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# Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: A randomized, double-blind, phase 2a trial

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***Background:*** Interleukin 22 promotes epidermal hyperplasia and inhibits skin barrier function.

***Objective:*** Evaluate interleukin 22 blockade in adults with moderate-to-severe atopic dermatitis (AD).

***Methods:*** We performed a randomized, double-blind, placebo-controlled trial with intravenous fezakinumab monotherapy every 2 weeks for 10 weeks, with follow-up assessments until 20 weeks. The change in SCOring AD (SCORAD) score from baseline at 12 weeks served as the primary end point.

***Results:*** At 12 weeks, the mean declines in SCORAD for the entire study population were 13.8 ± 2.7 in the fezakinumab arm and 8.0 ± 3.1 in the placebo arm ($P$ = .134). In the severe AD patient subset (with a

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Conflicts of interest: Dr Guttman-Yassky is an employee of Mount Sinai and has received research funds (grants paid to the institution) from Abbvie, Celgene, Eli Lilly, Janssen, Medimmune/Astra Zeneca, Novartis, Pfizer, Regeneron, Vitae, Glenmark, Galderma, Asana, Innovaderm, Dermira, and UCB. Dr Guttman-Yassky is also a consultant for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, Leo Pharma, Abbvie, Eli Lilly, Kyowa, Mitsubishi Tanabe, Asana Biosciences, and Promius. Dr Brunner has received personal fees from LEO Pharma and Sanofi. Dr Traidl-Hoffmann has received research support from Danone Nutricia and personal fees from Novartis and La Roche Posay. Dr Krueger is an employee of the Rockefeller University and has received research support (grants paid to his institution) and/or personal fees from Pfizer, Amgen, Janssen, Lilly, Merck, Novartis, Kadmon, Dermira, Boehringer, Innovaderm, Kyowa, BMS, Serono, BiogenIdec, Delenex, AbbVie, Sanofi, Baxter, Paraxel, Xenoport, and Kineta. Dr Lebwohl is an employee of Mount Sinai who receives research funds from Abbvie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen/Johnson & Johnson, Kadmon, Medimmune/Astra Zeneca, Novartis, Pfizer, and ViDac. Dr Lebwohl is also a consultant for Allergan and Promius. The rest of the authors have no relevant conflicts of interest to disclose.

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baseline SCORAD of ≥50), SCORAD decline was significantly stronger in the drug-treated patients than placebo-treated patients at 12 weeks (21.6 ± 3.8 vs 9.6 ± 4.2, $P$ = .029) and 20 weeks (27.4 ± 3.9 vs 11.5 ± 5.1, $P$ = .010). At 12 weeks, improvements in body surface area involvement in the entire population were significantly stronger in the drug-treated than placebo-treated patients (12.4% ± 2.4 vs 6.2% ± 2.7; $P$ = .009), and in the severe AD subset, the decline in Investigator Global Assessment was significantly higher in the drug-treated than placebo-treated patients (0.7 ± 0.2 vs 0.3 ± 0.1; $P$ = .034). All scores showed progressive improvements after last dosing (10 weeks) until end of study (20 weeks). Common adverse events were upper respiratory tract infections.

***Limitations:*** The limited sample size and lack of assessment with Eczema Area and Severity Index and a pruritus numerical rating scale were limiting factors. Significance was primarily obtained in severe AD.

***Conclusion:*** Fezakinumab was well-tolerated, with sustained clinical improvements after last drug dosing. (J Am Acad Dermatol 2018;78:872-81.)

***Key words:*** atopic dermatitis; fezakinumab; IL-22; placebo-controlled trial; moderate-to-severe AD.

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, with a prevalence of 7%-10% in adults.[1] It is characterized by pruritus; increased prevalence of allergic manifestations (asthma, allergic rhinitis, food allergies); and a predisposition to cutaneous infections.[2] In patients with moderate-to-severe AD (~20% of adult patients),[3] the disease often affects large body surface areas (BSAs), leading to profound effects on the patients' quality of life.[4]

## CAPSULE SUMMARY

- Interleukin (IL) 22 induces epidermal hyperplasia and compromises skin barrier function in model systems.
- This clinical trial demonstrates the efficacy of IL-22 blockade in humans, implying its possible therapeutic role in atopic dermatitis.
- IL-22 and T helper cell 22 targeting potentially offers a novel alternative for severe atopic dermatitis patients with limited therapeutic options.

However, treatment options for moderate-to-severe AD patients are limited, and topical treatments, including emollients, glucocorticosteroids, and calcineurin and phosphodiesterase-4 inhibitors are often unsatisfactory.[5] Systemic treatments (cyclosporine A, azathioprine, mycophenolate-mofetil, methotrexate) are largely not Food and Drug Administration–approved for AD, with the exception of the recently approved interleukin (IL) 4R$\alpha$ monoclonal antibody, dupilumab, inhibiting both T helper cell 2 ($T_H2$) cytokines, IL-4 and IL-13.[6,7] While dupilumab successfully treats a large portion of AD patients, a considerable subset has insufficient responses,[6,7] necessitating further treatment modalities.

Key pathogenic features of AD include a disturbed skin barrier with epidermal hyperplasia and abnormal keratinocyte differentiation, as well as robust activation of the $T_H2$ and $T_H22$ T-cell pathways. In vitro research and animal studies suggest that IL-22, the lead $T_H22$ cytokine, promotes hyperplasia and inhibits keratinocyte differentiation and skin barrier formation, 2 hallmarks of AD.[8-13] High levels of IL-22–producing T cells have also been identified in psoriasis, particularly in children.[14] To assess a possible role for IL-22 as a driver cytokine of AD, similar to the established pathogenic role of $T_H2$ cytokines,[6,15,16] we investigated the IL-22 antagonist, fezakinumab (ILV-094), in an investigator-initiated clinical trial.

## METHODS

### Study design and oversight

We conducted a phase 2a, randomized, double-blind, placebo-controlled, multicenter clinical trial to evaluate efficacy and safety of fezakinumab in 60 moderate-to-severe AD patients (clinicaltrials.gov, no. NCT01941537) at the Icahn School of Medicine at Mount Sinai (n = 40), and The Rockefeller University (n = 20), both in New York, New York. Patients were randomly assigned to either intravenous fezakinumab or placebo (2:1) (Fig 1), with a loading dose of 600 mg at baseline (day 0), followed by 300 mg at weeks 2, 4, 6, 8, and 10 (last dose). Primary outcome measures were assessed at week 12, with follow-up until week 20. Safety was assessed by the incidence of adverse events, vital signs, physical examination, clinical laboratory testing, and electrocardiography. The study protocol of this investigator-initiated trial was developed by the investigators and was approved by the local institutional review boards.

*Abbreviations used:*

| | |
|---|---|
| AD: | atopic dermatitis |
| BSA: | body surface area |
| BMI: | body mass index |
| EASI: | Eczema Area and Severity Index |
| IGA: | Investigator Global Assessment |
| ITT: | intention to treat |
| MMRM: | mixed-effect model repeated measures |
| SCORAD: | Scoring Atopic Dermatitis |

### Patients

Eligible patients were 18-75 years old, with moderate-to-severe AD for ≥6 months, as defined by a SCORing of Atopic Dermatitis (SCORAD) score of ≥30 and Investigator Global Assessment (IGA; 0 to 5 scale, 0 for clear and 5 for very severe) score of ≥3 (Table I). Patients had to fail or not sustain response to ≥1 conventional treatment, such as topical corticosteroids; calcineurin antagonists; and systemic treatments (corticosteroids, phototherapy, cyclosporine, or other immunomodulators). Disease duration was ≥6 months. All patients gave written informed consent before inclusion.

### Efficacy evaluations

The primary efficacy variable was the change from baseline at week 12 in the AD clinical severity index (SCORAD). SCORAD combines objective assessments of the extent of BSA involvement in AD, the severity of erythema, edema/papulation, oozing and crusting, excoriation, lichenification, and skin dryness, together with subjective measures such as pruritus and sleep loss, yielding an overall score of 0 (no AD) to 103 (worst possible AD).[17] Secondary efficacy end points included proportion of patients achieving SCORAD improvements of ≥50% (SCORAD50 responses), percent improvement in SCORAD, decline in BSA and IGA, and IGA complete response, defined as clear or almost clear or a decline of ≥2 in IGA.

### Statistical analysis

In accordance with study protocol, efficacy variables were analyzed in the modified intention-to-treat (ITT) population, where any patient that started treatment was included in the analysis, and patients that stopped treatment earlier than 12 weeks (N = 7, 11.6%) were defined as nonresponders. Continuous variables measured longitudinally during treatment were analyzed by the mixed-effect model repeated measures (MMRM, using R packages nlme and lme4) approach, with treatment arm, clinical site, baseline value, visit, treatment arm-by-visit and treatment arm-by-severity-by-visit interactions as covariates. For categorical variables, statistical significance of difference between treatment arms was tested by the Fisher's exact test. To test the robustness of the results we also conducted a per-protocol analysis, in which only patients who completed 12 weeks of treatment were included in the analysis. The thresholds 30% improvement in SCORAD (SCORAD30) and 15 percentage point decline in BSA involvement were used to define a positive response, based on the 95 percentiles of pretreatment variation (absolute difference between screening and baseline visit values) in SCORAD percent improvement and BSA decline, and, thus, were deemed objective indicators of a meaningful response (Supplemental Fig 1, *A* and *B*). Multivariate analyses of the primary efficacy variable were performed by linear regression for SCORAD decline, with the backward conditional method, including the covariates: treatment arm, baseline severity, sex, age, race, body mass index (BMI), AD duration, baseline IgE, and combinations of these factors with treatment arm. Statistical significance was set at a two-tailed $P$ value $< .05$.

### Role of the funding source

Fezakinumab was provided by Pfizer Inc (New York, NY). Data were collected and analyzed by the study investigators only. All authors interpreted the data, collaborated in manuscript preparation, made the decision to submit the manuscript for publication, and vouched for the completeness and accuracy of the data and analyses and the fidelity of the study to the protocol.

## RESULTS

### Patients

Enrollment and disposition of the patients are shown in Fig 1. The first patient was screened on March 4, 2014, and the entire study was concluded on February 29, 2016. Sixty-seven patients were assessed for eligibility, and 60 patients were randomized 2:1 to fezakinumab (n = 40) or placebo (n = 20). Demographic and clinical characteristics of the patients at baseline were similar between the study arms (Table I). Comparable numbers of moderate/nonsevere (30 ≤ SCORAD <50) and severe (SCORAD ≥50)[18] AD patients were randomized at baseline to the drug and placebo arms. Thirty-six patients completed treatment and 17 patients reached the primary end point (week 12); 36 patients in the fezakinumab group and 16 patients in the placebo group remained in the study until completion at week 20 (Fig 1). Two patients discontinued treatment because of serious adverse events, which were deemed not related to the study drug (facial cellulitis after a dental procedure; pregnancy with

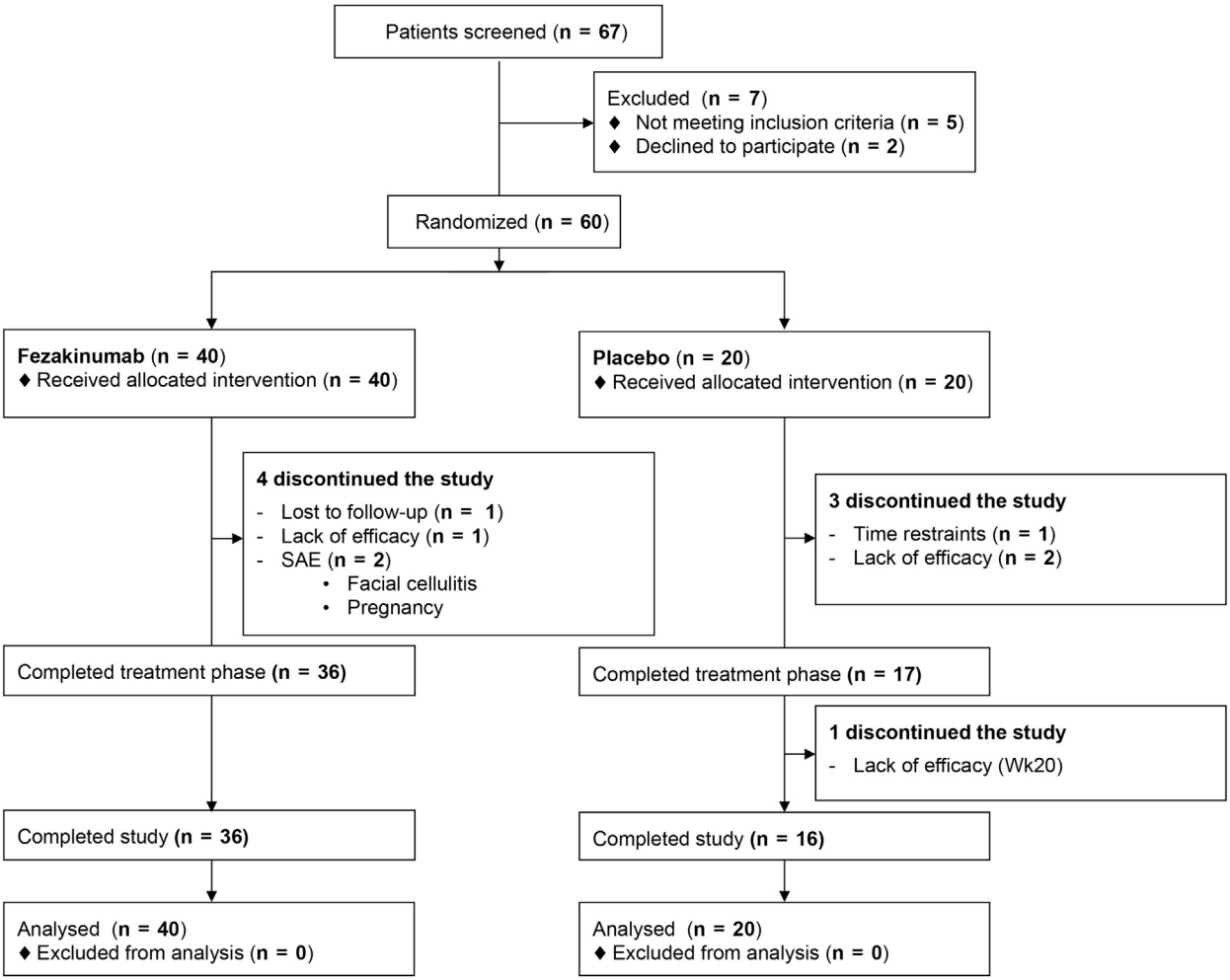


**Fig 1.** Patient disposition. *SAE*, Serious adverse event.

elective termination, Table II and Supplemental Table I; available at http://www.jaad.org). One patient in the drug arm was lost to follow-up, and 4 patients discontinued because of the lack of efficacy (1 in drug arm, 3 in placebo arm). One patient in the placebo arm discontinued early in the study (week 2) because of time restraints (Fig 1). All randomized patients were included in the intention-to-treat (ITT) population.

## Efficacy

Efficacy end points, analyzed by using a MMRM approach with the ITT population, are listed in Table III. Similar significance values were also obtained with the per-protocol population (Supplemental Table II; available at http://www.jaad.org), indicating the robustness of the results. Starting at week 4, the fezakinumab group showed a consistently stronger and more significant mean SCORAD decline from baseline than the placebo group (Fig 2, *A*), a difference that reached statistical significance at weeks 6-10 ($P < .05$). Differences between drug and placebo extended beyond the last dose (week 10), with nonsignificant mean ± standard error of the means SCORAD reductions of 13.8 ± 2.7 in the fezakinumab and 8.0 ± 3.1 in the placebo ($P = .134$) arms at week 12 (primary end point). Progressive reductions were also seen during weeks 14-20, with a significant difference between the drug and placebo arms (18.8 ± 2.9 and 11.7 ± 3.9, respectively; $P = .049$) observed at week 20 (end of study) (Fig 2, *A*; Table III). Although higher SCORAD50 and SCORAD30 responses (secondary end points) were seen with drug versus placebo, these were not statistically significant (Table III).

While SCORAD comprises both objective and subjective measures (sleep loss and pruritus), BSA evaluation is an objective measure. The mean decline in BSA was consistently stronger in the drug-treated group, and was significantly different from placebo starting from week 8 until the end of study, including at week 12 ($P = .009$, Fig 2, *B*;

**Table I.** Demographic and clinical characteristics of the participants at baseline

| Characteristic | Placebo, N = 20 | Drug, N = 40 | *P* value* |
|---|---|---|---|
| Age, mean (SD) | 41.3 (16.3) | 40.5 (14.9) | .855 |
| BMI, mean (SD)† | 27.4 (6.4) | 27.7 (5.9) | .866 |
| Sex, n (%) | | | .360 |
| Female | 11 (55.0) | 17 (42.5) | |
| Male | 9 (45.0) | 23 (57.5) | |
| Race, n (%) | | | .51 |
| Asian | 5 (25) | 10 (25) | |
| Black | 10 (50) | 14 (35) | |
| White | 5 (25) | 16 (40) | |
| IgE group, n, (%)‡ | | | .620 |
| Intrinsic | 4 (20) | 6 (15) | |
| Extrinsic | 16 (80) | 34 (85) | |
| Total serum IgE, kU/L, mean (SD) | 6592 (9720) | 3646 (4561) | .638 |
| SCORAD, mean (SD)§ | 55.5 (13.4) | 53.4 (13.1) | .568 |
| SCORAD range | 34.5-89 | 36-84.5 | |
| SCORAD <50, n (%) | 8 (40) | 20 (50) | .46 |
| SCORAD ≥50, n (%) | 12 (60) | 20 (50) | |
| IGA, n‖ | | | .66 |
| Moderate (3) | 15 | 32 | |
| Severe (4) | 5 | 7 | |
| Very severe (5) | 0 | 1 | |
| BSA, mean (SD)¶ | 38.15 (24.26) | 42.68 (27.7) | .52 |
| History of asthma, n (%)# | | | .89 |
| As child only | 4 (20) | 6 (15) | |
| No | 10 (50) | 22 (55) | |
| Yes | 6 (30) | 12 (30) | |

*BMI*, Body mass index; *BSA*, body surface area; *IGA*, Investigator Global Assessment; *SCORAD*, SCORing Atopic Dermatitis; *SCORAD50*, SCORAD improvement of 50%; *SD*, standard deviation.

*For numerical variables (age, BMI, SCORAD, BSA, total serum IgE), differences between the means by treatment were tested using a two-tailed Student *t* test for independent samples. The proportions by treatment for categorical variables (sex, race, IgE group, SCORAD50, IGA, history of asthma) were compared by using a Fisher's exact test.

†BMI is the weight in kilograms divided by the square of the height in meters.

‡Intrinsic and extrinsic patients were assigned according to baseline total serum IgE levels of <200 kU/L or >200 kU/L, respectively.

§Scores of SCORAD range 0-103, with higher scores indicating greater severity; nonsevere and severe disease were scored as SCORAD <50 and SCORAD ≥50, respectively.

‖IGA of severity of atopic dermatitis was scored on a scale of 0 (clear) to 5 (very severe).

¶BSA was graded from 0% (no skin involvement) to 100% (total skin involvement).

#History of asthma as per patient history.

Table III). Similarly, a decline in BSA involvement of >15 points, as defined by the <15 point pretreatment variation in BSA involvement between baseline and screening (Supplemental Fig 1, *B*), was present at significantly higher rates in the drug arm than the placebo arm (Table III). Also, mean improvements in IGA scores compared with baseline were stronger and earlier with fezakinumab treatment (Fig 2, *C*), significantly different from placebo at week 16 ($P < .001$). A higher, but not significant, IGA complete response rate (standardly defined as an IGA score of 0 or 1 or IGA decline of ≥2 after treatment) were seen in drug versus placebo-treated patients at week 12 ($P = .119$; Table III). Although no significant difference was detected in SCORAD pruritus scores between the drug and placebo arms, a sustained treatment effect was observed among patients with baseline pruritus >5 after week 12 and until end of study at week 20, with nonsignificant exacerbations in placebo-treated patients (Supplemental Fig 2; available at http://www.jaad.org).

In a multivariate linear regression analysis considering all relevant baseline factors (treatment arm, severity, race, sex, age, AD duration, BMI, IgE) the combined factors severity and treatment arm gave the highest and most significant association factor (B = 15.84, $P < .001$) with SCORAD decline at the primary end point week 12 (Supplemental Table III; available at http://www.jaad.org). In fact, the MMRM analysis showed that the severity-by-treatment arm-by-visit covariate had a significant

effect on SCORAD decline at all visits weeks 6-20 (Fig 2, *A*), and parallel significant effects on mean BSA change (Fig 2, *B*) and mean IGA change (Fig 2, *C*) from baseline.

Because severity showed the highest association with treatment response, we further stratified patients according to their baseline disease severity, into nonsevere (SCORAD <50) and severe (SCORAD ≥50) AD. In the severe AD patient subpopulation, there was a strong decline in SCORAD in the study drug group, which was significantly stronger than that seen in the placebo group starting at week 6, including the primary end point at week 12 (drug vs placebo, 21.6 ± 3.8 vs 9.6 ± 4.2; $P = .029$), an effect that continued until week 20 (drug vs placebo, 27.4 ± 3.9 vs 11.5 ± 5.1; $P = .010$) (Fig 3, *B*; Table III). The percentage of patients achieving a SCORAD50 response was higher in the drug-treated group than in the placebo-treated group in the severe AD patient population subset but the difference was not statistically significant (45% vs 16.7% at week 20; $P = .139$; Table III). The SCORAD30 response among patients in the severe AD patient population was significantly higher in the drug-treated patients than placebo-treated patients at week 20 (65.0% vs 16.7%, $P = .012$) but was not at week 12 (55% vs 16.7%, $P = .062$; Table III). The threshold of SCORAD30 was derived from the <30% variation in pretreatment SCORAD values between screening and baseline (Supplemental Fig 1, *A*).

The decline in BSA involvement was stronger and more significant in the patients with severe AD treated with drug versus those patients treated with placebo; $P = .011$ at week 12; Fig 3, *C-D*; Table III). IGA improvement was stronger in the severe patients treated with fezakinumab compared with those treated with placebo, with significant differences between the treatment arms at weeks 8, 10, 12, 14, 16, and 20 ($P = .034$ and $P = .014$ at weeks 12 and 20, respectively; Fig 3, *F*; Table III).

Among patients with nonsevere (or moderate) AD, none of these efficacy variables showed statistically significant differences between the drug and placebo arms (Fig 3, *A, C, E*; Table III). Overall, lower declines in SCORAD, BSA, and IGA were observed in drug-treated patients with moderate AD as compared with patients with severe AD, with larger declines in the placebo-treated moderate AD patients than placebo-treated severe AD patients.

### Safety

Adverse events occurred with a similar frequency in the fezakinumab and placebo groups (Table II; Supplemental Table I). All except 1 adverse event (facial cellulitis) were deemed mild or moderate in severity. Two serious adverse events occurred in the drug arm (facial cellulitis after a dental procedure and a pregnancy with elective termination) but were deemed as most likely unrelated to the drug exposure. The most common adverse events were viral upper respiratory tract infections, occurring in 4 patients receiving fezakinumab. A total of 9 and 18 adverse events were reported in the placebo and drug group, respectively; the numbers of adverse events were not significantly different between arms.

**Table II.** Adverse events

| Variable | Fezakinumab, N = 40 | Placebo, N = 20 | *P* value* |
|---|---|---|---|
| No. adverse events | 18 | 10 | |
| Severity | | | |
| Mild | 9 | 6 | |
| Moderate | 8 | 3 | |
| Severe | 1 | 0 | |
| Mean no. adverse events per patient | 0.45 | 0.5 | .82 |
| No. patients with any adverse event (%) | 14 (35) | 8 (40) | .78 |
| No. patients with serious adverse event (%)† | 2 (5)‡ | 0 | .55 |
| No. patients discontinue because of adverse event (%) | 2 (5) | 0 | .55 |
| Common adverse events§ | | | |
| No. patients with upper respiratory infection, viral (%) | 4 (10) | 0 | .29 |

*The differences of the proportions were tested by using Fisher's exact test.
†A serious adverse event was defined as an event that was fatal or life threatening, required prolonged hospitalization, caused persistent or substantial disability or incapacity, a congenital anomaly or birth defect, or an event that was considered by the investigator to be a medically important event.
‡Facial cellulitis after a dental procedure; pregnancy with elective termination.
§Common adverse events were those that occurred in >5% in any treatment group.

### Blood biomarkers

There were no significant changes overtime per arm or significant differences between groups in total serum IgE level changes during treatment and follow-up (Supplemental Fig 3; available at http://www.jaad.org).

## DISCUSSION

This is the first clinical trial investigating IL-22 blockade in patients with AD, and the first to suggest a pathogenic role of IL-22 in any human disease. Fezakinumab treatment in adults with moderate-to-severe AD resulted in consistent improvements in clinical and molecular disease scores as compared

**Table III.** Intention-to-treat analysis of efficacy at primary (week 12) and secondary (week 20) end points by treatment arm

| | All patients, N = 60 | | | Severe AD, baseline SCORAD ≥50, N = 32* | | | Nonsevere AD, baseline SCORAD <50, N = 28* | | |
|---|---|---|---|---|---|---|---|---|---|
| **End point** | **Drug, N = 40** | **Placebo, N = 20** | ***P* value†** | **Drug, N = 20** | **Placebo, N = 12** | ***P* value†** | **Drug, N = 20** | **Placebo, N = 8** | ***P* value†** |
| SCORAD decline, mean ± SEM | | | | | | | | | |
| Week 12 | −13.8 ± 2.7 | −8.0 ± 3.1 | .134 | −21.6 ± 3.8 | −9.6 ± 4.2 | **.029** | −6.0 ± 3.2 | −5.7 ± 4.6 | .764 |
| Week 20 | −18.8 ± 2.9 | −11.7 ± 3.9 | **.049** | −27.4 ± 3.9 | −11.5 ± 5.1 | **.010** | −10.2 ± 3.4 | −11.9 ± 6.4 | .639 |
| SCORAD % improvement, mean ± SEM | | | | | | | | | |
| Week 12 | −24.4 ± 5.0 | −14.7 ± 5.9 | .175 | −34.4 ± 6.1 | −15.8 ± 7.4 | **.039** | −14.3 ± 7.4 | −13.1 ± 10.1 | .897 |
| Week 20 | −34.1 ± 5.4 | −23.0 ± 7.4 | .072 | −43.9 ± 6.6 | −20.6 ± 8.8 | **.028** | −24.2 ± 8.0 | −26.6 ± 13.8 | .794 |
| SCORAD30, %‡ | | | | | | | | | |
| Week 12 | 42.5 | 20.0 | .150 | 55.0 | 16.7 | .062 | 30.0 | 25.0 | 1.000 |
| Week 20 | 52.5 | 30.0 | .168 | 65.0 | 16.7 | **.012** | 40.0 | 50.0 | .691 |
| SCORAD50, %§ | | | | | | | | | |
| Week 12 | 22.5 | 15.0 | .734 | 30.0 | 16.7 | .676 | 15.0 | 12.5 | 1.000 |
| Week 20 | 37.5 | 25.0 | .395 | 45.0 | 16.7 | .139 | 30.0 | 37.5 | 1.000 |
| Decline in BSA involvement, mean ± SEM | | | | | | | | | |
| Week 12 | −12.4 ± 2.4 | −6.2 ± 2.7 | **.009** | −15.7 ± 3.6 | −6.3 ± 4.5 | **.011** | −9.0 ± 3.1 | −6.1 ± 1.6 | .347 |
| Week 20 | −17.7 ± 3.2 | −7.6 ± 2.9 | **.001** | −23.3 ± 4.7 | −6.8 ± 4.7 | **.009** | −12.2 ± 4.2 | −8.8 ± 1.9 | .357 |
| Proportion of patients (%) with a decline in BSA involvement >15‖ | | | | | | | | | |
| Week 12 | 37.5 | 10.0 | **.034** | 45.0 | 16.7 | .139 | 30.0 | 0 | .141 |
| Week 20 | 42.5 | 10.0 | **.017** | 55.0 | 16.7 | .062 | 30.0 | 0 | .141 |
| IGA decline, mean ± SEM | | | | | | | | | |
| Week 12 | −0.6 ± 0.1 | −0.3 ± 0.1 | .119 | −0.7 ± 0.2 | −0.3 ± 0.1 | **.034** | −0.5 ± 0.2 | −0.4 ± 0.3 | .684 |
| Week 20 | −0.9 ± 0.2 | −0.6 ± 0.2 | .127 | −1.2 ± 0.2 | −0.4 ± 0.2 | **.014** | −0.7 ± 0.2 | −0.8 ± 0.3 | .724 |
| IGA % complete response¶ | | | | | | | | | |
| Week 12 | 15.0 | 5.0 | .407 | 20.0 | 0 | .271 | 10.0 | 12.5 | 1.000 |
| Week 20 | 25.0 | 15.0 | .513 | 35.0 | 8.3 | .204 | 15.0 | 25.0 | .606 |

*AD*, Atopic dermatitis; *BSA*, body surface area; *IGA*, Investigator Global Assessment; *SCORAD*, SCOring Atopic Dermatitis; *SEM*, standard error of the mean.

*Severe patients are defined as patients with a SCORAD ≥50 at week 0.

†Statistical significance of the difference in mean decline between treatment arms was assessed by mixed-effect model repeated measures. Statistical significance of difference in percent response between treatment arms was assessed by Fisher's exact test. Significant results ($P \leq .05$) are in bold.

‡SCORAD30 is defined as SCORAD improvement >30% compared with week 0; a 30% threshold was selected because it was the 95th percentile of pretreatment variation.

§SCORAD50 is defined as SCORAD improvement >50% compared with week 0.

‖The decline in BSA involvement threshold of 15 points was selected because it was the 95th percentile of pretreatment variation.

¶IGA complete response is defined as IGA ≤1 or an IGA decline ≥2 at the respective end point.

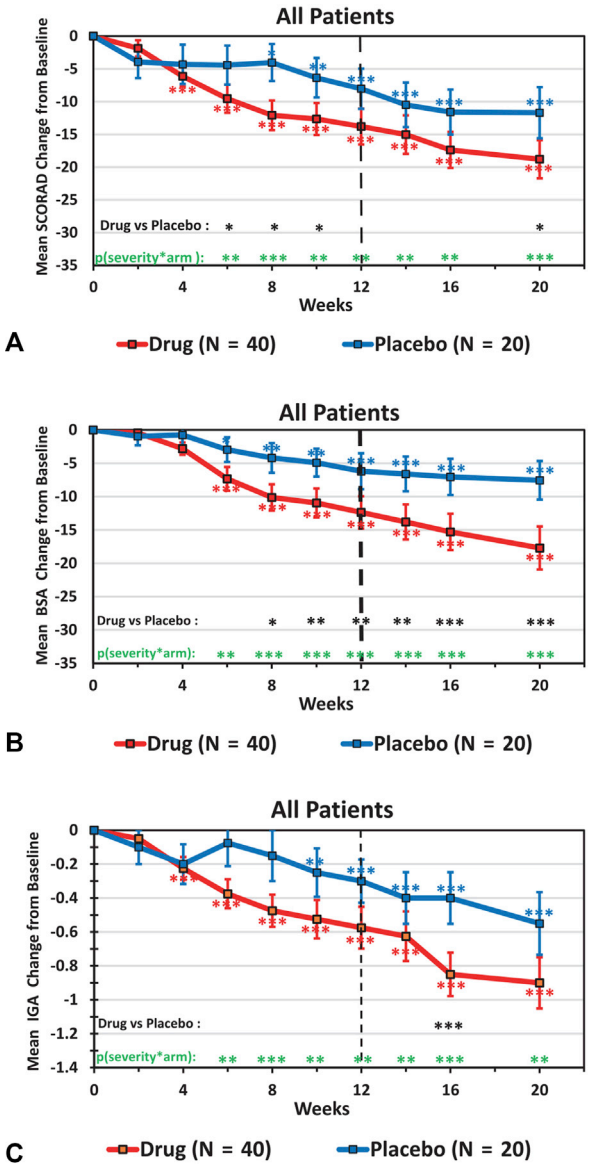


**Fig 2.** Time course of efficacy variables for entire study population. Clinical responses for SCORAD (**A**), BSA (**B**), and IGA (**C**) are shown for the fezakinumab (red) and placebo (blue) arms. All panels depict the mean ± SEM (standard error of the means) change from baseline. Data was analyzed by mixed-effect model repeated measures. *Red asterisks* and *blue asterisks* by each curve indicate significant change from baseline for each arm; *black asterisks* at bottom indicate significant differences between drug and placebo arms; *green asterisks* indicate the significance of the combined factor: baseline severity and treatment arm. *$P < .05$, **$P < .01$, ***$P < .001$. *BSA*, Body surface area; *IGA*, Investigator Global Assessment; *SCORAD*, SCOring Atopic Dermatitis.

with placebo. At week 12, significant clinical improvements in drug-treated compared with placebo-treated patients were best seen in severe AD patients (baseline SCORAD ≥50). Moreover, progressive improvements in all outcome measures were observed until week 20, which was 10 weeks after the last dose, suggesting sustained drug responses beyond end of treatment.

This study is the first evidence in humans that, similar to the $T_H2$ cytokines IL-4 and IL-13,[6,7,15,16] IL-22 is a key driver of AD. Whereas current monoclonal antibody treatment approaches approved or currently being tested in drug trials target the $T_H2$ pathway in AD,[6,19-21] these data provide a completely new mechanism for future therapeutic strategies for AD and other disease where IL-22 might have a role, such as pediatric psoriasis[14] or pediatric AD.[22]

Larger and more significant differences were specifically seen in the severe AD patient group. Possible reasons for reduced statistical significance in the moderate AD cohort might be higher variability and lower maximal differences because of lower baseline disease. Patients with severe AD start with higher disease severity and often show less fluctuations, allowing for greater differences in treatment responses.[23-27] The sensitivity of clinical outcome measures generally increases with higher baseline disease activity and shows less reproducibility with lower scores,[23-27] a fact that is now increasingly recognized in trial design.

Our study has several limitations. First, our study was designed >6 years ago, and only used SCORAD to measure disease severity, similar to many studies designed at the time,[17] while current AD trials often use Eczema Area and Severity Index (EASI) scores as primary outcomes, limiting the ability to compare with other clinical trials. Nevertheless, recent studies considered both measures, and in these studies, SCORAD appears to be a more stringent disease measure; changes in EASI scores tend to be much larger than respective SCORAD changes.[6,7] Second, our study was designed before emerging data that AD is a heterogeneous disease,[22,28-30] which necessitates a study design allowing for analyses of subset populations. To address this, we used a post-hoc analysis approach separating patients with severe from moderate disease. Larger studies are needed to compare with other treatments and to confirm efficacy in AD subgroups (eg, moderate vs severe disease, different ethnicities).

This study, supported by progressive clinical improvements with IL-22 antagonism versus placebo, reveals a novel therapeutic paradigm for AD, and particularly severe AD, a population that presents the largest unmet need for better therapeutics due to its debilitating nature and devastating effects on patients' quality of life.[31] Fezakinumab also showed a favorable safety profile with balanced

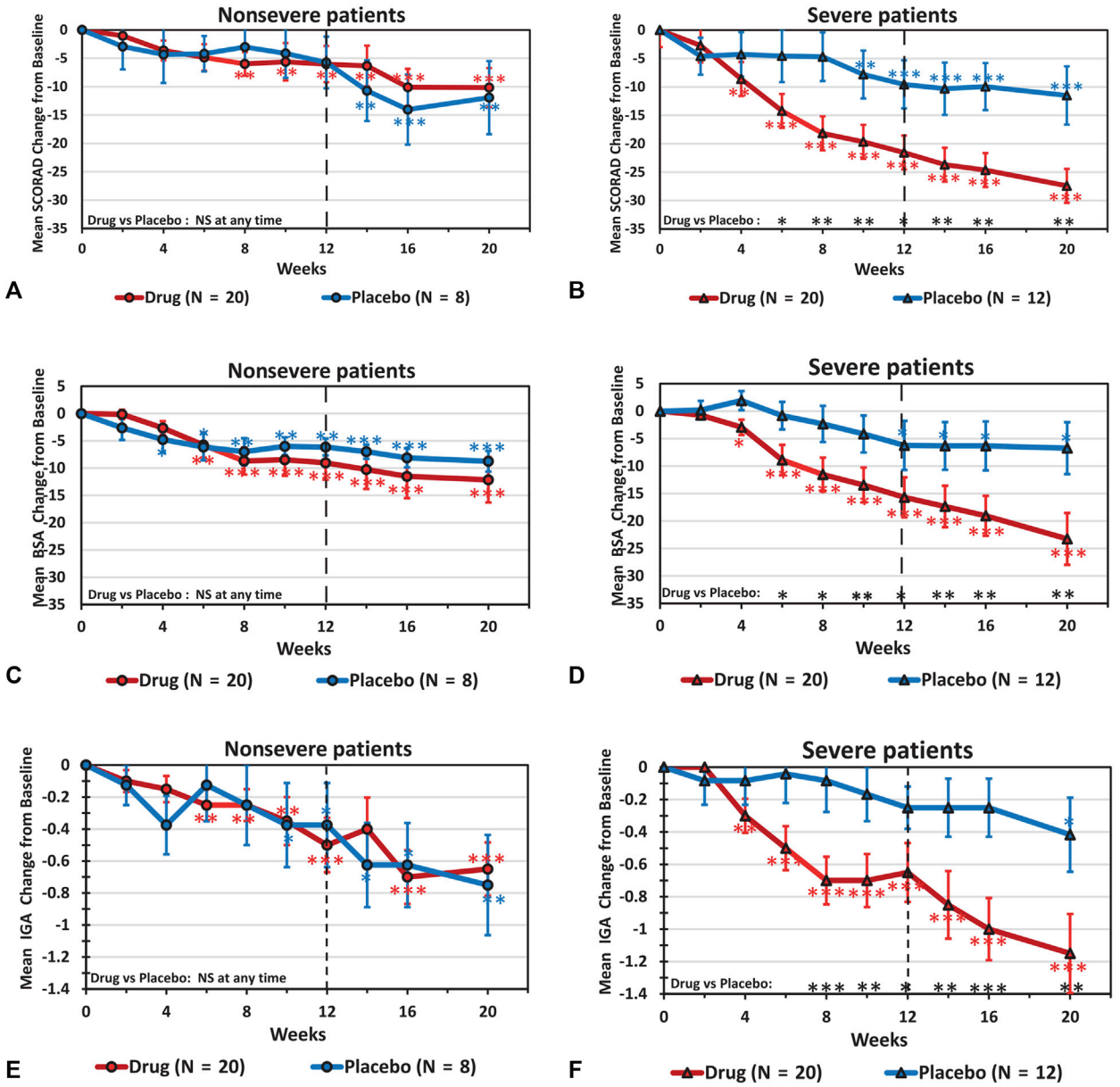


**Fig 3.** Time course of efficacy variables stratified for nonsevere and severe patients. Patients were stratified as having nonsevere (SCORAD <50) or severe (SCORAD ≥50) AD at baseline (week 0). Panels depict the mean ± SEM (standard error of the means) change from baseline for SCORAD (**A** and **B**), BSA (**C** and **D**), and IGA (**E** and **F**). Data was analyzed by mixed-effect model repeated measures. *Red asterisks* and *blue asterisks* by each curve indicate significant change from baseline for each arm; *black asterisks* at the bottom indicate significant differences between drug and placebo arm. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$. *BSA*, Body surface area; *IGA*, Investigator Global Assessment; *NS*, nonsignificant; *SCORAD*, SCOring Atopic Dermatitis.

adverse events, and similar study discontinuation rates between treatment arms. While the recently approved dupilumab, which targets $T_H2$ signaling, shows a good safety profile, a large subset of patients show insufficient responses,[6] and might benefit from treatment directed at an alternative pathway, such as the $T_H22$/IL-22 cytokine pathway.

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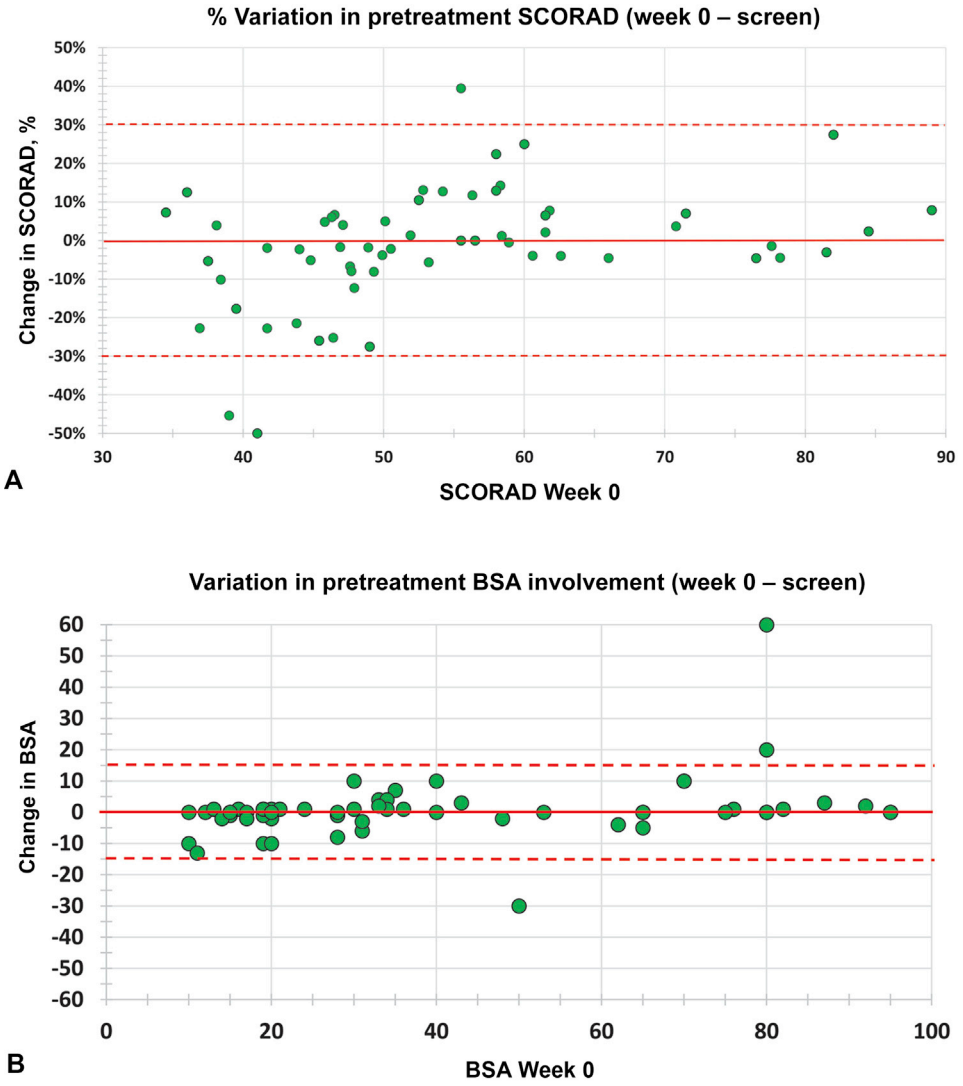
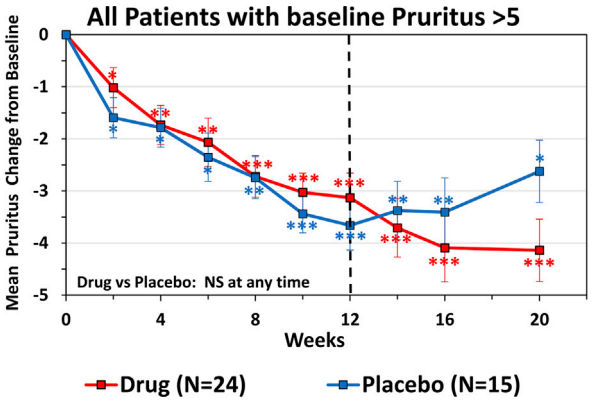
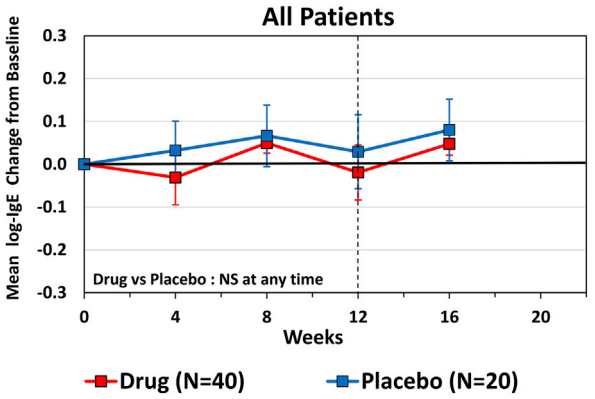



**Supplemental Fig 1.** SCORAD (**A**) and BSA (**B**) pretreatment variation from the screening visit to baseline (week 0). Pretreatment variation for SCORAD and BSA were consistently below 30% and 15, respectively. *BSA*, Body surface area; *SCORAD*, SCOring Atopic Dermatitis.




**Supplemental Fig 2.** Pruritus was assessed as component of SCOring Atopic Dermatitis (SCORAD) and shown for patients with a baseline pruritus >5. Panels depict the mean ± SEM (standard error of the means) change from baseline. Data was analyzed by mixed-effect model repeated measures. *Red asterisks* and *blue asterisks* by each curve indicate significant change from baseline for each arm; significant differences between fezakinumab and placebo arms were not found. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$. *NS*, Not significant.




**Supplemental Fig 3.** Change over time in $\log_{10}$ IgE per treatment arm. No significant change from baseline and no significant difference between the arms was observed. *NS*, Not significant.

**Supplemental Table I.** Adverse events

| Adverse event | Fezakinumab, N (%) | Placebo, N (%) | *P* value* |
|---|---|---|---|
| Upper respiratory infection, viral | 4 (10.00) | 0 (0) | .29 |
| Abscess of right cheek | 1 (2.50) | 0 (0) | 1 |
| Chronic furunculosis | 1 (2.50) | 0 (0) | 1 |
| Delayed wound healing | 1 (2.50) | 0 (0) | 1 |
| Facial cellulitis† | 1 (2.50) | 0 (0) | 1 |
| Headache | 1 (2.50) | 0 (0) | 1 |
| Infection in left eye | 1 (2.50) | 0 (0) | 1 |
| Lethargy after infusion | 1 (2.50) | 0 (0) | 1 |
| Occasional vertigo | 1 (2.50) | 0 (0) | 1 |
| Onychomycosis of bilateral thumbnails | 1 (2.50) | 0 (0) | 1 |
| Pregnancy or abortion† | 1 (2.50) | 0 (0) | 1 |
| Teeth extraction (no infection) | 1 (2.50) | 0 (0) | 1 |
| Tendinitis of left foot | 1 (2.50) | 0 (0) | 1 |
| Worsening of hypothyroidism | 1 (2.50) | 0 (0) | 1 |
| Allergic rhinitis | 0 (0) | 1 (5.00) | .33 |
| Increased blood creatinine | 0 (0) | 1 (5.00) | .33 |
| Headache | 0 (0) | 1 (5.00) | .33 |
| Hyperkalemia | 0 (0) | 1 (5.00) | .33 |
| Lesion right knee | 0 (0) | 1 (5.00) | .33 |
| Moderate nausea | 1 (2.50) | 2 (5.00) | .26 |
| Skin Infection | 0 (0) | 1 (5.00) | .33 |
| Vomiting | 0 (0) | 1 (5.00) | .33 |
| Worsening of hypertension | 0 (0) | 1 (5.00) | .33 |
| **Total** | **18 (35.00)** | **10 (40.00)** | **.78** |

Total is in bold.

*The differences of the proportions of each adverse event and the aggregated value were tested by using Fisher's exact test.

†A serious adverse event was defined as an event that was fatal or life threatening, required or prolonged hospitalization, caused persistent or substantial disability or incapacity, a congenital anomaly or birth defect, or an event that was considered by the investigator to be a medically important event.

**Supplemental Table II.** Per-protocol responses at week 12 and 20 end points in all study populations, by arm, by severity at baseline

| | All patients, N = 53 | | | Severe, baseline SCORAD ≥50, N = 29* | | | Nonsevere, baseline SCORAD <50, N = 24 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Response** | **Drug, N = 36** | **Placebo, N = 17** | ***P* value**[†] | **Drug, N = 18** | **Placebo, N = 11** | ***P* value**[†] | **Drug, N = 18** | **Placebo, N = 6** | ***P* value**[†] |
| SCORAD decline, mean ± SEM | | | | | | | | | |
| Week 12 | −14.8 ± 2.9 | −11.1 ± 2.9 | NS | −22.9 ± 4.0 | −12.1 ± 3.7 | .058 | −6.7 ± 3.4 | −9.3 ± 5.2 | NS |
| Week 20 | −20.3 ± 3.1 | −15.4 ± 3.9 | NS | −29.4 ± 4.0 | −14.2 ± 4.8 | **.023** | −11.3 ± 3.6 | −17.6 ± 7.1 | NS |
| SCORAD % improvement, mean ± SEM | | | | | | | | | |
| Week 12 | −26.2 ± 5.3 | −20.4 ± 5.7 | NS | −36.9 ± 6.5 | −20.0 ± 6.8 | .083 | −15.5 ± 7.9 | −21.1 ± 11.5 | NS |
| Week 20 | −37.0 ± 5.6 | −30.0 ± 7.4 | NS | −47.5 ± 6.7 | −25.2 ± 8.2 | **.047** | −26.5 ± 8.5 | −39.0 ± 14.9 | NS |
| SCORAD30, %[‡] | | | | | | | | | |
| Week 12 | 47.2 | 23.5 | NS | 61.1 | 18.2 | .052 | 33.3 | 33.3 | NS |
| Week 20 | 58.3 | 35.3 | NS | 72.2 | 18.2 | **.008** | 44.4 | 66.7 | NS |
| SCORAD50, %[§] | | | | | | | | | |
| Week 12 | 25.0 | 17.6 | NS | 33.3 | 18.2 | NS | 16.7 | 16.7 | NS |
| Week 20 | 41.7 | 29.4 | NS | 50.0 | 18.2 | NS | 33.3 | 50.0 | NS |
| Decline in BSA involvement, mean ± SEM | | | | | | | | | |
| Week 12 | −14.3 ± 2.5 | −7.9 ± 2.9 | .100 | −18.0 ± 3.6 | −8.2 ± 4.4 | .100 | −10.5 ± 3.2 | −7.5 ± 1.6 | NS |
| Week 20 | −20.2 ± 3.3 | −9.5 ± 3.0 | **.022** | −26.4 ± 4.7 | −8.7 ± 4.7 | **.013** | −14.0 ± 4.3 | −11.0 ± 1.5 | NS |
| Proportion of patients (%) with a decline in BSA involvement >15[‖] | | | | | | | | | |
| Week 12 | 41.7 | 11.8 | .056 | 50.0 | 18.2 | .125 | 33.3 | 0 | NS |
| Week 20 | 47.2 | 11.8 | **.015** | 61.1 | 18.2 | .052 | 33.3 | 0 | NS |
| IGA decline, mean ± SEM | | | | | | | | | |
| Week 12 | −0.6 ± 0.1 | −0.4 ± 0.1 | NS | −0.7 ± 0.2 | −0.3 ± 0.1 | .072 | −0.5 ± 0.2 | −0.5 ± 0.3 | NS |
| Week 20 | −1.0 ± 0.2 | −0.6 ± 0.2 | NS | −1.3 ± 0.3 | −0.5 ± 0.2 | **.028** | −0.7 ± 0.2 | −1.0 ± 0.4 | NS |
| IGA % complete response[¶] | | | | | | | | | |
| Week 12 | 16.7 | 5.9 | NS | 22.2 | 0 | NS | 11.1 | 16.7 | NS |
| Week 20 | 27.8 | 17.6 | NS | 38.9 | 9.1 | .110 | 16.7 | 33.3 | NS |

*BSA*, Body surface area; *IGA*, Investigator Global Assessment; *NS*, nonsignificant; *SCORAD*, SCOring Atopic Dermatitis; *SEM*, standard error of the mean.

*Severe patients are defined as patients with SCORAD ≥50 at week 0.

[†]Statistical significance of difference in mean decline between study arms was assessed by *t* test; statistical significance of difference in % response between study arms was assessed by Fisher's exact test; statistical significance of mean decline per visit compared with baseline was assessed by paired *t* test; significant results ($P < .05$) are in bold; *P* values > 0.1 were noted as NS.

[‡]SCORAD30 is defined as SCORAD improvement >30% from week 0 and was selected because it was the 95th percentile of pretreatment variation.

[§]SCORAD50 is defined as SCORAD improvement >50% compared with week 0.

[‖]The decline in BSA involvement threshold of 15 points was selected because it was the 95th percentile of pretreatment variation.

[¶]IGA complete response is defined as IGA ≤1 or an IGA decline of ≥2.

**Supplemental Table III.** Single variate and multivariate linear regression analysis of the primary end point, SCORAD decline at week 12 of treatment

| | Linear regression analysis, N = 60 | | | |
|---|---|---|---|---|
| | Single variable | Multivariable | | |
| Variable | *P* value | *P* value | B | 95% CI |
| Treatment arm | .062 | NS | — | — |
| Severity at baseline | .005 | NS | — | — |
| Severity * arm | — | .001 | 15.84 | 8.4 to 23.3 |
| Sex | NS | .080 | — | — |
| Age | .032 | .015 | −0.29 | −0.06 to −0.52 |
| AD duration | NS | NS | — | — |
| Race | NS | NS | — | — |
| Body mass index | NS | NS | — | — |
| IgE at baseline | NS | NS | — | — |

Linear regression was performed with the backward method using F probability of 0.05 for entry and 0.1 for removal.
*AD*, Atopic dermatitis; *B*, linear regression association factor; *CI*, confidence interval; *NS*, nonsignificant; *SCORAD*, SCOring Atopic Dermatitis.