

## ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

# Effect of abrocitinib on skin biomarkers in patients with moderate-to-severe atopic dermatitis

Emma Guttman-Yassky<sup>1</sup>  | Paola Facheris<sup>1,\*</sup>  | Pedro Jesus Gomez-Arias<sup>1</sup> | Ester Del Duca<sup>1</sup> | Joel Correa Da Rosa<sup>1</sup> | Stephan Weidinger<sup>2</sup> | Robert Bissonnette<sup>3</sup> | April W. Armstrong<sup>4</sup> | Julien Seneschal<sup>5,6</sup> | Kilian Eyerich<sup>7</sup>  | Yeriel D. Estrada<sup>1</sup> | Swaroop N. Bose<sup>1</sup> | Dan Xu<sup>8</sup> | Allshine Chen<sup>9</sup> | Svitlana Tatulych<sup>9</sup> | Erman Güler<sup>10</sup> | Gary Chan<sup>9</sup> | Karen M. Page<sup>11</sup> | Urs Kerkmann<sup>12</sup>

<sup>1</sup>Icahn School of Medicine at Mount Sinai Medical Center, New York, New York, USA

<sup>2</sup>University Hospital Schleswig-Holstein, Kiel, Germany

<sup>3</sup>Innovaderm Research Inc., Montreal, Quebec, Canada

<sup>4</sup>University of Southern California, Los Angeles, California, USA

<sup>5</sup>Department of Dermatology and Pediatric Dermatology, National Reference Center for Rare Skin Disorders, Hospital Saint-André, Bordeaux, France

<sup>6</sup>Bordeaux University, CNRS UMR 5164, Immunconcept, Bordeaux, France

<sup>7</sup>University of Freiburg, Freiburg, Germany

<sup>8</sup>Pfizer Inc., San Diego, California, USA

<sup>9</sup>Pfizer Inc., Groton, Connecticut, USA

<sup>10</sup>Pfizer Inc., Istanbul, Turkey

<sup>11</sup>Pfizer Inc., Cambridge, Massachusetts, USA

<sup>12</sup>Pfizer Pharma GmbH, Berlin, Germany

**Correspondence**

Emma Guttman-Yassky, Icahn School of Medicine at Mount Sinai Medical Center, 5 East 98 Street, New York, NY 10029, USA.  
Email: [emma.guttman@mountsinai.org](mailto:emma.guttman@mountsinai.org)

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**Abstract**

**Background:** This is the first report on the effects of abrocitinib, a Janus kinase 1–selective inhibitor, on the expression of skin biomarkers in patients with moderate-to-severe atopic dermatitis (AD).

**Methods:** JADE MOA (NCT03915496) was a double-blind Phase 2a trial. Adults were randomly assigned 1:1:1 to receive monotherapy with once-daily abrocitinib 200mg, abrocitinib 100mg, or placebo for 12 weeks. The primary endpoint was change from baseline in markers of inflammation (matrix metalloproteinase [MMP]-12), epidermal hyperplasia (keratin-16 [KRT16]), T-helper 2 (Th2) immune response (C-C motif chemokine ligand [CCL]17, CCL18, and CCL26), and Th22 immune response (S100 calcium binding protein A8, A9, and A12 [S100A8, S100A9, and S100A12]) in skin through 12 weeks.

**Results:** A total of 46 patients received abrocitinib 200 mg ( $n = 14$ ), abrocitinib 100 mg ( $n = 16$ ), or placebo ( $n = 16$ ). Abrocitinib improved AD clinical signs and reduced itch. Gene expression of *MMP-12*, *KRT16*, *S100A8*, *S100A9*, and *S100A12* was significantly decreased from baseline with abrocitinib 200mg (at Weeks 2, 4, and 12) and abrocitinib 100mg (at Weeks 4 and 12) in a dose-dependent manner. Abrocitinib 200mg resulted in significant decreases from baseline in *CCL17* expression at Week 12 and *CCL18* expression at Weeks 2, 4, and 12; no significant decreases were observed for *CCL26*.

**Conclusions:** Alongside improvements in clinical signs and symptoms of AD, 12 weeks of abrocitinib treatment resulted in downregulation of genes associated with inflammation, epidermal hyperplasia, and Th2 and Th22 immune responses in the skin of patients with moderate-to-severe AD.

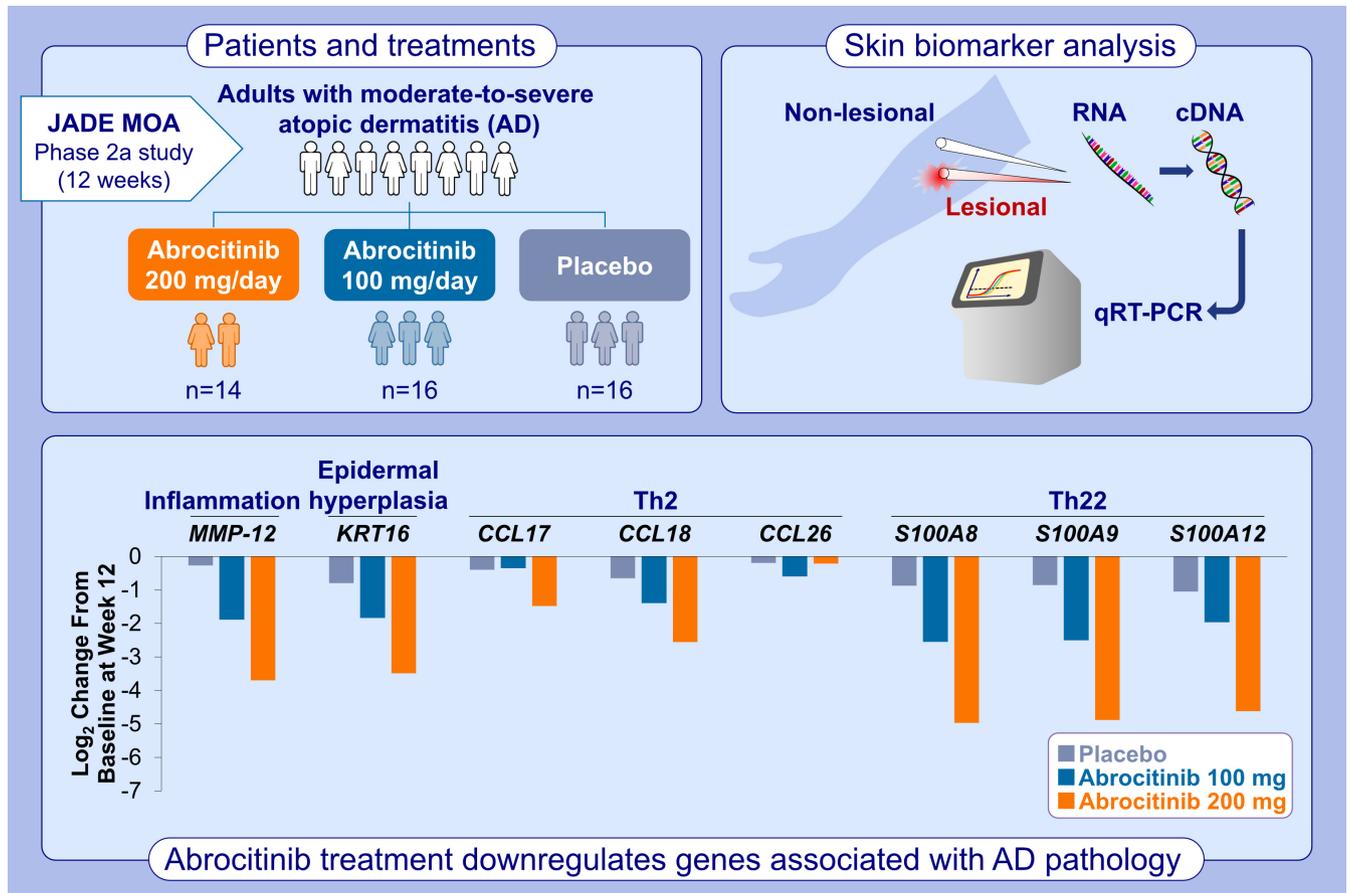
**KEYWORDS**

atopic dermatitis, biomarkers, dermatology

<sup>a</sup>Affiliation at the time of the study.

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## GRAPHICAL ABSTRACT

AD is characterized by skin barrier and immune abnormalities. We assessed treatment response biomarkers of disease activity in the skin of patients with moderate-to-severe AD who received 12 weeks of treatment with abrocitinib, a JAK1-selective inhibitor, or placebo. Markers of inflammation, epidermal hyperplasia, and Th2- and Th22-related immune responses in skin lesions were significantly modulated with abrocitinib.

Abbreviations: AD, atopic dermatitis; CCL, chemokine C-C motif ligand; cDNA, complementary DNA; JAK1, Janus kinase 1; KRT16, keratin-16; MMP-12, matrix metalloproteinase 12; MOA, mechanism of action; qRT-PCR, quantitative real-time polymerase chain reaction; RNA, ribonucleic acid; S100A, S100 calcium-binding protein A; Th, T-helper cell.

## 1 | BACKGROUND

Atopic dermatitis (AD) is a chronic inflammatory skin disease with complex pathophysiology,<sup>1</sup> characterized by skin barrier dysfunction, innate immune system activation, and T-helper 2 (Th2)- and Th22-driven inflammation.<sup>2</sup> Th1 and Th17 activation in AD may also play a role alongside Th2/Th22 inflammation and varies by patient race and age.<sup>3</sup>

Oral abrocitinib is approved for the treatment of moderate-to-severe AD.<sup>4</sup> Abrocitinib 200 mg or 100 mg once daily (QD) demonstrated greater efficacy versus placebo and dupilumab in reducing AD clinical signs and itch in multiple clinical trials of patients with moderate-to-severe AD.<sup>5-9</sup> The exact mechanism by which abrocitinib improves signs and symptoms of AD is not fully elucidated. In vitro, abrocitinib preferentially inhibits Janus kinase 1 (JAK1) signaling over JAK2 (by 28-fold) or JAK3 (by >340-fold).<sup>10</sup> JAK1 signaling modulates the expression of key biomarkers associated with AD pathways, including genes downstream of Th2 cytokine (interleukin [IL]-4, IL-13, and IL-31) and Th22 cytokine (IL-22) signaling,<sup>1,2</sup> whereas the Th17 cytokine (IL-17) does not act via JAK signaling.<sup>11</sup>

We hypothesized that abrocitinib inhibits the action of Th2 and Th22 cytokines that act via JAK1 signaling, thereby reducing AD inflammation as well as the expression of biomarkers of epidermal hyperplasia and skin barrier dysfunction.

The JADE MOA trial was designed to characterize the mechanism of action of abrocitinib in patients with moderate-to-severe AD. The primary objective of the trial was to assess the effects of abrocitinib on the expression of lesional and nonlesional skin biomarkers, understand the cutaneous effects of a JAK1-selective inhibitor in AD, and correlate changes in biomarkers with clinical efficacy.

## 2 | METHODS

### 2.1 | Study design and treatment

JADE MOA (NCT03915496) was a randomized, double-blind, placebo-controlled, parallel-group, Phase 2a trial conducted at sites across the United States and Canada. After a 4-week

screening period, eligible patients were randomly assigned 1:1:1 to receive monotherapy with abrocitinib 200 mg QD, abrocitinib 100 mg QD, or placebo QD for 12 weeks. There was a follow-up period of 4 weeks after the last dose of study intervention was administered. After the end of the study, patients had the option to enroll in the ongoing Phase 3 extension study JADE EXTEND (NCT03422822). A sample size of 17 patients per treatment group was estimated to provide about 92% chance that the 95% CI for the mean fold change (postbaseline relative to baseline) has a half-width of no more than 3.2 (which is within 64% of an assumed maximal standard deviation of 5 for the fold change).

The study was conducted in accordance with the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines, and applicable Good Clinical Practice guidelines. Each study site obtained institutional review board/ethics committee approval before the study was initiated. Patients provided written informed consent before any study-specific activity was performed.

## 2.2 | Study participants

Eligible adults ( $\geq 18$  years old) had chronic ( $\geq 1$  year) moderate-to-severe AD (percentage of body surface area [%BSA]  $\geq 10$ , Investigator's Global Assessment [IGA] score  $\geq 3$ , Eczema Area and Severity Index [EASI] score  $\geq 16$ , and Peak Pruritus Numerical Rating Scale [PP-NRS; used with permission of Regeneron Pharmaceuticals, Inc., and Sanofi] score  $\geq 4$ ) and a recent history (within the past 6 months) of inadequate response to medicated topical therapy that was used for  $\geq 4$  consecutive weeks or a requirement for systemic therapies for AD control. Patients were excluded if they had received prior treatment with a systemic JAK inhibitor. All treatments for AD were required to have been washed out prior to Day 1; the use of only topical nonmedicated emollients and oral antihistamines was permitted during the study.

## 2.3 | Randomization

A computer-generated randomization schedule assigned patients to the treatment groups using an interactive response technology. Treatment assignment was based on a central randomization list consisting of randomly permuted blocks.

## 2.4 | Study endpoints

The primary endpoint was changes from baseline in skin expression of selected key biomarkers previously shown to be associated with AD pathways, including inflammatory markers (matrix

metalloproteinase [MMP]-12), epidermal hyperplasia markers (keratin-16 [KRT16]), and markers of Th2 immune response (chemokine C-C motif ligand [CCL]17, CCL18, and CCL26]) and Th22 immune response (S100 calcium-binding protein A [S100A]8, S100A9, and S100A12).<sup>12-15</sup>

A secondary endpoint of this study was changes from baseline in gene expression in skin lesions (complete list of genes shown in Table S1). Many of the genes analyzed in this study are considered key biomarkers associated with AD pathways, including Th1, Th2, Th17, and Th22 immune responses, and were based on known correlations with AD observed in a previous study.<sup>16</sup> Additional secondary endpoints of this study were changes from baseline in inflammatory infiltrates/cellular markers (T cell and dendritic cell) using immunohistochemistry (IHC) in skin biopsies, changes from baseline in epidermal hyperplasia markers (thickness, KRT16, and Ki-67) using IHC and reverse transcriptase polymerase chain reaction (RT-PCR) in skin biopsies, and response based on PP-NRS  $\geq 4$ -point improvement from baseline and correlation with changes from baseline in the primary endpoint biomarkers and IHC in lesional skin.

Efficacy endpoints for this study were responses based on an IGA score of 0 (clear) or 1 (almost clear; IGA 0/1);  $\geq 50\%$ ,  $\geq 75\%$ , and  $\geq 90\%$  improvement in EASI score (EASI-50, EASI-75, and EASI-90, respectively); and a PP-NRS  $\geq 4$ -point improvement and change from baseline in %BSA affected by AD.

Safety endpoints for this study were incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to discontinuation, and clinical abnormalities, as well as changes from baseline in clinical laboratory values and vital signs. Safety evaluation occurred during 12 weeks of abrocitinib treatment and up to 28 days after the last study dose.

Post hoc analyses assessed the association between efficacy endpoints and change from baseline in IHC and mRNA biomarkers in lesional skin.

## 2.5 | Study procedures

Lesional skin biopsies (4.5 mm punch biopsy) were collected at baseline and at Week 2 (optional), Week 4, and Week 12 after treatment (Table S2). Nonlesional biopsies (4.5-mm punch biopsy) were also collected at baseline and Week 12 after treatment (optional) from the most normal-appearing skin in a relative proximity to the lesional skin biopsy site, at least 5 cm away from the lesion, when feasible. One-half of each biopsy specimen was used for RT-PCR and the other half was used for IHC analysis. The Taqman low-density array (TLDA) quantitative RT-PCR was used to assess gene expression levels of all primary and the majority of secondary endpoint biomarkers (Table S1). IHC was performed on frozen skin sections as previously described<sup>17,18</sup> using purified mouse anti-human antibodies (Table S3). Further details on the study procedures are provided in supplementary material.

## 2.6 | Statistical analyses

Data were analyzed using SAS Analytics Software (version 9.4); R (version 4.1.0) was used to generate heatmaps. TLDA quantitative RT-PCR and IHC values were log-transformed, adding an offset to avoid logarithm of zero. After transformation, a mixed-effects model with time-treatment-tissue interaction and all lower-order effects as fixed effects and a random effect for each patient was fitted to the data (using the R nlme package). This mixed-effects model allowed for imbalance in the number of samples per patient while accounting for intra-subject correlation. For efficacy outcomes, linear mixed models were used to estimate the change from baseline of each gene after treatment. Differences between placebo and abrocitinib treatment arms were also analyzed. Correlation between clinical response (as measured by percent change from baseline in BSA) and the reduction in immune markers (as measured by the difference in the expression at Week 12 and baseline) was performed to assess if the  $\log_2$ -fold change from baseline in biomarkers correlated with change from baseline in PP-NRS, IGA, and EASI scores. Responder-based analyses were based on nonresponder imputation (if a patient withdrew from the study, then that patient was considered a nonresponder from the time of withdrawal). Change from baseline in %BSA affected by AD was based on as-observed data (no imputation of missing data).  $p < .05$  was considered significant (\*\* $p < .001$ , \*\* $p < .01$ , \* $p < .05$ , + $p < .1$ ).

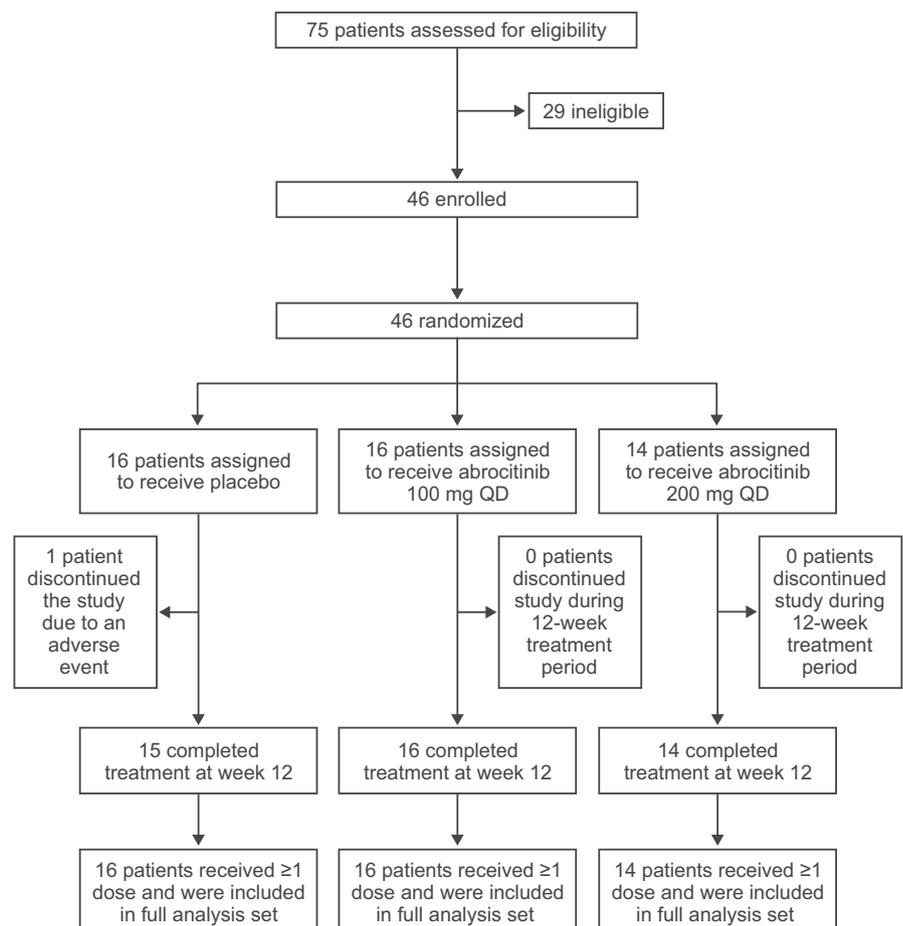
## 3 | RESULTS

### 3.1 | Patient disposition and characteristics

Participant recruitment started on June 18, 2020, and the study was completed on November 16, 2021 (last participant last visit). A total of 46 patients were randomly assigned to a treatment group, received  $\geq 1$  dose of study treatment, and were included in the full analysis set (Figure 1). A total of 14 patients were assigned to the abrocitinib 200 mg group, 16 to the abrocitinib 100 mg group, and 16 to the placebo group. Most patients (abrocitinib 200 mg, 14/14 [100%]; abrocitinib 100 mg, 16/16 [100%]; placebo, 15/16 [94%]) completed 12 weeks of double-blind treatment. One patient in the placebo group discontinued the study during the 12-week double-blind treatment period. Four patients discontinued the study during the 28-day follow-up period: one patient in the 200-mg group, two patients in the 100-mg group, and one patient in the placebo group. Baseline patient characteristics were not entirely balanced between treatment groups, with differences evident for Asian race and AD severity based on IGA, EASI, and %BSA (Table 1).

### 3.2 | Efficacy

Abrocitinib treatment, compared with placebo, improved several measures of clinical efficacy, with more patients achieving EASI-50, EASI-75, EASI-90, IGA 0/1, and a  $\geq 4$ -point improvement in PP-NRS



**FIGURE 1** Patient disposition. Of the 45 patients who completed the 12-week treatment period, 40 entered the long-term JADE EXTEND study (NCT03422822) and 5 continued to the 28-day follow-up period; a total of four patients discontinued the study during the follow-up period: one patient in the 200-mg group, two patients in the 100-mg group, and one patient in the placebo group. QD, once daily.

	Placebo n = 16	Abrocitinib 100 mg QD n = 16	Abrocitinib 200 mg QD n = 14
Age in years, mean ± SD	38.9 ± 15.6	46.6 ± 19.4	41.4 ± 16.7
Age group, n (%)			
18–44 years	10 (63)	8 (50)	8 (57)
45–64 years	4 (25)	4 (25)	4 (29)
≥65 years	2 (13)	4 (25)	2 (14)
Sex, n (%)			
Female	3 (19)	11 (69)	7 (50)
Male	13 (81)	5 (31)	7 (50)
Race, n (%)			
White	11 (69)	10 (63)	5 (36)
Black/African American	2 (13)	4 (25)	1 (7)
Asian	2 (13)	1 (6)	6 (43)
Multiracial	1 (6)	0	1 (7)
Not reported	0	1 (6)	1 (7)
Duration of AD in years, mean ± SD	27.6 ± 15.3	21.4 ± 16.5	27.1 ± 18.3
IGA, n (%)			
Moderate (3)	7 (44)	9 (56)	10 (71)
Severe (4)	9 (56)	7 (44)	4 (29)
EASI, mean ± SD	30.7 ± 12.1	25.2 ± 9.4	23.5 ± 7.1
%BSA affected, mean ± SD	43.1 ± 21.1	39.2 ± 13.4	32.8 ± 15.3
PP-NRS, mean ± SD	7.7 ± 1.3	7.3 ± 1.6	7.3 ± 1.8
Night time itch scale, mean ± SD	7.6 ± 1.2	7.0 ± 1.8	7.4 ± 2.3

Abbreviations: AD, atopic dermatitis; %BSA, percentage of body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; SD, standard deviation.

score from baseline, along with greater reductions in %BSA affected by AD (Figure 2A–F).

### 3.3 | Primary endpoint: expression of MMP-12, KRT16, CCL17, CCL18, CCL26, S100A8, S100A9, and S100A12

MMP-12, KRT16, S100A8, S100A9, and S100A12 expression was significantly decreased from baseline with abrocitinib 200 mg (at Weeks 2, 4, and 12) and abrocitinib 100 mg (at Weeks 4 and 12) in a dose-dependent manner (Figure 3A,B,D). A similar trend was observed for CCL18 expression, with significant decreases from baseline observed with abrocitinib 200 mg treatment at Weeks 2, 4, and 12 and with abrocitinib 100 mg at Week 12 (approaching significance at Week 4; Figure 3C). Abrocitinib 200 mg resulted in significant decreases from baseline in CCL17 expression at Week 12 (Figure 3C); no significant decreases were observed for CCL26 with either abrocitinib dose at any timepoint (decrease with abrocitinib 100 mg approached significance at Week 4; Figure 3C), suggesting that abrocitinib treatment has a more pronounced effect

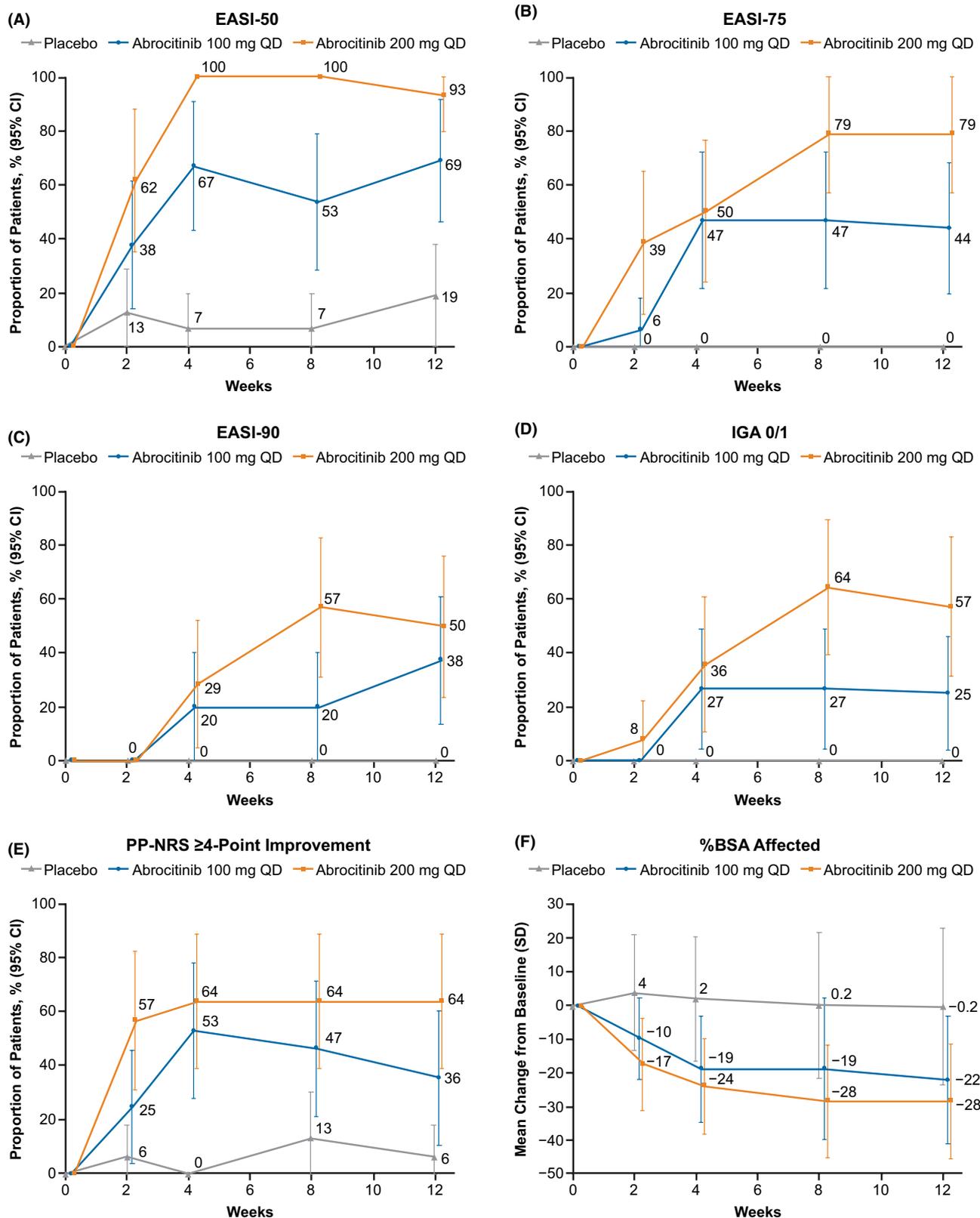
on Th22 and hyperplasia-related markers compared with most Th2 markers.

Compared with placebo, biomarker levels were significantly lower with abrocitinib 200 mg for KRT16, S100A8, S100A9, and S100A12 at Weeks 2, 4, and 12 and for MMP-12 and CCL18 at Week 12 (difference approached significance at Week 2; Figure 3A–D).

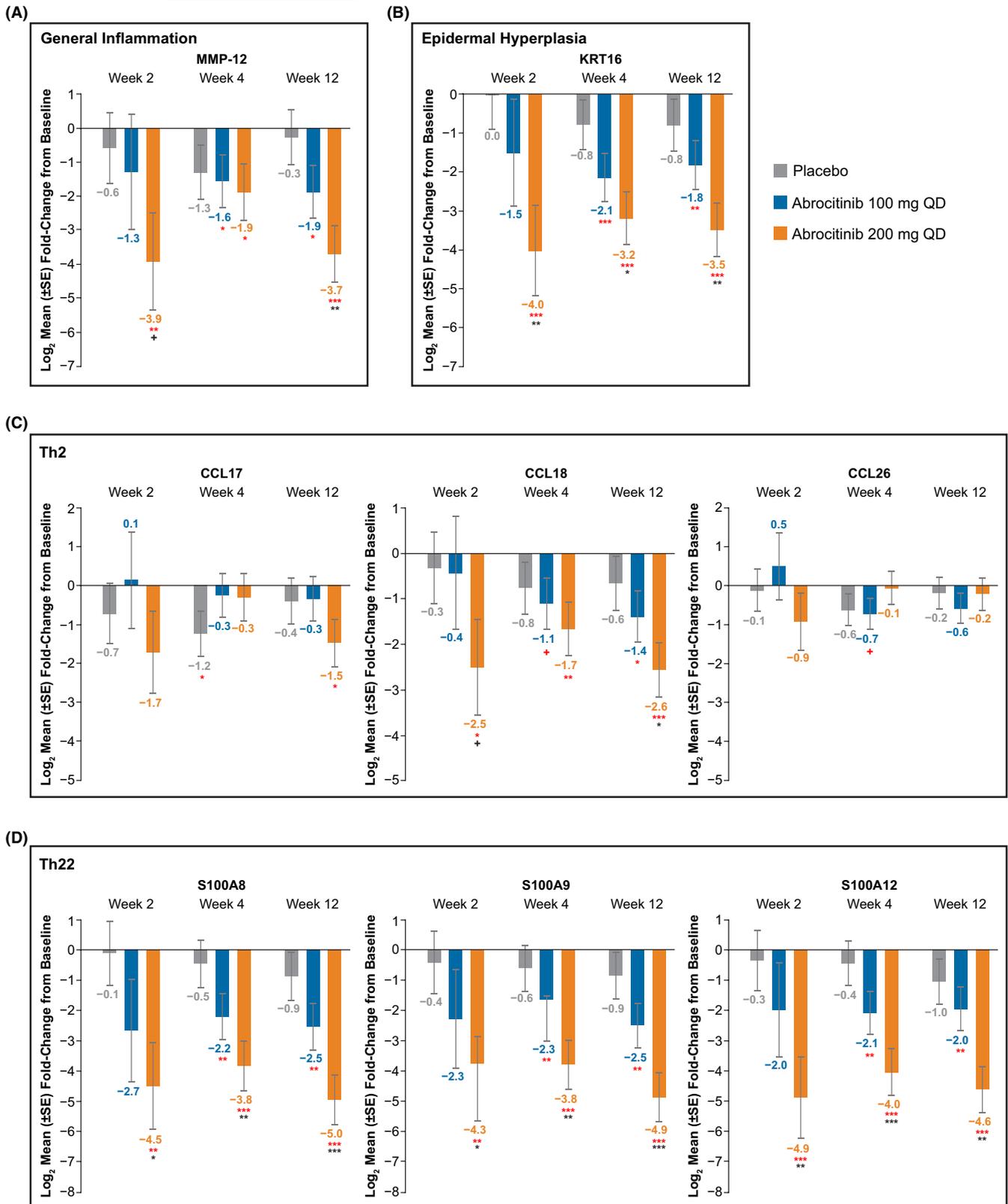
### 3.4 | Secondary endpoint: cutaneous gene expression results

The expression of all assessed Th1, Th2, Th17, and Th22 immune response markers was elevated in lesional versus nonlesional skin at baseline (Table S4). As expected, abrocitinib treatment resulted in significant decreases from baseline in the expression of various Th2 and Th17/22 inflammatory markers at Weeks 2, 4, and 12; decreases were larger with abrocitinib 200 mg than 100 mg (Figure 4). In contrast, with placebo the expression of various Th2 and Th17/22 inflammatory markers remained high up to Week 12, across timepoints. Many Th17-related genes were also significantly inhibited by abrocitinib treatment, including *IL-36G*, *PI3*, *DEFB4B*,

TABLE 1 Baseline patient characteristics.



**FIGURE 2** Efficacy outcomes based on (A) EASI-50, (B) EASI-75, (C) EASI-90, (D) IGA 0/1, (E) PP-NRS  $\geq 4$ -point improvement, and (F) %BSA affected at Weeks 2, 4, 8, and 12. The responder-based analyses were based on nonresponder imputation (if a patient withdrew from the study, that patient was considered a nonresponder in the analyses after the time of withdrawal). Change from baseline in %BSA affected by AD is based on as-observed data (no imputation of missing data). %BSA, percentage of body surface area; CI, confidence interval; EASI-50,  $\geq 50\%$  improvement in Eczema Area and Severity Index score; EASI-75,  $\geq 75\%$  improvement in Eczema Area and Severity Index score; EASI-90,  $\geq 90\%$  improvement in Eczema Area and Severity Index score; IGA 0/1, Investigator's Global Assessment score of 0 (clear) or 1 (almost clear); PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; SD, standard deviation.



**FIGURE 3** Change from baseline in gene expression of biomarkers for (A) inflammation, (B) epidermal hyperplasia, (C) Th2 immune response, and (D) Th22 immune response based on RT-PCR of skin biopsies taken at Weeks 2, 4 and 12. Expression levels from RT-PCR are normalized to the housekeeping gene *RPLP0* by negatively transforming the cycle threshold values to  $-dCt$ . Analyzed by mixed-effects model with time, treatment, and tissue interaction as a fixed effect and a random effect for each patient. Red stars indicate significance versus baseline; black stars indicate significance versus placebo. \*\*\* $p < .001$ , \*\* $p < .01$ , \* $p < .05$ , + $p < .1$ . CCL, chemokine C-C motif ligand; KRT16, keratin-16; MMP-12, matrix metalloproteinase-12; QD, once daily; RT-PCR, reverse transcriptase polymerase chain reaction; S100A, S100 calcium-binding protein A; SE, standard error; Th, T-helper.

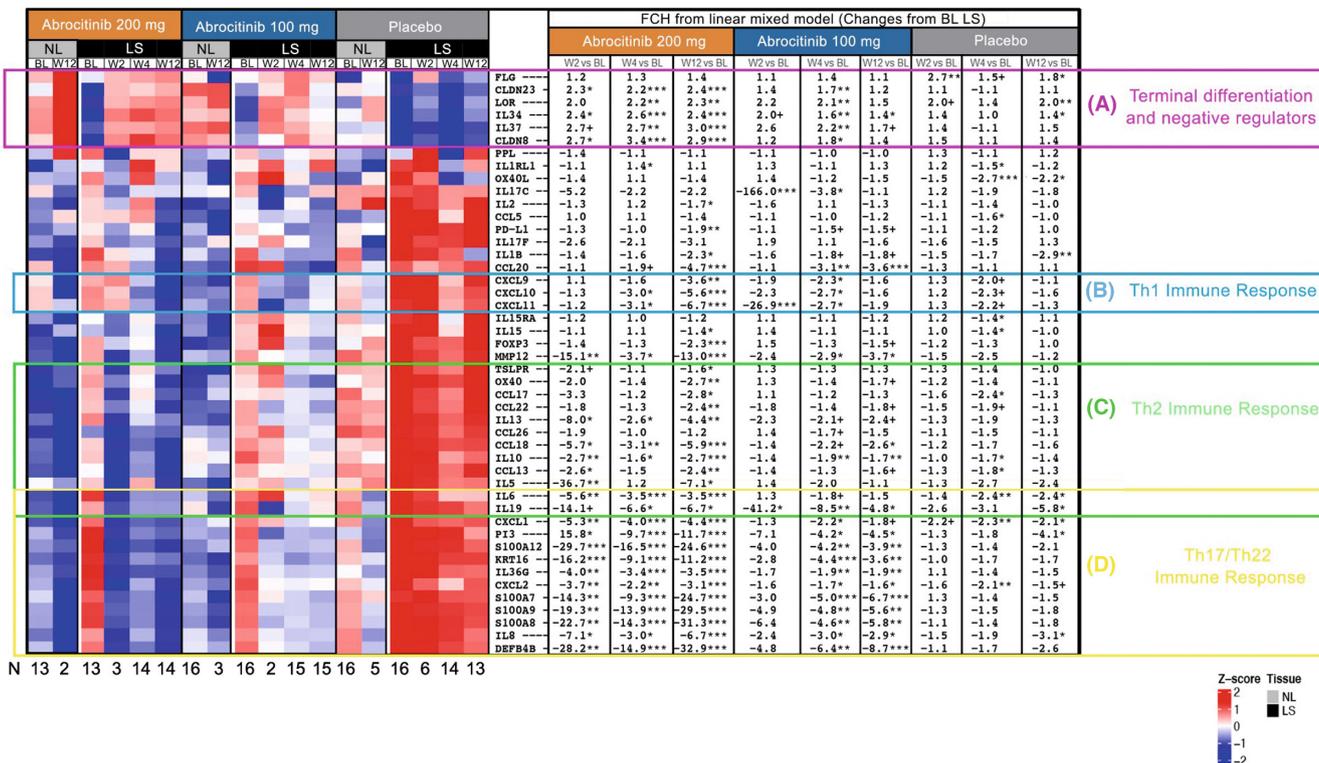


FIGURE 4 Heat map of gene expression related to (A) terminal differentiation and negative regulation, (B) Th1 immune response, (C) Th2 immune response, and (D) Th17/Th22 immune response by treatment group, timepoint, and tissue type. Sample numbers (N) are shown below the map. \*\*\* $p < .001$ , \*\* $p < .01$ , \* $p < .05$ , + $p < .1$ . BL, baseline; CCL, chemokine C-C motif ligand; CLDN, claudin; CXCL, chemokine C-X-C motif ligand; DEFB4B, human beta-defensin-2; FLG, filaggrin; FOXP3, Forkhead box-p3; IL, interleukin; KRT16, keratin-16; LOR, loricrin; LS, lesional; MMP-12, matrix metalloproteinase-12; NL, nonlesional; OX40, tumor necrosis factor receptor superfamily member 4 (CD134); OX40L, tumor necrosis factor superfamily member 4 (OX40 ligand; CD252); PD-L1, programmed death ligand 1; PI3, peptidase inhibitor 3; PPL, periplakin; R, receptor; RA, receptor subunit alpha; RL, receptor-like; S100A, S100 calcium-binding protein A; Th, T-helper cell; TSLPR, thymic stromal lymphopoietin receptor; W, week.

CXCL1, CXCL2, and IL-19. Significant decreases from baseline were observed with abrocitinib 200mg in the expression of the Th1 immune response markers CXCL10 and CXCL11 at Weeks 4 and 12, and CXCL9 at Week 12; responses with abrocitinib 100mg were more variable. Abrocitinib treatment increased the expression of epidermal barrier-associated genes *claudin-8*, *claudin-23*, *loricrin*, and anti-inflammatory (or negative regulator) genes *IL-34* and *IL-37* in a dose-dependent manner. Expression of the epidermal barrier-associated gene *FLG* was increased relative to baseline at Weeks 2, 4, and 12 in the placebo arm and was comparable to baseline levels at all assessed timepoints in both abrocitinib arms.

### 3.5 | Secondary endpoint: IHC results: changes in cellular infiltrates

Markers of epidermal hyperplasia were significantly decreased from baseline with abrocitinib 200mg at Week 12 for Ki-67 and at Weeks 2, 4, and 12 for epidermal thickness; a significant decrease in Ki-67 from baseline was also detected with abrocitinib 100mg at Week 4 (Figure S1). T cells (CD3<sup>+</sup>) and epidermal dendritic cells (CD11c<sup>+</sup>, FcεR1<sup>+</sup>, and CD206<sup>+</sup>) were significantly decreased from baseline

with abrocitinib 200mg at Weeks 2 and 4. Significant decreases from baseline were observed with abrocitinib 100mg for CD3<sup>+</sup> (at Week 2), CD11c<sup>+</sup> (at Weeks 2 and 4), and FcεR1<sup>+</sup> cells (at Week 2).

Compared with placebo, significantly lower levels were detected with abrocitinib 200mg for epidermal thickness (at Week 12), CD3<sup>+</sup> cells (at Weeks 2 and 4), CD11c<sup>+</sup> cells (at Week 2), and FcεR1<sup>+</sup> cells (at Week 2); a significant decrease was detected with abrocitinib 100mg versus placebo for FcεR1<sup>+</sup> levels at week 2.

### 3.6 | Secondary endpoint: changes in skin biomarkers by pruritus response status

At Week 12 in the abrocitinib 200-mg treatment arm, the mean-fold decreases from baseline in gene expression of MMP-12, KRT16, CCL17, CCL18, CCL26, S100A8, S100A9, and S100A12 were greater in patients with an itch response (≥4-point improvement in PP-NRS score) than patients without an itch response (Figure S2). Largely comparable decreases were observed between responders versus nonresponders in the abrocitinib 100-mg treatment arm. Similar trends were observed for the mean-fold decreases from baseline in Ki-67, epidermal thickness, CD11c<sup>+</sup>, FcεR1<sup>+</sup>, and CD206<sup>+</sup> epidermal

dendritic cells, and CD3<sup>+</sup> T cells in patients with an itch response versus those without an itch response (Figure S3).

### 3.7 | Post hoc correlation analyses

Spearman correlations between change from baseline in EASI, IGA, and PP-NRS scores and fold change from baseline in molecular and cellular biomarkers in lesional skin are shown in Figure S4A–C. A summary heatmap showing the correlations between skin biomarkers and clinical scores at Week 12 in the pooled abrocitinib 200 and 100mg treatment groups is shown in Figure S4D. With abrocitinib treatment, significant correlations between changes in EASI, IGA, or PP-NRS score and lesional biomarkers were shown for *KRT-16*, *CCL18*, *S100A8*, *S100A9*, and *S100A12* gene expression. *MMP12* and *CCL26* levels were not correlated with abrocitinib efficacy based on any of the three clinical assessments; *CCL17* expression was correlated with changes in EASI but not with changes in IGA or PP-NRS score.

### 3.8 | Safety

During the study treatment period (or up to 28 days after last study dose), 25 of 46 patients (54%) reported experiencing  $\geq 1$  TEAE of any cause (Table 2). Nausea, dizziness, and headache were the most common TEAEs reported by patients treated with abrocitinib.

One patient in the placebo group had serious TEAEs of eczema herpeticum, periorbital cellulitis, and sepsis. No patients in the abrocitinib groups had a serious TEAE. Five patients in the study had TEAE(s) that led to study discontinuation: one patient in the abrocitinib 200-mg

group, two patients in the abrocitinib 100-mg group, and two patients in the placebo group. In the abrocitinib 200-mg group, study discontinuation was caused by dizziness (one patient); in the abrocitinib 100-mg group, study discontinuation was caused by thrombocytopenia (one patient) and gastritis (one patient); in the placebo group, study discontinuation was caused by eczema herpeticum (one patient) and stasis dermatitis (one patient). There were no cardiovascular events or malignancies in any treatment group and no opportunistic infection events in the abrocitinib groups.

## 4 | DISCUSSION

Atopic dermatitis is a heterogeneous disease and it may be necessary to target more than one cytokine pathway to achieve high treatment efficacy.<sup>3,19</sup> This is supported by the more rapid and, for some outcomes, more pronounced efficacy seen with JAK inhibition (at higher approved dosages of abrocitinib and upadacitinib) as compared with dupilumab, which targets only the Th2 immune pathway.<sup>9,20</sup> This is the first study that evaluated the molecular changes associated with JAK1 inhibition with abrocitinib (200 and 100 mg) compared with placebo in moderate-to-severe AD as well as skin biomarkers that correlate with treatment response. Abrocitinib treatment of patients with moderate-to-severe AD over 12 weeks significantly reduced, in a dose-dependent manner, the cutaneous expression of selected genes involved in inflammation, epidermal hyperplasia, and Th2 (*CCL18*) and Th22 (*S100A8*, *S100A9*, and *S100A12*) responses. Reductions in epidermal hyperplasia, *CCL18*, and *S100A8*, *S100A9*, and *S100A12* were also correlated with clinical efficacy of abrocitinib based on improvements in disease severity measures (PP-NRS, IGA, or EASI score). These

TABLE 2 Safety summary.

	Placebo n = 16	Abrocitinib 100mg QD n = 16	Abrocitinib 200mg QD n = 14
Patients evaluable for TEAEs, n	16	16	14
Number of TEAEs, n	12	21	16
Patients with TEAE(s), n (%)	8 (50)	10 (63)	7 (50)
Patients with serious TEAE(s), n (%)	1 (6)	0	0
Patients who discontinued study due to TEAE(s), n (%)	2 (13)	2 (13)	1 (7)
Patients with TEAE(s) occurring in $\geq 2$ patients in any group, n (%)			
Dizziness	0	2 (13)	1 (7)
Headache	0	1 (6)	2 (14)
Nausea	1 (6)	3 (19)	4 (29)
Patients with TEAE(s) of interest, n (%)			
Eczema herpeticum	1 (6)	0	0
Herpes simplex	0	0	1 (7)
Herpes zoster	0	1 (6)	0

Note: Includes data up to 28 days after last dose of study drug. Except for the number of TEAEs, patients are counted only once per treatment in each row. Serious TEAEs were determined per investigator assessment.

Abbreviations: QD, once daily; TEAE, treatment-emergent adverse event of any cause.

findings contribute to understanding the mechanism of action of JAK1 inhibition and of abrocitinib in AD skin.

Decreases in gene expression from baseline were particularly large with abrocitinib 200 mg versus placebo for the genes downstream of the Th2 immune response. S100A proteins have proinflammatory functions, including chemotaxis of T-cells.<sup>21</sup> Although S100A8, S100A9, and S100A12 expression is induced by both Th22 cytokine (IL-22) and Th17 cytokine (IL-17) signaling in AD skin,<sup>22,23</sup> IL-22 acts via JAK1 signaling, whereas IL-17 does not (Figure S5).<sup>1,11</sup> Therefore, abrocitinib, a JAK1 inhibitor, likely reduced S100A8, S100A9, and S100A12 expression by inhibiting IL-22 signaling. Previous studies have demonstrated that gene expression of IL-22, S100A8, S100A9, and S100A12 is increased in AD lesional skin from infants, children, adolescents, and adults,<sup>24-27</sup> irrespective of their racial or ethnic background.<sup>28-30</sup> Furthermore, previous studies correlated IL-22 and S100A gene expression levels in skin with AD clinical severity and decreased expression was correlated with clinical therapeutic response<sup>31</sup>; IL-22 expression is also correlated with epidermal hyperplasia, and reduced IL-22 levels may result in reduction in epidermal thickness.<sup>32</sup> Findings from this study were consistent with the efficacy profile of abrocitinib; reduced expression of S100A genes was correlated with itch improvement and skin clearance. Future studies could explore whether the reduction in epidermal thickness observed in abrocitinib-treated patients is correlated with the abrocitinib-mediated reduction of IL-22 and S100A gene expression levels. Interestingly, dupilumab has also been shown to decrease expression of S100A8, S100A9, and S100A12 in AD skin,<sup>14,33-35</sup> and downregulation of S100A8 and S100A12 is strongly correlated with improvements in EASI score at week 16.<sup>34</sup> The mechanism behind this downregulation is likely to differ from that observed with abrocitinib; one hypothesis is that dupilumab-mediated inhibition of IL-4 precludes activation of the IL-4R $\alpha/\gamma$  heterodimer, suppressing Th2 cell differentiation and TARC synthesis. Decreased production of TARC decreases Th22 cell recruitment to lesional skin, suppressing the expression of Th22-related genes, such as S100A8 and S100A9.<sup>35</sup> Alternatively, dupilumab may target dendritic cell-bound IL-4 receptors, thus indirectly inhibiting IL-22 and IL-22-induced S100A8, S100A9, and S100A12.<sup>33,35-38</sup>

The CCL18 chemokine is considered a key biomarker of the Th2 response in AD, and has been identified as a potential AD treatment response biomarker.<sup>22,31</sup> It is induced by the Th2 cytokines IL-4 and IL-13 and contributes to T-cell infiltration.<sup>39</sup> We propose that abrocitinib reduced CCL18 expression in this study by JAK1 inhibition of IL-4 and IL-13 signaling. We also found that some dendritic cell subsets, including those that characterize inflammatory epidermal dendritic cells (CD11c<sup>+</sup>, Fc $\epsilon$ R1<sup>+</sup>, and CD206<sup>+</sup>), which produce CCL18,<sup>40</sup> are significantly reduced with treatment, and the reductions are associated with clinical improvement. JAK1/2 inhibition has recently been demonstrated to impair the development of inflammatory epidermal dendritic cells in AD.<sup>41</sup> Previous studies have demonstrated that gene expression of CCL18 is increased in lesional skin of patients with AD across all

age groups<sup>24,42</sup> and racial or ethnic backgrounds,<sup>28-30</sup> indicating a role in the pathogenesis of AD. Furthermore, previous studies assessing gene expression levels of CCL18 in skin with AD clinical severity showed that decreased expression of this gene was correlated with clinical therapeutic response.<sup>31</sup> Findings of this study were consistent; reduced expression of CCL18 was correlated with itch improvement and skin clearance.

In this study, a reduction from baseline in CCL17 at Week 12 was detected in the abrocitinib 200-mg group (but not in the abrocitinib 100-mg group). CCL17 is considered to be a marker for Th2 immune responses because the Th2 chemokines IL-4 and IL-13 stimulate dendritic cells and dermal fibroblasts to produce CCL17.<sup>43</sup> However, CCL17 is also induced through other mechanisms in AD: epidermal barrier disruption stimulates keratinocytes to express CCL17,<sup>2</sup> interferon- $\gamma$  and tumor necrosis factor- $\alpha$  in AD lesional skin stimulate keratinocytes to produce CCL17,<sup>44</sup> and thymic stromal lymphopoietin upregulates CCL17 production by dendritic cells (Figure S5).<sup>43</sup> We propose that abrocitinib reduces CCL17 expression in this study by JAK1 inhibition of IL-4 and IL-13 signaling but that other mechanisms of CCL17 induction partly compensate for this reduction. Interestingly, a long-term analysis of patients who received dupilumab treatment has indicated the persistence of dendritic cells expressing CCL17 in AD skin despite blockade of the IL-4 receptor- $\alpha$  (receptor component for both IL-4 and IL-13 signaling) and clinical efficacy.<sup>33</sup>

Expression of CCL26, considered to be another marker of Th2 immune responses,<sup>45</sup> was not clearly reduced from baseline by both doses of abrocitinib in this study as expected based on JAK1 inhibition of IL-4 and IL-13 signaling. In contrast, previous studies of dupilumab and ASN002 (an inhibitor of JAK1, JAK2, and JAK3, as well as spleen tyrosine kinase) in the treatment of patients with AD have demonstrated reductions in CCL26.<sup>34,46</sup> Further research is needed to determine whether CCL26 may be upregulated in skin of AD patients by mechanisms that do not involve JAK1 signaling.

Secondary analyses showed that abrocitinib treatment upregulated gene expression of epidermal barrier products, including the tight junction markers, claudin-8, and claudin-23, and the terminal differentiation marker, loricrin, in lesional skin, representing an improved epidermal barrier. This is consistent with abrocitinib's JAK1 inhibition of Th2 cytokine signaling, which negatively affects expression of these genes.<sup>25,47</sup> We also observed increased expression of negative regulators (IL-34 and IL-37), suggesting tissue normalization.

The efficacy and safety profile of abrocitinib treatment in patients with moderate-to-severe AD in this study was consistent with the overall JADE clinical program. Abrocitinib was associated with rapid improvement in AD clinical signs and itch reduction. Abrocitinib was well tolerated; no new or unexpected safety findings were observed in either abrocitinib treatment group.

Limitations of this study include the small sample size ( $N=46$ ) which may have also influenced the imbalances observed in baseline demographics and disease severity, with more patients of Asian race in the abrocitinib 200-mg group and more severe AD

based on IGA and EASI scores and %BSA in the placebo group. Additionally, the randomization strategy used to assign patients to treatment groups did not include stratification factors (i.e., race, ethnicity, and disease severity). Further limitations include the high level of variability in the number of biopsy specimens collected per time point, and the lack of a target lesion score for the biopsy area.

## 5 | CONCLUSION

In this study, abrocitinib decreased the expression of genes downstream of Th2 and Th22 immune responses. Conversely, abrocitinib treatment upregulated barrier molecules shown to be downregulated by Th2/Th22 cytokines, as well as negative regulators. These changes were correlated with itch improvement and skin clearance, demonstrating the therapeutic effect of blocking the Th2/Th22 pathways in patients with moderate-to-severe AD.

### AUTHOR CONTRIBUTIONS

Substantial contributions to the conception and design of the study: **Emma Guttman-Yassky, Robert Bissonnette, Svitlana Tatulych, Urs Kerkmann.** Acquisition of data: **Paola Facheris, Pedro Jesus Gomez-Arias, Robert Bissonnette, Yeriel D. Estrada, Dan Xu, Svitlana Tatulych.** Statistical analyses: **Paola Facheris, Joel Correa Da Rosa.** Participated in the interpretation of the data: **all authors.** Drafting of the manuscript: **Emma Guttman-Yassky, Ester Del Duca, Paola Facheris.** Critical feedback for important intellectual content: **all authors.** Final approval for submission: **all authors.** Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: **all authors.**

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### CONFLICT OF INTEREST STATEMENT

E.G.-Y. is an advisory board member for Pfizer Inc., Asana Biosciences, Celgene, Dermira, Galderma, Glenmark, MedImmune, Novartis, Regeneron, Sanofi, Stiefel/GlaxoSmithKline, and Vitae (honorarium); a consultant for Pfizer Inc., AbbVie, Almirall, Anacor, Asana Biosciences, Celgene, Dermira, Galderma, Eli Lilly and Company, Glenmark, Kyowa Kirin, LEO Pharma, MedImmune,

Mitsubishi Tanabe, Novartis, Regeneron, Sanofi, Stiefel/GlaxoSmithKline, and Vitae (honorarium); and an investigator for Celgene, Eli Lilly and Company, LEO Pharma, MedImmune, and Regeneron (grants to institution). P.F. has performed consultancies for Eli Lilly and Company. P.J.G.-A., E.D.D., J.C.D.R., Y.D.E., and S.N.B. report no conflicts of interest. S.W. has received institutional research grants from Pfizer Inc., LEO Pharma, La Roche Posay, and Sanofi Deutschland GmbH; has performed consultancies for Pfizer Inc., AbbVie, Almirall, Boehringer, Eli Lilly and Company, Kymab, LEO Pharma, Regeneron, and Sanofi; has lectured at educational events sponsored by Pfizer Inc., AbbVie, Almirall, Eli Lilly and Company, LEO Pharma, Regeneron, and Sanofi; and is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic dermatitis. R.B. is an advisory board member, consultant, speaker and/or investigator for and receives honoraria and/or grants from Pfizer Inc., AbbVie, Arcutis, Arena Pharma, Asana BioSciences, Bellus Health, Boehringer Ingelheim, Cara, Dermavant, Eli Lilly and Company, EMD Serono, Galderma, Incyte, Kiniksa, Kyowa Kirin, LEO Pharma, Novan, Ralexar, RAPT, Regeneron, Sanofi Genzyme, and Sienna; and is an employee and shareholder of Innovaderm Research. A.W.A. has served as a research investigator and/or scientific advisor for Pfizer Inc., AbbVie, Boehringer Ingelheim, BMS, Dermavant, Dermira, Eli Lilly and Company, EPI Health, Incyte, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Regeneron, Sanofi, Sun, and UCB. J.S. is a scientific adviser, consultant, and/or clinical study investigator for Pfizer Inc., AbbVie, Eli Lilly and Company, Janssen, LEO Pharma, Les Laboratoires Pierre Fabre, Le Laboratoire La Roche-Posay, Novartis, and Sanofi-Genzyme. K.E. is an advisor/investigator or speaker for Pfizer Inc., AbbVie, Almirall, BMS, Boehringer Ingelheim, Eli Lilly and Company, Janssen, LEO Pharma, Novartis, Sanofi, and UCB. D.X., A.C., E.G., G.C., and K.M.P. are employees and shareholders of Pfizer Inc. U.K. is an employee and shareholder of Pfizer Pharma GmbH. S.T. was an employee and shareholder of Pfizer Inc at the time of the study design, execution and reporting.

### 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.

### ORCID

Emma Guttman-Yassky  <https://orcid.org/0000-0002-9363-324X>

Paola Facheris  <https://orcid.org/0000-0002-5171-9854>

Kilian Eyerich  <https://orcid.org/0000-0003-0094-2674>

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## SUPPORTING INFORMATION

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

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