigator for AbbVie, Eli Lilly and Company, Galderma, Merck, Novartis, and Sanofi Genzyme and an advisory board member, consultant, and/or invited lecturer for Pfizer Inc., AbbVie, ALK, Almirall, Eli Lilly and Company, LEO Pharma, Mylan, Merck, Novartis, and Sanofi Genzyme. J. Spergel has received grants from Novartis, Regeneron Pharmaceuticals, and Sanofi Genzyme and is a consultant/advisory board member

for Novartis, Readysetfood, Regeneron Pharmaceuticals, Sanofi Genzyme, and Takeda. A. Selfridge, H. Fan, J. Alderfer, M. Watkins, and H. Koppensteiner are employees and shareholders of Pfizer.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.