Received: 10 March 2023 | Revised: 1 June 2023 | Accepted: 9 June 2023

DOI: 10.1002/jvc2.203

JEADV CLINICAL PRACTICE
OPEN ACCESS JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

ORIGINAL ARTICLE

Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis with prior exposure to oral systemic immunosuppressants or biologic therapies: A post hoc analysis of the JADE clinical trials

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Abstract

Background: Patients with moderate-to-severe atopic dermatitis (AD) refractory to topical therapy might require treatment with systemic therapies, including biologics.

Objectives: To assess the efficacy and safety of abrocitinib monotherapy in patients who previously received systemic therapies.

Methods: This post hoc analysis included patients receiving abrocitinib (200 mg/100 mg) or placebo in the phase 2b and phase 3 JADE MONO-1 and MONO-2, REGIMEN (abrocitinib 200 mg; open-label period) and EXTEND (patients enrolled from MONO-1 and MONO-2) trials. Patients who were systemic therapy-naive or had received prior oral systemic or biologic therapies were assessed for Investigator's Global Assessment (IGA) response of 0 (clear) or 1 (almost clear) and ≥2-point improvement from baseline, ≥75% or ≥90% improvement in Eczema Area and Severity Index (EASI-75 or EASI-90), ≥4-point improvement in Peak Pruritus Numerical Rating Scale (PP-NRS4), PP-NRS score of 0 or 1 and change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) and Patient-Oriented Eczema Measure (POEM) scores. Safety was assessed.

Results: This analysis included 1579 patients (systemic therapy-naive, $n = 997$; prior exposure to oral systemic, $n = 429$; biologic therapies, $n = 153$). At Week 12, IGA 0/1 response rates (95% confidence intervals) among patients who were systemic therapy-naive, had received prior oral systemic therapy or had received biologic therapy were 44.4% (37.5–51.4), 34.5% (22.3–46.7) and 43.5% (23.2–63.7) with abrocitinib 200 mg, 30.9%

Wing S. Chiu: affiliated with affiliation 10 at the time the study was conducted.

(24.2–37.5), 16.4% (7.1–25.7) and 24.1% (8.6–39.7) with abrocitinib 100 mg and 9.6% (4.2–14.9), 5.9% (0.0–13.8) and 0.0% (0.0–23.2) with placebo in the pooled monotherapy trials; and 67.0% (62.8–71.2), 62.2% (56.4–68.0) and 53.5% (42.9–64.0) in REGIMEN. Across subgroups, abrocitinib showed greater improvement in EASI-75, PP-NRS4, EASI-90, PP-NRS 0/1, PSAAD and POEM scores versus placebo. Similar results were seen at Week 48. No new safety signals were observed.

Conclusions: Prior use of oral systemic or biologic therapies did not seem to impact the efficacy and safety of abrocitinib in patients with moderate-to-severe AD.

KEYWORDS

atopic dermatitis, biologics, eczema, immunomodulatory therapies

INTRODUCTION

Patients with moderate-to-severe atopic dermatitis (AD) that is refractory to topical therapy or phototherapy might require treatment with conventional systemic immunosuppressants (ISs)[1–3] or biologic therapies.[1,4] Availability of conventional and biologic therapies and preferred first-line treatment vary across different regions and among treatment guidelines.[2,4–8]

Treatment history has been known to influence the effectiveness of subsequent treatments, particularly in chronic inflammatory conditions. Results of studies have shown that patients with psoriasis, ulcerative colitis and Crohn's disease who have failed prior biologic treatments were more likely to have a reduced response to subsequent biologic therapies.[9,10] There is a paucity of robust data from randomised clinical trials for patients with moderate or severe AD who received previous treatment with systemic therapies. This is partly attributable to the eligibility criteria in clinical trials of novel AD therapies; some trials exclude patients with prior exposure to systemic IS or biologic therapies.[11,12] Because inadequate control of moderate-to-severe AD with conventional systemic therapies occurs frequently,[13] it is important to assess the efficacy of new treatment options and the potential for further improvement in patients with AD who have also had prior exposure to those conventional systemic therapies.

Abrocitinib is an oral, once-daily, Janus kinase 1-selective inhibitor approved for the treatment of adults[14–17] and adolescents[14,15,17] with moderate-to-severe AD. The efficacy and safety of abrocitinib was previously seen in several randomised clinical trials.[18–22] Here, we evaluated the impact of the efficacy of abrocitinib administered as monotherapy in patients with moderate-to-severe AD who had previously received oral systemic/IS and biologic therapies.

METHODS

Study design and patients

This post hoc analysis included data from patients in the phase 2b study (NCT02780167),[18] the phase 3 JADE MONO-1 (NCT03349060)[19] and JADE MONO-2 (NCT03575871)[20] trials, the 12-week open-label run-in period of the JADE REGIMEN trial (NCT03627767)[21] and those in the JADE MONO-1 and JADE MONO-2 trials who were subsequently enrolled in the JADE EXTEND trial (NCT03422822; planned interim analysis with a data cutoff, 24 July 2020). The studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation of Good Clinical Practice Guidelines.

Eligible patients were aged ≥12 years (18–75 years in the phase 2b study) with moderate-to-severe AD for ≥1 year. In the pooled monotherapy population (phase 2b, JADE MONO-1 and MONO-2), patients were randomly assigned to receive oral abrocitinib (200 or 100 mg) or placebo for 12 weeks. In JADE REGIMEN, patients were enrolled in a 12-week open-label run-in period to receive induction treatment with abrocitinib 200 mg. After completing the full treatment period in JADE MONO-1 or JADE MONO-2, eligible patients could enrol in long-term JADE EXTEND. Patients who had received abrocitinib 200 or 100 mg in JADE MONO-1 or JADE MONO-2 continued to receive this dose in JADE EXTEND; using a computer-generated randomisation

schedule, eligible patients who had previously received placebo were randomly assigned to the abrocitinib 200–mg or 100–mg arms (Supporting Information: Figure S1).

In this analysis, patients were classified into subgroups of systemic therapy-naive (previously received only topical therapies; referred as 'systemic therapy-naive'), previously exposed to oral systemic/IS therapy (excluding those who received only corticosteroids) but not biologic therapy (referred as 'prior oral systemic/IS therapy'), or previously exposed to biologic therapy (patients may have received nonbiologic and/or topical therapy in addition to biologic therapy; referred as 'prior biologic therapy').

Assessments

Efficacy end points were analysed at baseline and at Weeks 2, 4, 8 and 12 in the pooled monotherapy population and the JADE REGIMEN open-label run-in period and up to Week 48 in JADE EXTEND. Assessments included the proportion of patients achieving Investigator's Global Assessment (IGA) response (IGA 0/1 [clear or almost clear]), with ≥2 points improvement from baseline, ≥75% and ≥90% improvement in Eczema Area and Severity Index (EASI-75 and EASI-90), ≥4-point improvement from baseline in Peak Pruritus Numerical Rating Scale (PP-NRS4; PP-NRS used with permission from Regeneron Pharmaceuticals, Inc. and Sanofi), PP-NRS score of 0/1 (PP-NRS 0/1) and least-squares mean (LSM) change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD; only pooled monotherapy trials) and Patient-Oriented Eczema Measure (POEM) scores. Short-term safety was evaluated in the pooled monotherapy population at Week 12. Long-term safety was evaluated at Week 48 in patients receiving monotherapy who were enrolled in JADE EXTEND.

Statistical analysis

This analysis included the full analysis set, defined as all patients who were randomly assigned to and received at least one dose of study medication. For the PSAAD score, baseline was defined as the average of all values recorded between Day −6 and Day 1. For other variables, baseline was defined as the last measurement before the first dosing (Day 1), except for the Dermatology Life Quality Index) and POEM in JADE MONO-1 and JADE MONO-2, in which baseline was defined as the measurement collected on or before Day 1. For analysis of binary end points, patients who withdrew from the study were counted as nonresponders. The confidence interval for the response rate was based on normal approximation or the Clopper–Pearson exact method when there were 0% or 100% responders. Continuous end points (e.g., LSM change from baseline) were analysed using linear mixed-effects repeated-measures models. No imputation of missing data was performed.

RESULTS

Patient demographics and baseline disease characteristics by prior systemic therapy exposure

A total of 1579 patients were included in the pooled monotherapy population and the JADE REGIMEN open-label run-in period; of these, 997 patients were systemic therapy-naive, 429 were exposed to prior oral systemic/IS therapy and 153 were exposed to prior biologic therapy. A total of 487 patients from JADE MONO-1 and JADE MONO-2 were enrolled in JADE EXTEND; of these, 319 patients were systemic therapy-naive, 117 had been exposed to prior oral systemic/IS therapy and 51 had been exposed to prior biologic therapy.

Baseline demographics and clinical characteristics of patients in the evaluated trials are shown in Supporting Information: Tables S1 and S2. Baseline characteristics were largely comparable across the subgroups. Across the evaluated trials, AD was more severe (IGA = 4) in patients in the prior oral systemic/IS therapy and biologic therapy subgroups than in those in the systemic therapy-naive subgroup.

Abrocitinib efficacy at Week 12 by prior systemic therapy exposure

As early as Week 2 through Week 12, more patients treated with abrocitinib 200 mg and 100 mg achieved IGA 0/1 (Figure 1a), EASI-75 (Figure 1b) and PP-NRS4 (Figure 1c) responses than those treated with placebo, regardless of whether they were systemic therapy-naive or had received prior oral systemic/IS therapy or biologic therapy. In the abrocitinib 200-mg treatment arm, IGA 0/1, EASI-75 and PP-NRS4 responses at Week 12 were largely similar across all subgroups. In patients treated with abrocitinib 100 mg, IGA 0/1 and EASI-75 response rates at Week 12 were numerically lower (with overlapping 95% confidence intervals [CIs]) in the subgroups with prior oral systemic/IS therapy and biologic therapy than the systemic therapy-naive group (Figure 1a,b). Week 12 PP-NRS4 response rates were also numerically lower with abrocitinib 100 mg in the prior oral systemic/

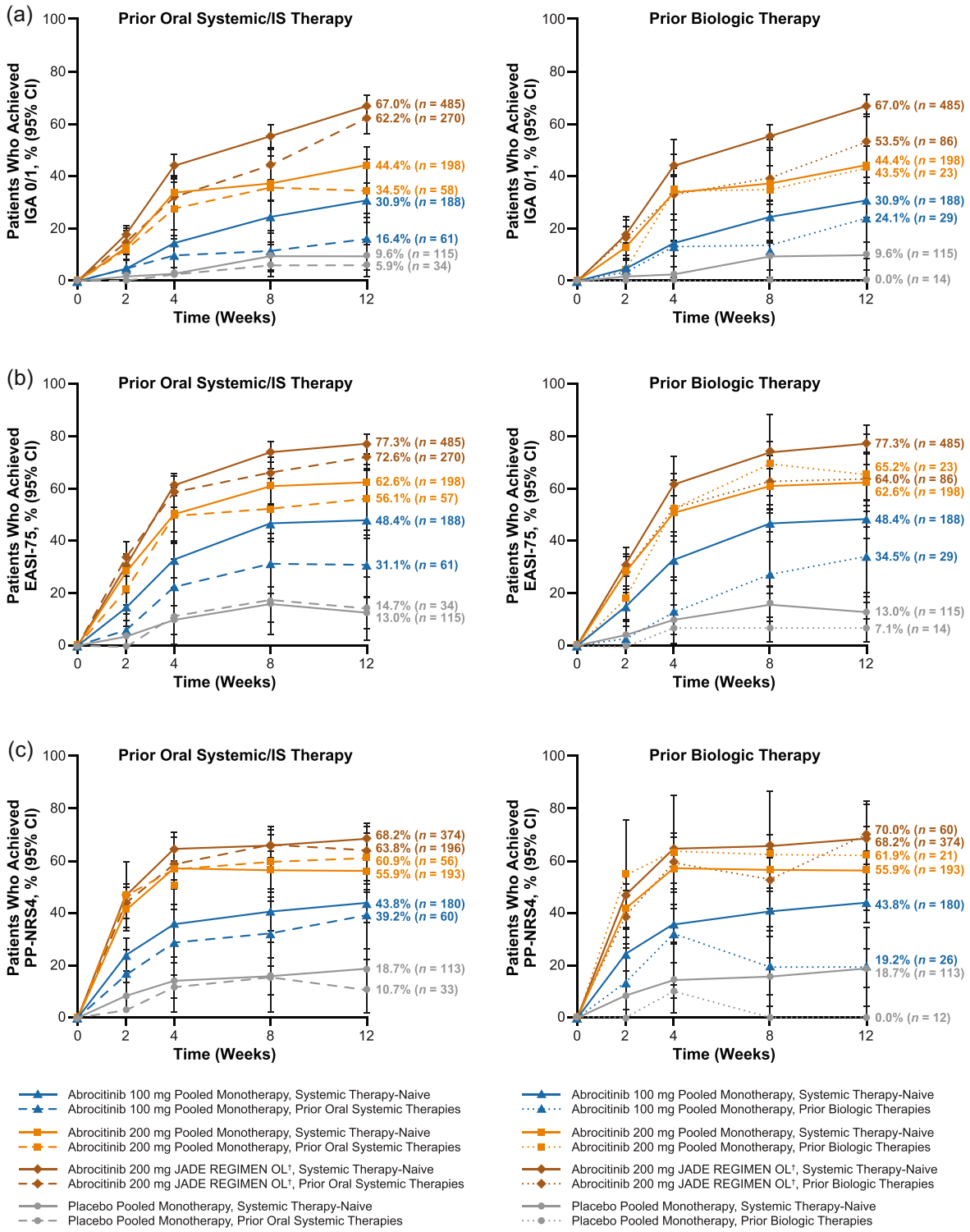

FIGURE 1 Short-term efficacy outcomes assessed by (a) IGA 0/1, (b) EASI-75 and (c) PP-NRS4 response rates over 12 weeks in patients with or without prior systemic therapies. †Patients received abrocitinib 200 mg as monotherapy during the 12-week open-label induction period of JADE REGIMEN. EASI-75, ≥75% improvement from baseline in EASI; IGA 0/1, score of 0 (clear) or 1 (almost clear) with ≥2-point improvement from baseline on the IGA score. CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IS, immunosuppressant; OL, open label; PP-NRS4, ≥4-point improvement from baseline on Peak Pruritus Numerical Rating Scale.

IS therapy subgroup and significantly lower (based on 95% CIs) in the prior biologic therapy group than in the systemic therapy-naive group (Figure 1c).

More patients treated with abrocitinib 200 mg achieved stringent efficacy responses than those treated with placebo, as evidenced by greater EASI-90, PP-NRS 0/1 and EASI-90 + PP-NRS 0/1 responses across all subgroups, regardless of prior use of oral systemic/IS or biologic therapies (Supporting Information: Table S3). These responses with abrocitinib occurred as early as Week 2 and increased through Week 12 across all subgroups.

Abrocitinib efficacy at Week 48 by prior systemic therapy exposure

Efficacy response rates with abrocitinib monotherapy were maintained long-term through Week 48 in the JADE EXTEND study, regardless of whether the patients were systemic therapy-naive or had received prior oral systemic/IS therapy or biologic therapy (Figure 2a–c). Efficacy responses at the stringent thresholds of EASI-90, PP-NRS 0/1 and EASI-90 + PP-NRS 0/1 were maintained long-term through Week 48 with abrocitinib 200 mg and abrocitinib 100 mg across all subgroups in a dose-dependent manner (Supporting Information: Table S4).

Patient-reported outcomes at Weeks 12 and 48 by prior systemic therapy exposure

In the pooled monotherapy population and JADE REGIMEN induction period, improvements in PSAAD, the patient-reported measures of AD severity, were greater with abrocitinib 200 mg and abrocitinib 100 mg than with placebo at Weeks 2–12, regardless of whether the patients were systemic therapy-naive or had received prior oral systemic/IS therapy or biologic therapy (Figure 3). Similarly, greater improvements were observed in LSM change from baseline in POEM scores with abrocitinib 200 mg and abrocitinib 100 mg than with placebo from Weeks 2–12 in all subgroups (Figure 4). These improvements in patient-reported outcomes with the use of abrocitinib were maintained long-term through Week 48 across all subgroups (Figure 5).

Abrocitinib safety at Weeks 12 and 48 by prior systemic therapy exposure

The safety profile across subgroups was consistent with the overall population, with no new safety signals observed in the pooled monotherapy population over 12 weeks (Supporting Information: Table S5) or 48 weeks (Supporting Information: Table S6).

At Week 12, adverse event (AE) rates were comparable between the abrocitinib 200-mg and abrocitinib 100-mg treatment arms across all subgroups (Supporting Information: Table S5). The rates of serious and severe AEs in the abrocitinib treatment arms were generally comparable between patients who were systemic therapy-naive and those who had received prior oral systemic/IS therapy. Among patients who received prior biologic therapy, none had serious or severe AEs in the abrocitinib 200-mg or placebo groups; in the abrocitinib 100-mg group, serious and severe AEs occurred in 6.7% and 10.0% of patients, respectively.

The most frequent AEs up to Week 12 were AD, nasopharyngitis and upper respiratory tract infection, regardless of whether patients were systemic therapy-naive or had received prior oral systemic/IS therapy or biologic therapy. Headache and nausea were more frequent with abrocitinib (200 and 100 mg) than placebo (Supporting Information: Table S5).

The rates of study discontinuation due to AEs were higher among placebo-treated patients than in other treatment arms in the systemic therapy-naive and the prior oral systemic/IS therapy groups through Week 12 (Supporting Information: Table S5). In the prior biologic therapy group, discontinuation rates were the highest with abrocitinib 100-mg treatment than in other treatment arms.

Similarly, at Week 48 in JADE EXTEND, rates of AEs, serious AEs and severe AEs were comparable between abrocitinib arms and across all subgroups (Supporting Information: Table S6). The most frequent AEs were AD, nasopharyngitis and upper respiratory tract infection, regardless of prior use of oral systemic/IS or biologic therapies. In the systemic therapy-naive and prior oral systemic/IS therapy subgroups, rates of study discontinuation due to AEs were higher with abrocitinib 200 mg than abrocitinib 100 mg, whereas, in patients who had received biologic therapy, discontinuation rates were higher with abrocitinib 100 mg.

DISCUSSION

In this post hoc analysis, exposure to prior oral systemic/IS therapy or biologic therapy did not impact the ability of abrocitinib to improve the signs and symptoms of AD and provide meaningful improvements in quality of life (QoL) outcomes compared with placebo. IGA 0/1, EASI-75 and PP-NRS4 response rates with abrocitinib were generally greater than those with placebo across all subgroups of

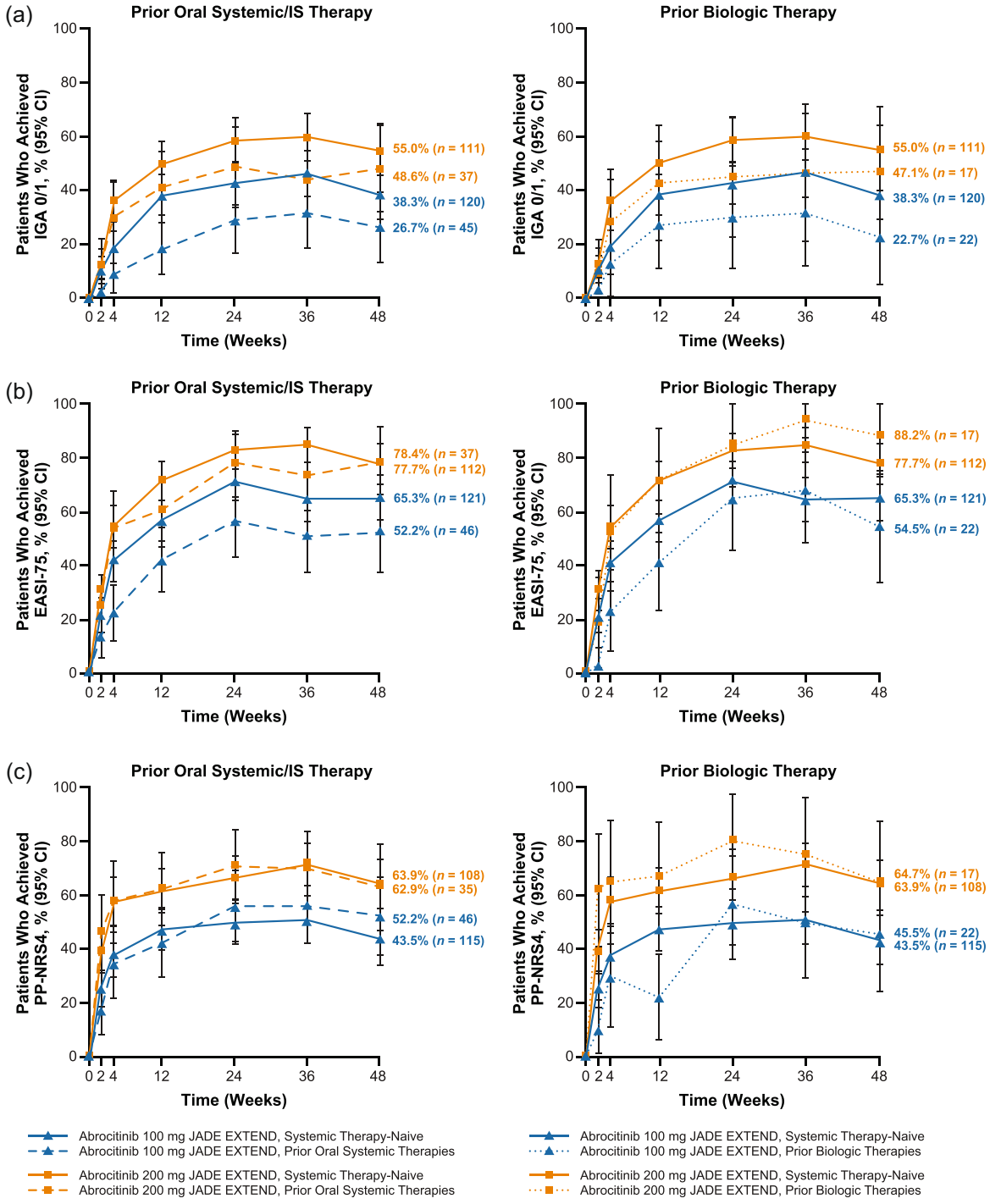

FIGURE 2 Long-term efficacy outcomes assessed by (a) IGA 0/1, (b) EASI-75 and (c) PP-NRS4 response rates over 48 weeks in patients with or without prior systemic therapies. EASI-75, ≥75% improvement from baseline in EASI; IGA 0/1, score of 0 (clear) or 1 (almost clear) with ≥2-point improvement from baseline on the IGA score. CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IS, immunosuppressant; PP-NRS4, ≥4-point improvement from baseline on Peak Pruritus Numerical Rating Scale.

patients, regardless of whether they were systemic therapy-naive or had received prior oral systemic/IS or biologic therapies. These improvements occurred rapidly as early as Week 2 and were sustained long-term through 48 weeks. Furthermore, abrocitinib was efficacious through 48 weeks of treatment at stringent thresholds of improvements in skin clearance and itch response across all subgroups of patients who did and who did not previously receive systemic therapies. This is notable given the inadequate disease control and poor benefit:risk profile of long-term treatment with conventional systemic therapies.[1,3]

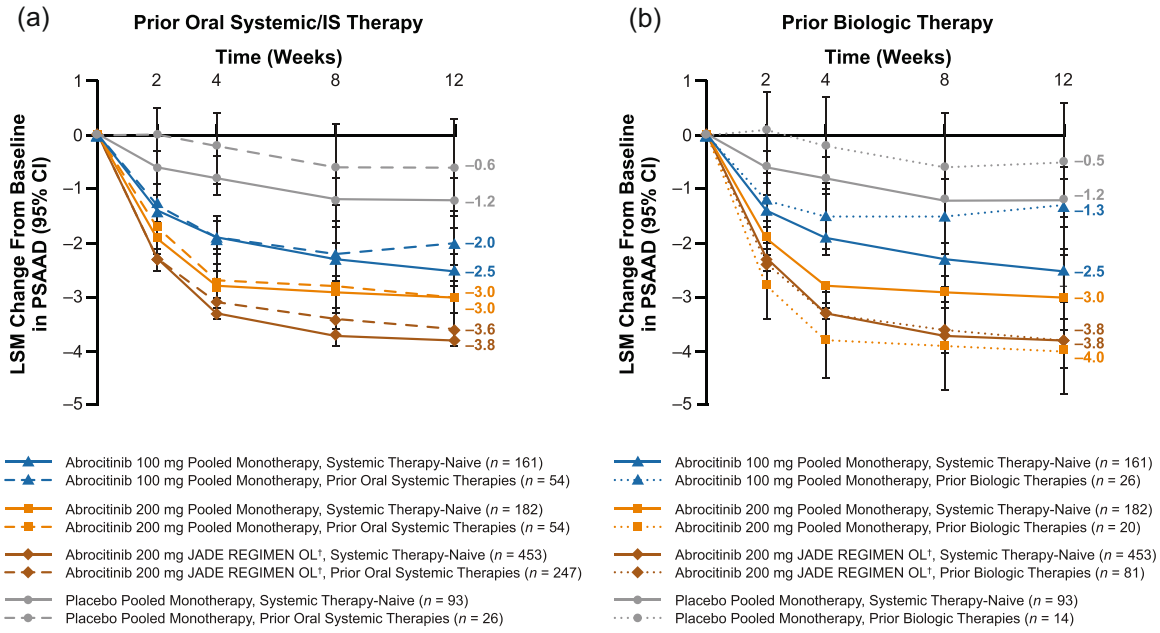

FIGURE 3 LSM change from baseline to Week 12 in PSAAD score in patients who were systemic therapy-naive and those who had prior exposure to (a) oral systemic/IS therapy and (b) biologic therapy. †Patients received abrocitinib 200 mg as monotherapy during the 12-week open-label induction period of JADE REGIMEN. CI, confidence interval; IS, immunosuppressant; LSM, least-squares mean; OL, open label; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

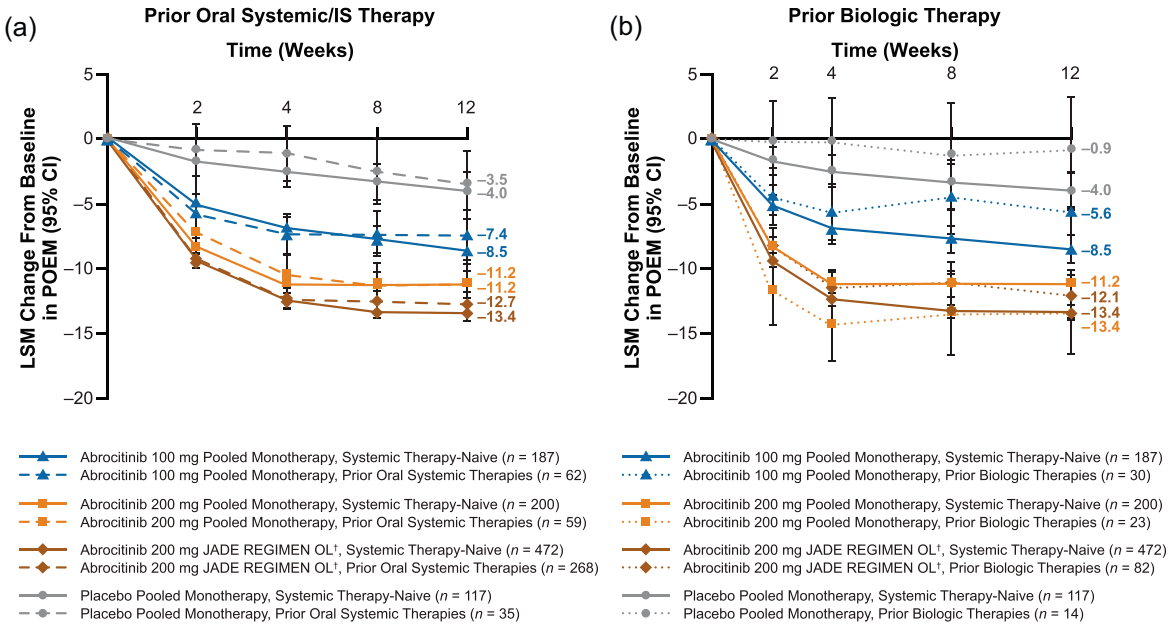

FIGURE 4 LSM change from baseline to Week 12 in POEM score in patients who were systemic therapy-naive and those who had prior exposure to (a) oral systemic/IS therapy and (b) biologic therapy. †Patients received abrocitinib 200 mg as monotherapy during the 12-week open-label induction period of JADE REGIMEN. CI, confidence interval; IS, immunosuppressant; LSM, least-squares mean; OL, open label; POEM, Patient-Oriented Eczema Measure.

Improvements with abrocitinib were dose-dependent for all evaluated end points across the subgroups. IGA 0/1 responses with abrocitinib 100 mg were lower in patients with prior oral systemic/IS therapy and biologic therapy than those who were systemic therapy-naive, albeit with overlapping CIs. These differences could be attributed to the higher baseline disease severity in patients with prior use of systemic therapies; hence,

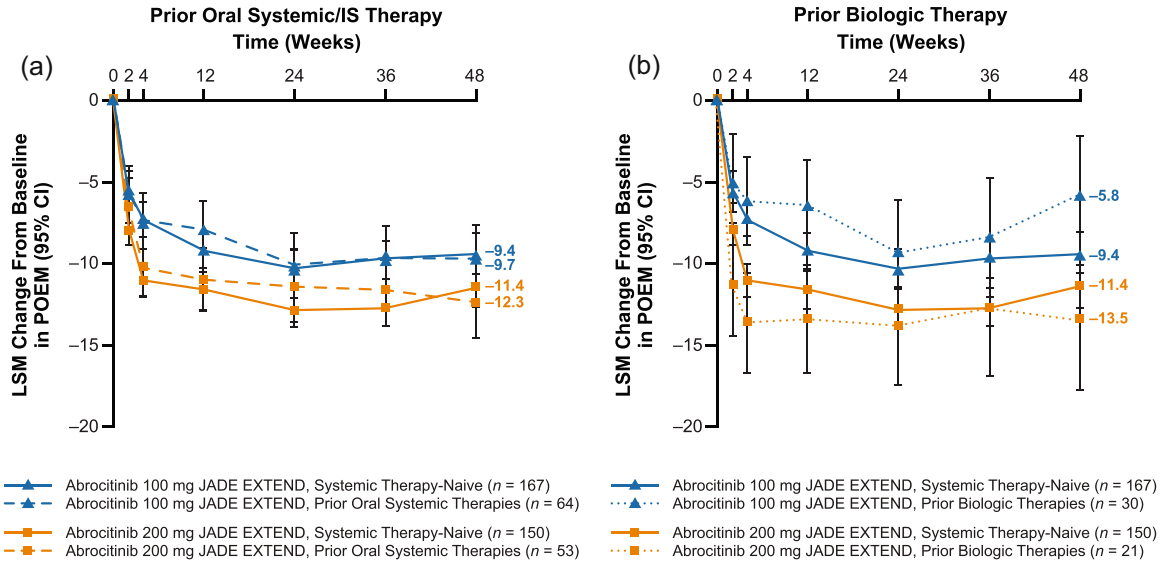

FIGURE 5 LSM change from baseline to Week 48 in POEM score in patients who were systemic therapy-naive and those who had prior exposure to (a) oral systemic/IS therapy and (b) biologic therapy. CI, confidence interval; IS, immunosuppressant; LSM, least-squares mean; POEM, Patient-Oriented Eczema Measure.

treatment with abrocitinib at the 200 mg dose may be warranted in this population.

Across all subgroups, abrocitinib provided greater improvements in patient-reported outcomes, as assessed by PSAAD and POEM, compared with placebo. Clinically meaningful improvements in QoL with the use of abrocitinib in patients who previously received systemic therapies (oral or biologic) highlight the broad efficacy of abrocitinib and the potential for further improvement in this subset of patients with high disease burden due to inadequate disease control.[13,23] Results of the current analysis are consistent with those of previous studies of dupilumab, a monoclonal antibody therapy approved for moderate-to-severe AD, showing benefit in patients regardless of prior use of nonsteroidal ISs.[24,25] A recent post hoc analysis of dupilumab-treated patients from the JADE COMPARE trial showed that switching to abrocitinib (200 mg or 100 mg) in JADE EXTEND resulted in improved disease severity (EASI-75) and itch (PP-NRS4) regardless of prior dupilumab response status.[26] Immunogenicity due to biologic therapy and associated loss of clinical response were documented in other dermatologic conditions.[27–29] In the current analysis, improvements were seen in the signs and symptoms of AD with once-daily oral abrocitinib in patients who received prior biologic therapy, including dupilumab. Results of larger studies could provide further information on the response rates to treatments after the use of biologic therapies.

The safety profile of abrocitinib was consistent with that of the overall JADE clinical trial population,[18–20,22,30] with no new safety signals in patients who were systemic therapy-naive or had prior exposure to oral systemic/IS or biologic therapies. The key strength of this analysis is the evaluation of short- and long-term efficacy, safety and QoL outcomes with abrocitinib across different subgroups of patients from randomised clinical trials with or without prior exposure to systemic therapies in a well-defined population with moderate-to-severe AD. Limitations of this study should also be noted. This was a post hoc analysis (not prespecified) of subgroups with small sample sizes, and therefore, not powered for assessing statistical significance or controlled for Type 1 error. Any differences observed in efficacy responses between patients who were systemic therapy-naive and those who had prior exposure to systemic therapy (oral or biologic) should be interpreted with caution due to the overlapping CIs. Large real-world studies from claims databases will provide further evidence of the therapeutic efficacy of abrocitinib in patients who previously received systemic therapy.

CONCLUSION

Previous use of oral systemic/IS or biologic therapies did not seem to impact the efficacy and safety of abrocitinib in patients with moderate-to-severe AD. Improvements were dose dependent with more patients with prior oral systemic/IS therapy and biologic therapy achieving IGA 0/1 responses with abrocitinib 200 mg than with abrocitinib 100 mg. The use of abrocitinib rapidly lessened the

signs and symptoms of AD and provided clinically meaningful improvements in QoL outcomes, which were sustained long-term. The results of this analysis highlight the potential for further improvements in a subset of patients who have a high burden of AD because of inadequate disease control despite having previously received various systemic therapies.

AUTHOR CONTRIBUTIONS

Melinda J. Gooderham, Michael R. Ardern-Jones, Emma Guttman-Yassky, Mahreen Ameen, Eric L. Simpson, Gary Chan, Wing S. Chiu and Melissa Watkins made substantial contributions to the study's conception and design. Pinaki Biswas performed data acquisition and analysis. All authors contributed to data interpretation, critical review of the drafts, had full editorial control of the manuscript and provided final approval to submit the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank Irina Lazariciu for her critical review of the manuscript. Editorial/medical writing support under the guidance of the authors was provided by Renata Cunha, PharmD and Megan Elder, PhD, at ApotheCom, San Francisco, CA, USA, and was funded by Pfizer Inc., New York, NY, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (Ann Intern Med. 2022;175(9):1298–1304. doi: 10.7326/M22-1460).

CONFLICTS OF INTEREST STATEMENT

Melinda J. Gooderham has received research funds and honoraria for consulting from Pfizer Inc., AbbVie, Akros Pharma Inc., Amgen, AnaptysBio, Arcutis Pharmaceuticals, Arena Pharmaceuticals, Aristea, Asana Bio Sciences, Bausch Health, Boehringer Ingelheim International, Bristol Myers Squibb, Celgene, Coherus Biosciences, Dermavant, Dermira, Eli Lilly and Company, Galderma SA., GSK, Incyte, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Merck & Co., Meiji, Moonlake, Novartis Pharmaceuticals, Nimbus Therapeutics, Regeneron Pharmaceuticals, Reistone, Sanofi Genzyme, Sun Pharmaceuticals and UCB; honoraria for speaking engagements from Pfizer Inc., AbbVie, Akros Pharma Inc., Amgen, AnaptysBio, Arcutis Pharmaceuticals, Aristea, Asana Bio Sciences, Bausch Health, Boehringer Ingelheim International, Bristol Myers Squibb, Celgene, Coherus Biosciences, Dermavant, Dermira, Eli Lilly and Company, Galderma SA., GSK, Janssen, Kyowa Kirin, LEO Pharma, Novartis Pharmaceuticals, Regeneron Pharmaceuticals, Sanofi Genzyme, Sun Pharmaceuticals and UCB; travel related to speaking engagements or advisory boards from Pfizer Inc., AbbVie, Amgen, Arcutis Pharmaceuticals, Bristol Myers Squibb, Eli Lilly and Company, Janssen, LEO Pharma, Sanofi Genzyme and UCB; and participation on a Data Safety Monitoring Board or Advisory Board from Pfizer Inc., AbbVie, Akros Pharma Inc., Amgen, Arcutis Pharmaceuticals, Arena Pharmaceuticals, Bausch Health, Boehringer Ingelheim International, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Galderma SA., Janssen, Kyowa Kirin, LEO Pharma, Novartis Pharmaceuticals, Regeneron Pharmaceuticals, Sanofi Genzyme, Sun Pharmaceuticals and UCB. Michael R. Ardern-Jones has received grants, consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, and support for attending meetings and/or travel from Pfizer Inc., AbbVie, Almirall, Ducentis, Galderma, Heptares, Janssen, LEO Pharma, Eli Lilly and Company, Novartis Pharmaceuticals, Regeneron Pharmaceuticals, Sanofi Genzyme, UCB and Unilever. Emma Guttman-Yassky has received payment from Pfizer Inc., Amgen, AnaptysBio, Asana Biosciences, AstraZeneca, Boehringer Ingelheim, Cara Therapeutics, Celgene, Eli Lilly and Company, Innovaderm, Kyowa Kirin, LEO Pharma, Novartis Pharmaceuticals and Regeneron Pharmaceuticals; personal fees from Pfizer Inc., AbbVie, Almirall, Amgen, Arena, Asana Biosciences, ASLAN Pharmaceuticals, AstraZeneca, Biolojic Design Ltd., Boehringer Ingelhiem, Bristol Meyers Squibb, Cara Therapeutics, Celgene, Connect Pharma, DBV Technologies, Eli Lilly and Company, EMD Serono, Evidera, Galderma, Gate Bio, Genentech, Ichnos Sciences, Incyte, Inmagene, Janssen, Kyowa Kirin, LEO Pharma, Merck, Pandion Therapeutics, Q32 Bio Inc., RAPT Therapeutics, Regeneron Pharmaceuticals, Sanofi Genzyme, SATO Pharmaceutical, Siolta Therapeutics, Target Pharma Solutions, UCB and Ventyx Biosciences. Mahreen Ameen has served as a consultant and/or scientific advisor and/or principal investigator of clinical trials with Pfizer Inc., Regeneron Pharmaceuticals, Sanofi Genzyme, LEO Pharma, AbbVie and Eli Lilly and Company. Eric L. Simpson has received grants from Pfizer Inc., AbbVie, Amgen, Arcutis Pharmaceuticals, ASLAN Pharmaceuticals, Castle Biosciences Inc., Celgene, CorEvitas, Dermavant, Dermira, Eli Lilly and Company, Galderma, Incyte, Kymab, Kyowa Kirin, LEO Pharma, Merck, Novartis Pharmaceuticals, Regeneron Pharmaceuticals, Sanofi Genzyme and Target RWE; consulting fees from Pfizer Inc., Advances in Cosmetic Medical Derm Hawaii LLC, AbbVie, Amgen, AOBiome, Arcutis Pharmaceuticals, Arena Pharmaceuticals, ASLAN Pharmaceuticals, Boehringer Ingelheim, Boston Consulting Group, Bristol Myers Squibb, Collective Acumen, CorEvitas, Dermira, Eli Lilly and Company, Evelo Biosciences, Evidera, ExcerptaMedica, FIDE, Forte Bio RX, Galderma, Gesellschaft Z, GSK, Incyte, Janssen, Johnson & Johnson, Kyowa Kirin, LEO Pharma, Medscape, Merck, MauiDerm, MLG Operating, MJH Holdings, Physicians World LLC, PRImE, Regeneron Pharmaceuticals, Revolutionizing Atopic Dermatitis Inc., Roivant,

Sanofi Genzyme, Trevi Therapeutics, Valeant, Vindico Medical Education and WebMD; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer Inc., AbbVie, Eli Lilly and Company, LEO Pharma, Medscape LLC, Regeneron Pharmaceuticals and Sanofi Genzyme; support for attending meetings and/or travel from FIDE, MauiDerm and Sanofi Genzyme; participation on a Data Safety Monitoring Board or Advisory Board from Pfizer Inc., Global Strategic Group—Improving Quality of Care in Atopic Dermatitis (Sanofi/Regeneron), Harmonizing Outcome Measures in Eczema (HOME), Kyowa Kirin, LEO Pharma AMAZE, National Eczema Association, and TARGET-DERM; and leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid from Sanofi Genzyme and Regeneron US (Medical Advisory Board; Chair), National Eczema Association (Scientific Advisory Committee; Chair of Research), American Academy of Dermatology (Atopic Dermatitis Expert Resource Group; Chair), International Society for Atopic Dermatitis (Board Member) and International Harmonizing Outcome Measures in Eczema (HOME) Working Group (Executive Member). Gary Chan, Pinaki Biswas and Melissa Watkins are employees and shareholders of Pfizer Inc. Wing S. Chiu is an employee and shareholder of Pfizer Ltd.

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.

ETHICS STATEMENT

Study documents and procedures were approved by the appropriate institutional review boards/ethics committees at each study site. All five studies were conducted in compliance with the ethical principles from the Declaration of Helsinki and all International Council for Harmonisation Good Clinical Practice Guidelines. Informed consent was obtained from all individual participants included in the five studies.

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SUPPORTING INFORMATION

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

How to cite this article: Gooderham MJ, Ardern-Jones MR, Guttman-Yassky E, Ameen M, Simpson EL, Chan G, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis with prior exposure to oral systemic immunosuppressants or biologic therapies: a post hoc analysis of the JADE clinical trials. JEADV Clin Pract. 2023;2:753–763. https://doi.org/10.1002/jvc2.203