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Efficacy and safety of fezakinumab (an anti-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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83 **Abbreviation list**

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85	AD	Atopic dermatitis
86	BSA	Body surface area
87	BMI	Body mass index
88	EASI	Eczema Area and Severity Index
89	IGA	Investigator Global Assessment
90	ITT	Intention to treat
91	MMRM	Mixed-effect model repeated measures
92	NRS	Numerical Rating Scale
93	SCORAD	Scoring Atopic Dermatitis
94	Wks	Weeks

95

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Abstract**Background**

IL-22 promotes epidermal hyperplasia and inhibits skin barrier function.

Objective

Evaluate IL-22 blockade in adults with moderate-to-severe atopic dermatitis (AD).

Methods

Randomized, double-blind, placebo-controlled trial with intravenous fezakinumab monotherapy every 2wks for 10wks, with follow-up assessments until 20wks. SCORAD change from baseline at 12wks served as primary endpoint.

Results

At 12wks, mean SCORAD decline was 13.8 ± 2.7 (fezakinumab) vs. 8.0 ± 3.1 (placebo) for the entire population ($p=0.134$). In severe patients (baseline $\text{SCORAD} \geq 50$), SCORAD decline was significantly stronger in drug vs. placebo at 12wks (21.6 ± 3.8 vs. 9.6 ± 4.2 , $p=0.029$) and 20wks (27.4 ± 3.9 vs. 11.5 ± 5.1 , $p=0.010$). At 12wks, improvements were significantly stronger in drug vs. placebo ($12.4\% \pm 2.4$ vs. $6.2\% \pm 2.7$; $p=0.009$) for BSA in the entire population, and for IGA in severe patients (0.7 ± 0.2 vs. 0.3 ± 0.1 ; $p=0.034$). All scores showed progressive improvements after last dosing (10wks) until end of study (20wks). Common adverse events were upper respiratory tract infections.

Limitations

Limited sample size, lack of EASI and numerical rating scale (NRS) pruritus assessments; significance primarily obtained in severe AD.

Conclusion

Fezakinumab was well-tolerated, with sustained clinical improvements after last drug dosing.

Capsule summary

- 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/AD.
- IL-22/Th22 targeting potentially offers a novel alternative for severe AD patients with limited therapeutic options.

Introduction

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 (approximately 20% of adult patients),³ the disease often affects large body surface areas, leading to profound effects on patients' quality of life.⁴ 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 are largely not FDA-approved for AD (cyclosporine A, azathioprine, mycophenolate-mofetil, methotrexate), with the exception of the recently approved anti-IL-4R α monoclonal antibody, dupilumab, inhibiting both Th2 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 Th2 and Th22 T-cell pathways. *In vitro* and animal studies suggest that IL-22, the lead Th22 cytokine, promotes hyperplasia and inhibits keratinocyte differentiation and skin barrier formation, two hallmarks of AD.⁸⁻¹³ High levels of IL-22-producing T-cells have also been identified in psoriasis, particularly in

161 children.¹⁴ To assess a possible role for IL-22 as a driver cytokine of AD, similar
162 to the established pathogenic role of Th2 cytokines,^{6,15,16} we investigated the IL-
163 22 antagonist, fezakinumab (ILV-094), in an investigator-initiated clinical trial.
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Methods

Study design and oversight

We conducted a phase 2a, randomized, double-blind, placebo-controlled, multi-center clinical trial to evaluate efficacy and safety of fezakinumab in 60 moderate-to-severe AD patients (clinicaltrials.gov #NCT01941537) at the Icahn School of Medicine at Mount Sinai (n=40), and The Rockefeller University (n=20), both in New York City. Patients were randomly assigned to either intravenous fezakinumab or placebo (2:1 drug and placebo randomization, respectively, Figure 1), with a loading dose of 600mg at baseline (day 0), followed by 300mg 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 (see Supplementary Material) of this investigator-initiated trial was developed by the investigators, and has been approved by the local institutional review boards.

Patients

Eligible patients were 18-75 years old, with moderate-to-severe AD for ≥ 6 months, as defined by SCORAD ≥ 30 (SCORing of Atopic Dermatitis), and IGA ≥ 3 (Investigator Global Assessment on a 0 to 5 scale for “clear-0” to “very severe-5”) (Table 1). Patients had to fail or not sustain response with one or more conventional treatments, including topical corticosteroids or calcineurin

antagonists, and/or systemic treatments (corticosteroids, phototherapy, cyclosporine, or other immunomodulators). Disease duration was ≥ 6 months. All patients gave written informed consent prior to inclusion.

Efficacy evaluations

The primary efficacy variable was the change from baseline at week 12 in the AD clinical severity index (SCORAD). The SCORAD combines objective assessments of the extent of body-surface area (BSA) involvement in AD, the severity of erythema, edema/papulation, oozing/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 endpoints included proportion of patients achieving SCORAD improvements of at least 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 ≥ 2 in IGA. See Supplementary Material for further information.

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 non-responders. 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-by-visit and treatment-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 (PP) analysis, where only patients who completed 12 weeks of treatment were included in the analysis (See Supplementary Material). The thresholds of 30% improvement in SCORAD (SCORAD30) and 15 point decline in BSA 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-%-improvement and BSA-decline, and are thus objective indicators of meaningful response (see Supplementary Material). Multivariate analyses of the primary efficacy variable was performed by linear regression for SCORAD decline, with the backward-conditional method, including the co-variables: treatment arm, baseline severity, gender, age, race, BMI, AD duration, baseline IgE, and the combinations of these factors with treatment-arm. Statistical significance was set at a two-tailed p -value <0.05 .

Role of the funding source

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234 decision to submit the manuscript for publication, and vouched for the
235 completeness and accuracy of the data and analyses and the fidelity of the study
236 to the protocol.
237

Results

Patients

Enrollment and disposition of the patients are shown in Figure 1. The first patient was screened on March 4, 2014, and the entire study was concluded on February 29, 2016. 67 patients were assessed for eligibility, and 60 patients were randomized 2:1 to either fezakinumab (n=40) or placebo (n=20). Demographic and clinical characteristics of the patients at baseline were similar between the study arms (Table 1). Comparable numbers of moderate ($30 \leq \text{SCORAD} < 50$) and severe ($\text{SCORAD} \geq 50$)¹⁸ AD patients at baseline were randomized in both drug and placebo arms. 36 and 17 patients completed treatment and reached the primary endpoint (week 12), and 36 and 16 patients completed the study until week 20 in the fezakinumab and placebo groups, respectively (Figure 1). Two patients discontinued treatment due to serious adverse events, which were deemed non-related to the drug (facial cellulitis after a dental procedure; pregnancy with elective termination, Table 2 and Supplementary Table S1). One patient in the drug-arm was lost to follow-up, and 4 patients discontinued due to lack of efficacy (n=1 in drug-arm, and n=3 in placebo-arm). One patient in the placebo-arm discontinued early (week 2) due to time restraints (Figure 1). All randomized patients were included in the intention-to-treat (ITT) population.

Efficacy

Efficacy endpoints analyzed using a mixed effect model repeated measures (MMRM) approach on the ITT population are listed in Table 3. Similar significance values were also obtained with the per-protocol population (Supplementary Table S2), 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 (Figure 2A), a difference that reached statistical significance between drug and placebo at weeks 6-10 ($p < 0.05$). Differences between drug and placebo extended beyond the last dose (week 10), with non-significant mean $\pm$ SEM SCORAD reductions of 13.8 ± 2.7 in fezakinumab vs. 8.0 ± 3.1 in placebo ($p = 0.134$) at week 12 (primary endpoint), and progressive reductions seen between weeks 14-20, with significant difference between drug and placebo observed at week 20 (end of study) of 18.8 ± 2.9 vs. 11.7 ± 3.9 ($p = 0.049$), respectively (Figure 2A, Table 3). While higher SCORAD50, and SCORAD30 responses were seen with drug vs. placebo, these were not statistically significant (secondary endpoint; Table 3). While SCORAD comprises both objective and subjective measures (sleep loss and pruritus), BSA is an objective measure. The mean decline in BSA was consistently stronger in the drug group, and was significantly different from placebo from week 8 until the end of study, including at week 12 ($p = 0.009$, Figure 2B, Table 3). Similarly, a BSA decline >15 , as defined by less than 15 point pre-treatment variation in BSA between baseline and screening (Supplementary Figure S2B), was present at significantly higher rates in drug vs. placebo arm (Table 3). Also, mean improvements in IGA scores compared to

baseline were stronger and earlier with fezakinumab treatment (Figure 2C), significantly different from placebo at week 16 ($p<0.001$). Higher, but not significant IGA complete response rate (standardly defined as an IGA score of 0 or 1 or IGA decline ≥ 2 after treatment) were seen in drug vs. placebo-treated patients at week 12 ($p=0.119$; Table 3). While no significant difference was detected in SCORAD pruritus scores between 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 non-significant exacerbations in placebo treated patients (Supplementary Figure S1).

In a multivariate linear regression analysis considering all relevant baseline factors (treatment arm, severity, race, gender, age, AD duration, BMI, IgE) the combined factor of severity and treatment arm gave the highest ($B=15.84$) and most significant ($p<0.001$) association with SCORAD decline at the primary endpoint week 12 (Supplementary Table S3). 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 from week 6 to 20 (green stars in Figure 2A), and parallel significant effects on mean BSA change (green stars in Figure 2B), as well as mean IGA change (green stars in Figure 2C) from baseline.

Since severity showed the highest association with treatment response, we further stratified patients according to their baseline disease severity, into moderate ($SCORAD<50$) and severe ($SCORAD\geq 50$) AD. There was a strong drug effect on SCORAD decline in severe patients (Figure 3B, Table 3), which was significantly stronger than in placebo starting at week 6, including at the

primary endpoint at week 12 (21.6 ± 3.8 vs. 9.6 ± 4.2 ; $p=0.029$), an effect that continued until week 20 (27.4 ± 3.9 vs. 11.5 ± 5.1 ; $p=0.010$; Figure 3B, Table 3). SCORAD50 responses were higher in severe drug vs. placebo group but did not show statistical significance (45% vs. 16.7% at week 20; $p=0.139$; Table 3). SCORAD30 responses at end of study (week 20) were significantly higher in severe drug vs. placebo patients (65.5% vs. 16.7%, $p=0.012$), but not significant at week 12 (55% vs. 16.7%, $p=0.062$; Table 3). The threshold of SCORAD30 was derived from less than 30% variation in pre-treatment SCORAD values between screening and baseline (Supplementary Figure S2A). BSA decline showed stronger, significant improvements in severe patients treated with drug vs. placebo; $p=0.011$ at week 12; Figures 3C-3D, Table 3). IGA improvement was stronger in fezakinumab treated severe patients compared to placebo, with significant differences between treatment arms at weeks 8, 10, 12, 14, 16 and 20 ($p=0.034$ and $p=0.014$ at weeks 12 and 20, respectively; Figure 3F, Table 3). None of the efficacy variables showed statistically significant difference between drug and placebo arms in non-severe (moderate) AD patients (Figures 3A,C,E; Table 3). Overall, lower declines in SCORAD, BSA and IGA were observed in drug-treated moderate patients as compared to severe patients, with larger declines in the placebo-treated moderate as compared to placebo severe patients.

Safety

Adverse events occurred with a similar frequency in fezakinumab and placebo groups (Table 2, Supplementary Table S1). All except one adverse event (facial cellulitis) were deemed mild or moderate in severity. 2 serious adverse events occurred in the drug arm (facial cellulitis after dental procedure, and pregnancy), but were deemed as likely unrelated to drug. 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, that were not significantly different between arms.

Blood biomarkers

There were neither significant changes over-time per arm nor differences between groups in total serum IgE levels changes during treatment and follow-up (Supplementary Figure S3).

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 to placebo. At week 12, significant clinical improvements in drug-treated compared to placebo-treated patients were best seen in severe patients (baseline SCORAD $\geq$ 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 Th2 cytokines IL-4 and IL-13,^{6,7,15,16} IL-22 is a key driver of AD. Whereas current monoclonal antibody treatment approaches, either approved or currently tested in trials, target the Th2 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 may have a role, such as pediatric psoriasis¹⁴ 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 due to higher variability in this group, and inability to obtain maximal differences due to lower baseline disease, whereas the severe patients started with higher 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: 1) It was designed >6 years ago, and only utilized SCORAD to measure disease severity, similar to many studies at the time,¹⁷ while current AD trials often use EASI scores as primary outcomes, limiting the ability to compare to other clinical trials. Nevertheless, recent studies considered both measures, and in these SCORAD appears to be a more stringent disease measure, and changes in EASI scores tend to be much larger than respective SCORAD changes.^{6,7} 2) It was designed prior to 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 employed a post-hoc analysis approach separating severe from moderate patients. Larger studies are needed to compare to other treatments, and to confirm efficacy in AD subgroups (moderate vs. severe, different ethnicities, etc.).

This study, supported by progressive clinical improvements with IL-22 antagonism versus placebo, opens 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 adverse events, and similar study discontinuation rates between treatment arms. While the recently approved dupilumab, that targets Th2 signaling, shows a good safety profile, a large subset of patients show insufficient

389 responses,⁶ and may benefit from treatment directed at an alternative pathway
390 such as the Th22/IL-22 cytokine pathway.

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Figure legends

Figure 1. Patient disposition. *SAE – Serious adverse event; ITT – intention to treat.*

Figure 2. Time course of efficacy variables in the 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 $\pm$ SEM change from baseline. Data was analyzed by MMRM: red and blue asterisks by each curve indicate significant change from baseline for each arm (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$); black asterisks at the bottom indicate significant differences between drug and placebo arm; green asterisks indicate the significance of the combined factor: baseline severity and treatment arm.

Figure 3. Time course of efficacy variables stratified for moderate and severe patients.

Patients were stratified as having moderate (SCORAD between 25 and 50) or severe (SCORAD ≥ 50) AD at baseline (week 0). Panels depict the mean $\pm$ SEM change from baseline for SCORAD (A, B), BSA (C, D), and IGA (E, F). Data was analyzed by MMRM: red and blue asterisks by each curve indicate significant change from baseline for each arm (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$); black asterisks at the bottom indicate significant differences between drug and placebo arm.

Table 1. Demographic and clinical characteristics of the participants at baseline.

	PLACEBO	DRUG	P-VALUE†
	n= 20	n= 40	
Age (mean, SD)	41·3 (16·3)	40·5 (14·9)	0·855
BMI (mean, SD)¶	27·4 (6·4)	27·7 (5·9)	0·866
Gender (n,%)			0·360
Female	11 (55·0%)	17 (42·5%)	
Male	9 (45·0%)	23 (57·5%)	
Race (n, %)			0·51
Asian	5 (25%)	10 (25%)	
African American	10 (50%)	14 (35%)	
Caucasian	5 (25%)	16 (40%)	
IgE Group (n,%)*			0·620
Intrinsic	4 (20%)	6 (15%)	
Extrinsic	16 (80%)	34 (85%)	
Total serum IgE, kU/L (mean, SD)	6,592 (9,720)	3,646 (4,561)	0·638
SCORAD (mean, SD)§	55·5 (13·4)	53·4 (13·1)	0·568
SCORAD (range)	34·5-89	36-84·5	
SCORAD <50 (n,%)	8 (40%)	20 (50%)	0·46
SCORAD ≥50 (n,%)	12 (60%)	20 (50%)	
IGA (n, %)#			0·66
Moderate (3)	15	32	
Severe (4)	5	7	
Very severe (5)	0	1	
BSA (mean, SD)\$	38·15 (24·26)	42·68 (27·7)	0·52
HISTORY OF ASTHMA (n,%) ‡			0·89
As child only	4 (20%)	6 (15%)	

No	10 (50%)	22 (55%)	
Yes	6 (30%)	12 (30%)	

Data are given as mean $\pm$ SD (standard deviation) or as percentage (%). ¶ Body mass index (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 <200kU/L or >200kU/L, respectively. § Scores on the SCORAD (SCORing Atopic Dermatitis) range from 0 to 103, with higher scores indicating greater severity; non-severe and severe disease was scored as SCORAD<50 and SCORAD $\geq$ 50, respectively. # The Investigator's Global Assessment (IGA) of the severity of atopic dermatitis was scored on a scale of 0 (clear) to 5 (very severe); \$ Body surface area (BSA) was graded from 0 (no skin involvement) to 100% (total skin involvement); ‡ History of asthma as per patient history. †For numerical variables (Age, BMI, SCORAD, BSA, total serum IgE), differences between the means by treatment were tested using a two-tailed Student's t-test for independent samples. The proportions by treatment for categorical variables (gender, race, IgE group, SCORAD50, IGA, History of Asthma) were compared using a Fisher's exact test.

Table 2. Adverse events.

Variable		Fezakinumab	Placebo	P-value ^{\$}
		N=40	N=20	
No. of adverse events		18	10	
Severity	Mild	9	6	
	Moderate	8	3	
	Severe	1	0	
Mean no. of adverse events per patient		0.45	0.5	0.82
Any adverse event—no. of patients (%)		14 (35%)	8 (40%)	0.78
Serious adverse event*—no. of patients (%)		2 (5%)**	0	0.55
Study discontinuation due to adverse event—no. of patients (%)		2 (5%)	0	0.55
Common adverse events: ‡				
Upper respiratory infection, viral—no. of patients (%)		4 (10%)	0	0.29

Table 2. Adverse events. *A serious adverse event was defined as an event that was fatal or life threatening, required or prolonged hospitalization, or caused persistent or substantial disability or incapacity or 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. \$The differences of the proportions were tested using a Fisher's exact test.

Table 3. Efficacy end points by ITT (MMRM) analysis.

	All patients (N=60)			Severe AD (Baseline SCORAD $\geq$ 50) (N=32) ^(a)			Non-Severe AD (Baseline SCORAD<50) (N=28) ^(a)		
	Drug (N=40)	Placebo (N=20)	p- value	Drug (N=20)	Placebo (N=12)	p- value	Drug (N=20)	Placebo (N=8)	p- value
<u>SCORAD Decline (Mean $\pm$SEM)</u>									
Week 12	-13.8 $\pm$ 2.7	-8.0 $\pm$ 3.1	0.134	<u>-21.6 $\pm$3.8</u>	<u>-9.6 $\pm$4.2</u>	<u>0.029</u>	-6.0 $\pm$ 3.2	-5.7 $\pm$ 4.6	0.764
Week 20	<u>-18.8 $\pm$2.9</u>	<u>-11.7 $\pm$3.9</u>	<u>0.049</u>	<u>-27.4 $\pm$3.9</u>	<u>-11.5 $\pm$5.1</u>	<u>0.010</u>	-10.2 $\pm$ 3.4	-11.9 $\pm$ 6.4	0.639
<u>SCORAD Improvement (Mean $\pm$SEM)</u>									
Week 12	-24.4% $\pm$ 5.0%	-14.7% $\pm$ 5.9%	0.175	<u>-34.4% $\pm$6.1%</u>	<u>-15.8% $\pm$7.4%</u>	<u>0.039</u>	-14.3% $\pm$ 7.4%	-13.1% $\pm$ 10.1%	0.897
Week 20	-34.1% $\pm$ 5.4%	-23.0% $\pm$ 7.4%	0.072	<u>-43.9% $\pm$6.6%</u>	<u>-20.6% $\pm$8.8%</u>	<u>0.028</u>	-24.2% $\pm$ 8.0%	-26.6% $\pm$ 13.8%	0.794
<u>SCORAD30^(b)</u>									
Week 12	42.5%	20.0%	0.150	55.0%	16.7%	0.062	30.0%	25.0%	1.000
Week 20	52.5%	30.0%	0.168	<u>65.0%</u>	<u>16.7%</u>	<u>0.012</u>	40.0%	50.0%	0.691
<u>SCORAD50^(c)</u>									
Week 12	22.5%	15.0%	0.734	30.0%	16.7%	0.676	15.0%	25.0%	1.000
Week 20	37.5%	25.0%	0.395	45.0%	16.7%	0.139	30.0%	37.5%	1.000
<u>BSA Decline (Mean $\pm$SEM)</u>									
Week 12	<u>-12.4 $\pm$2.4</u>	<u>-6.2 $\pm$2.7</u>	<u>0.009</u>	<u>-15.7 $\pm$3.6</u>	<u>-6.3 $\pm$4.5</u>	<u>0.011</u>	-9.0 $\pm$ 3.1	-6.1 $\pm$ 1.6	0.347
Week 20	<u>-17.7 $\pm$3.2</u>	<u>-7.6 $\pm$2.9</u>	<u>0.001</u>	<u>-23.3 $\pm$4.7</u>	<u>-6.8 $\pm$4.7</u>	<u>0.009</u>	-12.2 $\pm$ 4.2	-8.8 $\pm$ 1.9	0.357

BSA Decline > 15^(d)									
Week 12	37.5%	10.0%	0.034	45.0%	16.7%	0.139	30.0%	0.0%	0.141
Week 20	42.5%	10.0%	0.017	55.0%	16.7%	0.062	30.0%	0.0%	0.141
IGA Decline (Mean ±SEM)									
Week 12	-0.6 ±0.1	-0.3 ±0.1	0.119	-0.7 ±0.2	-0.3 ±0.1	0.034	-0.5 ±0.2	-0.4 ±0.3	0.684
Week 20	-0.9 ±0.2	-0.6 ±0.2	0.127	-1.2 ±0.2	-0.4 ±0.2	0.014	-0.7 ±0.2	-0.8 ±0.3	0.724
IGA Complete Response^(e)									
Week 12	15.0%	5.0%	0.407	20.0%	0.0%	0.271	10.0%	12.5%	1.000
Week 20	25.0%	15.0%	0.513	35.0%	8.3%	0.204	15.0%	25.0%	0.606

Table 3. Summary of responses by treatment arm at primary endpoint (week 12), and at end of study (week 20). Statistical significance of difference in mean decline between treatment arms was assessed by MMRM. Statistical significance of difference in % response between treatment arms was assessed by Fisher's exact test. Significant results ($p \leq 0.05$) are in bold.

(a) Severe patients are defined as patients with a SCORAD ≥ 50 at week 0. (b) SCORAD30 is defined as SCORAD improvement >30% compared to week 0; a 30% threshold was selected because it is the 95% percentile of pre-treatment variation. (c) SCORAD50 is defined as SCORAD improvement >50% compared to week 0. (d) BSA (body surface area) decline threshold of 15 points was selected because it is the 95% percentile of pre-treatment variation. (e) IGA (Investigator Global Assessment) complete response is defined as IGA ≤ 1 or IGA decline ≥ 2 at the respective end-point.

Figure 1

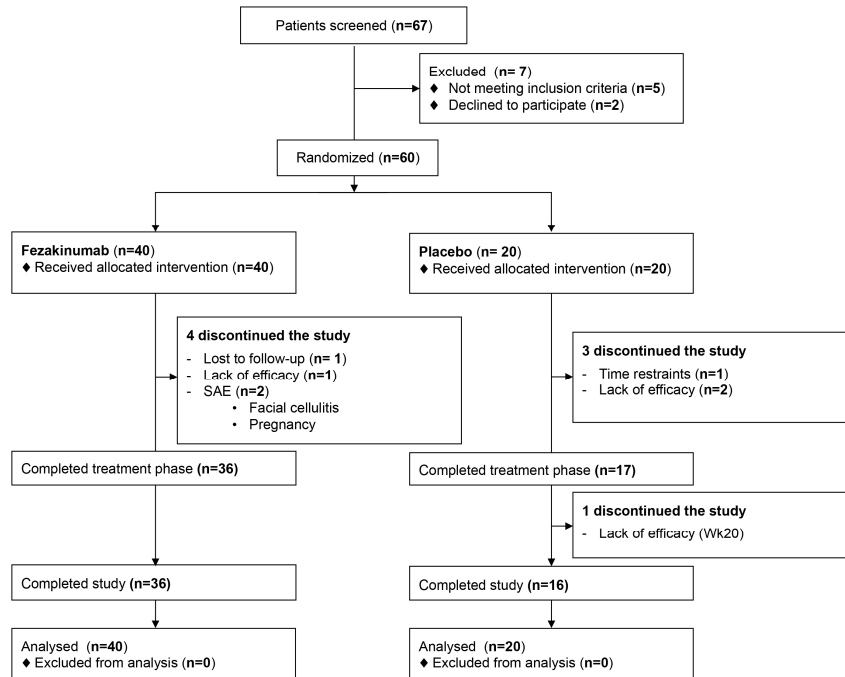
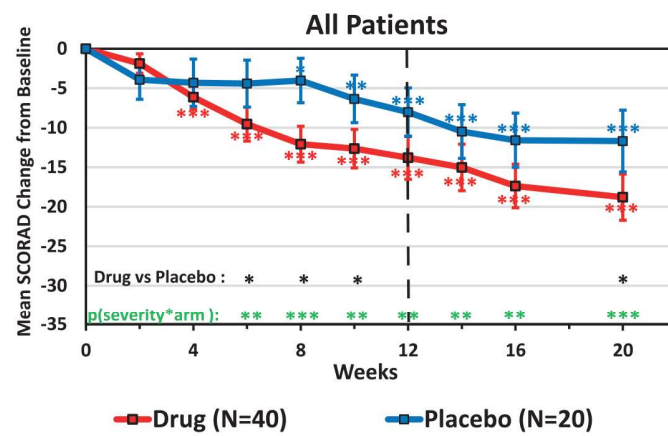
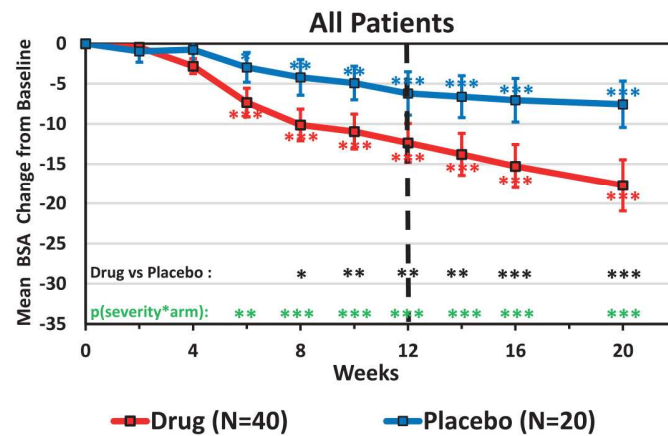


Figure 2

A



B



C

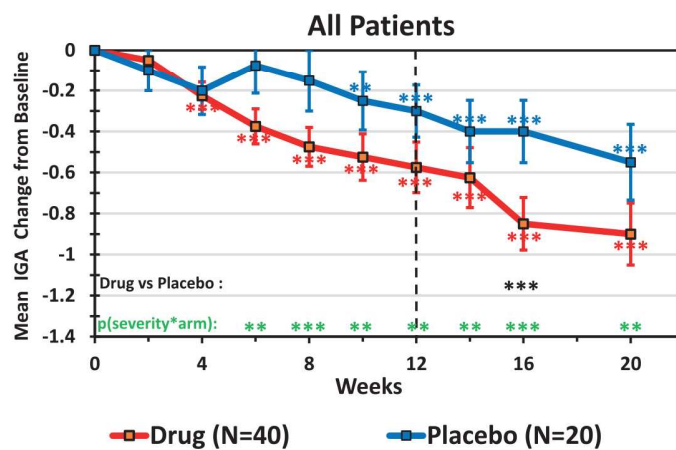
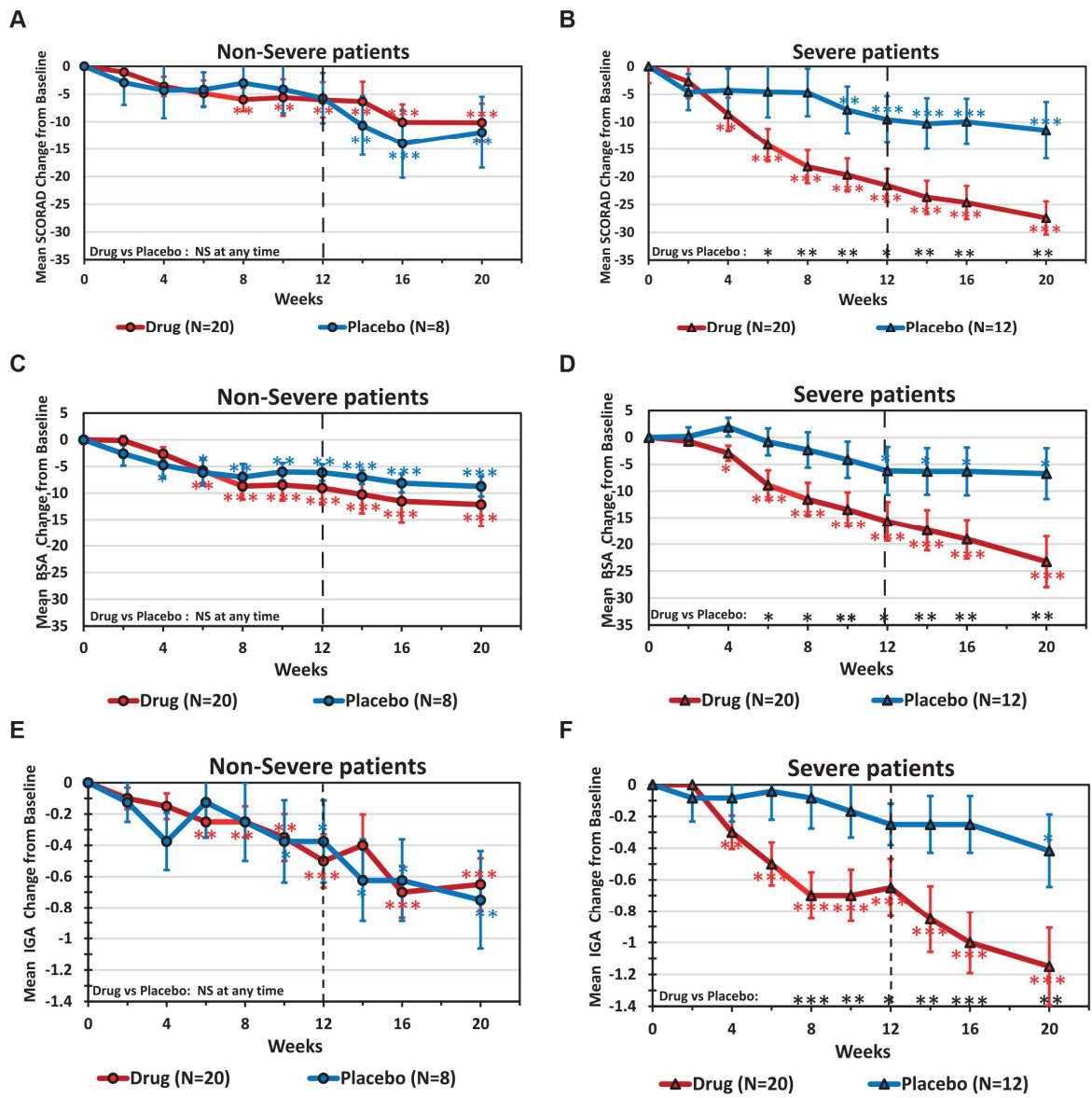


Figure 3



Supplementary Appendix

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

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Study Number

The study was funded by the National Institutes of Health/NIAMS, project # 5UM1AR063917; ClinicalTrials.gov number NCT01941537;

Additional Methods

RNA extraction, microarray, and Real Time PCR (RT-PCR) analysis: Skin biopsies from lesional and non-lesional skin at baseline, week 4 and week 12 were stored in RNA^{later}® (Invitrogen) until further processing. RNA was extracted (Covance Genomics Lab) and Affymetrix Human U133Plus 2.0 arrays (Affymetrix, Santa Clara, CA) were used as previously described.¹ Quality control of Affymetrix chips was done using standard QC metrics and R packages.

Microarray quality control images were scrutinized for spatial artifacts using Harshlight.² Expression measures were obtained using GC Robust Multi-array Average (GCRMA) algorithm.³ Batch effects corresponding to the hybridization date and chip lot number were detected by principal component analyses and adjusted using ComBat algorithm⁴ from R's sva package. Probe sets with expression >3 in at least 15 samples were used for further analyses. Gene expression changes were modeled using mixed-effect models, with treatment, time and tissue type as a fixed interaction term, and a random effect for each patient. Fold changes (FCHs) for the comparisons of interest were estimated, and hypothesis testing was conducted with contrasts under the general framework of linear models in the R limma package.⁵ P-values were adjusted for multiple hypotheses using the Benjamini-Hochberg procedure, which controls the false discovery rate (FDR).

Biomarker evaluation: Total serum IgE was measured using the ImmunoCAP assay (Thermo Fisher Scientific).

Disease Assessments

SCORing Atopic Dermatitis (SCORAD): SCORAD measures activity of disease based on five clinical characteristics and two patient-reported subjective symptoms.⁶ Patient-reported symptoms are pruritus and sleep loss, which are measured by a visual analogue scale. Clinical characteristics include erythema, edema/population, oozing/crusts, excoriation, and lichenification, which are assessed by a clinician. The score range is 0-103, with higher scores indicating greater severity. The minimal clinically important difference in SCORAD has been reported to be an 8.7-point change.⁷

Investigator Global Assessment (IGA): The IGA is a clinician-evaluated measure of overall disease severity at the time of assessment. The severity of disease is rated on a 6-point scale, namely 0=clear, 1=almost clear, 2=mild disease, 3=moderate disease, 4=severe disease and 5=very severe disease. Severity is evaluated based on the entirety of erythema, infiltration, population, oozing and crusting. IGA, however has not been validated.⁸

Body Surface Area (BSA): The BSA that is affected by atopic dermatitis is assessed for each major section of the body (head, trunk, arms, and legs) and reported as a percentage of all major body sections combined.

Pruritus. Pruritus was measured as part of SCORAD using a visual analogue scale 0-10, with 0 indicating no itch, and 10 indicating the worst possible itch.

Supplementary Figure Legends

Figure S1. Pruritus was assessed as component of SCORAD and shown for patients with a baseline pruritus >5 . Panels depict the mean $\pm$ SEM change from baseline. Data was analyzed by MMRM: red and blue asterisks by each curve indicate significant change from baseline for each arm (* $p<0.05$, ** $p<0.01$, *** $p<0.001$); there were no significant (NS) differences between fezakinumab and placebo arms.

Figure S2. SCORAD (A) and BSA (B) pre-treatment variation from the screening visit to baseline (week 0). Pre-treatment variation for SCORAD and BSA were consistently below 30% and 15%, respectively.

Figure S3. Change over time in $\log(10)$ IgE per treatment arm. No significant change from baseline, nor a significant difference between the arms, was observed.

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Table S1. Adverse events

ADVERSE EVENT	FEZAKINUMAB (N, %)^{\$}	PLACEBO (N, %)^{\$}	P-value[‡]
Upper respiratory infection, viral	4 (10.00)	0 (0.00)	0.29
Abscess of right cheek	1 (2.50)	0 (0.00)	1
Chronic furunculosis	1 (2.50)	0 (0.00)	1
Delayed wound healing	1 (2.50)	0 (0.00)	1
Facial cellulitis*	1 (2.50)	0 (0.00)	1
Headache	1 (2.50)	0 (0.00)	1
Infection in left eye	1 (2.50)	0 (0.00)	1
Lethargy after infusion	1 (2.50)	0 (0.00)	1
Occasional vertigo	1 (2.50)	0 (0.00)	1
Onychomycosis of bilateral thumbnails	1 (2.50)	0 (0.00)	1
Pregnancy-abortion*	1 (2.50)	0 (0.00)	1
Teeth extraction (no infection)	1 (2.50)	0 (0.00)	1
Tendinitis of left foot	1 (2.50)	0 (0.00)	1
Worsening of hypothyroidism	1 (2.50)	0 (0.00)	1
Allergic rhinitis	0 (0.00)	1 (5.00)	0.33
Increased blood creatinine	0 (0.00)	1 (5.00)	0.33
Headache	0 (0.00)	1 (5.00)	0.33
Hyperkalemia	0 (0.00)	1 (5.00)	0.33
Lesion right knee	0 (0.00)	1 (5.00)	0.33
Moderate nausea	1 (2.50)	2 (5.00)	0.26
Skin Infection	0 (0.00)	1 (5.00)	0.33
Vomiting	0 (0.00)	1 (5.00)	0.33
Worsening of hypertension	0 (0.00)	1 (5.00)	0.33
Total	18 (35.00)	10 (40.00)	0.78

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

‡The differences of the proportions of each adverse event and the aggregated value were tested using a Fisher's exact test. \$ *N* total number of adverse events; % percentage of patients with this adverse event.

Table S2. Summary of per-protocol responses by arm at week 12 and week 20 end-points in all study population and by severity at baseline.

	All patients (N=53)			Severe (Baseline SCORAD $\geq$ 50) (N=29) ^(a)			Non-Severe (Baseline SCORAD<50) (N=24) ^(a)		
	Drug (N=36)	Placebo (N=17)	p-value ⁽¹⁾	Drug (N=18)	Placebo (N=11)	p-value ⁽¹⁾	Drug (N=18)	Placebo (N=6)	p-value ⁽¹⁾
<u>SCORAD decline (Mean $\pm$SEM)</u>									
Week 12	-14.8 $\pm$ 2.9	-11.1 $\pm$ 2.9	NS	-22.9 $\pm$ 4.0	-12.1 $\pm$ 3.7	0.058	-6.7 $\pm$ 3.4	-9.3 $\pm$ 5.2	NS
Week 20	-20.3 $\pm$ 3.1	-15.4 $\pm$ 3.9	NS	-29.4$\pm$4.0	-14.2$\pm$4.8	0.023	-11.3 $\pm$ 3.6	-17.6 $\pm$ 7.1	NS
<u>SCORAD Improvement (Mean $\pm$SEM)</u>									
Week 12	-26.2% $\pm$ 5.3%	-20.4% $\pm$ 5.7%	NS	-36.9% $\pm$ 6.5%	-20.0% $\pm$ 6.8%	0.083	-15.5% $\pm$ 7.9%	-21.1% $\pm$ 11.5%	NS
Week 20	-37.0% $\pm$ 5.6%	-30.0% $\pm$ 7.4%	NS	-47.5% $\pm$6.7%	-25.2% $\pm$8.2%	0.047	-26.5% $\pm$ 8.5%	-39.0% $\pm$ 14.9%	NS
<u>SCORAD-30^(b)</u>									
Week 12	47.2%	23.5%	NS	61.1%	18.2%	0.052	33.3%	33.3%	NS
Week 20	58.3%	35.3%	NS	72.2%	18.2%	0.008	44.4%	66.7%	NS
<u>SCORAD-50^(c)</u>									
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
<u>BSA decline (Mean $\pm$SEM)</u>									
Week 12	-14.3 $\pm$ 2.5	-7.9 $\pm$ 2.9	0.100	-18.0 $\pm$ 3.6	-8.2 $\pm$ 4.4	0.100	-10.5 $\pm$ 3.2	-7.5 $\pm$ 1.6	NS
Week 20	-20.2$\pm$3.3	-9.5$\pm$3.0	0.022	-26.4$\pm$4.7	-8.7$\pm$4.7	0.013	-14.0 $\pm$ 4.3	-11.0 $\pm$ 1.5	NS
<u>BSA decline > 15^(d)</u>									

Week 12	41.7%	11.8%	0.056	50.0%	18.2%	0.125	33.3%	0.0%	NS
Week 20	47.2%	11.8%	0.015	61.1%	18.2%	0.052	33.3%	0.0%	NS
<u>IGA decline (Mean $\pm$SEM)</u>									
Week 12	-0.6 $\pm$ 0.1	-0.4 $\pm$ 0.1	NS	-0.7 $\pm$ 0.2	-0.3 $\pm$ 0.1	0.072	-0.5 $\pm$ 0.2	-0.5 $\pm$ 0.3	NS
Week 20	-1.0 $\pm$ 0.2	-0.6 $\pm$ 0.2	NS	-1.3$\pm$0.3	-0.5$\pm$0.2	0.028	-0.7 $\pm$ 0.2	-1.0 $\pm$ 0.4	NS
<u>IGA complete response^(e)</u>									
	-	-	-	-	-	-	-	-	-
Week 12	16.7%	5.9%	NS	22.2%	0.0%	NS	11.1%	16.7%	NS
Week 20	27.8%	17.6%	NS	38.9%	9.1%	0.110	16.7%	33.3%	NS

(1) Statistical significance of difference in mean decline between the arms was assessed by T-test; statistical significance of difference in % response between the arms was assessed by Fisher's exact test; statistical significance of mean decline per visit compared to baseline was assessed by paired T-test; significant results ($p < 0.05$) are in bold; p -values > 0.1 were noted as NS (not significant). (a) Severe patients are defined as patients with SCORAD ≥ 50 at week 0. (b) SCORAD-30 is defined as SCORAD improvement $> 30\%$ from week 0 and was selected because it is the 95% percentile of pre-treatment variation. (c) SCORAD-50 is defined as SCORAD improvement $> 50\%$ compared to week 0. (d) BSA (body surface area) decline threshold of 15 points was selected because it is the 95% percentile of pre-treatment variation. (e) IGA (Investigator Global Assessment) complete response is defined as IGA ≤ 1 or IGA decline ≥ 2 .

Table S3. Single- and multi-variate linear regression analysis of the primary end-point: SCORAD decline at week 12 of treatment.

Variable	Linear Regression Analysis (N=60)			
	<u>Single-Variable</u>	<u>Multi-Variable</u>		
	p-value	p-value	B	[95% CI]
Treatment arm	0.062	NS	--	--
Severity at Baseline	0.005	NS	--	--
Severity * Arm	--	0.001	15.84	[8.4 - 23.3]
Gender	NS	0.080	--	--
Age	0.032	0.015	-0.29	[-0.06 - -0.52]
AD Duration	NS	NS	--	--
Race	NS	NS	--	--
BMI	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.

Figure S1

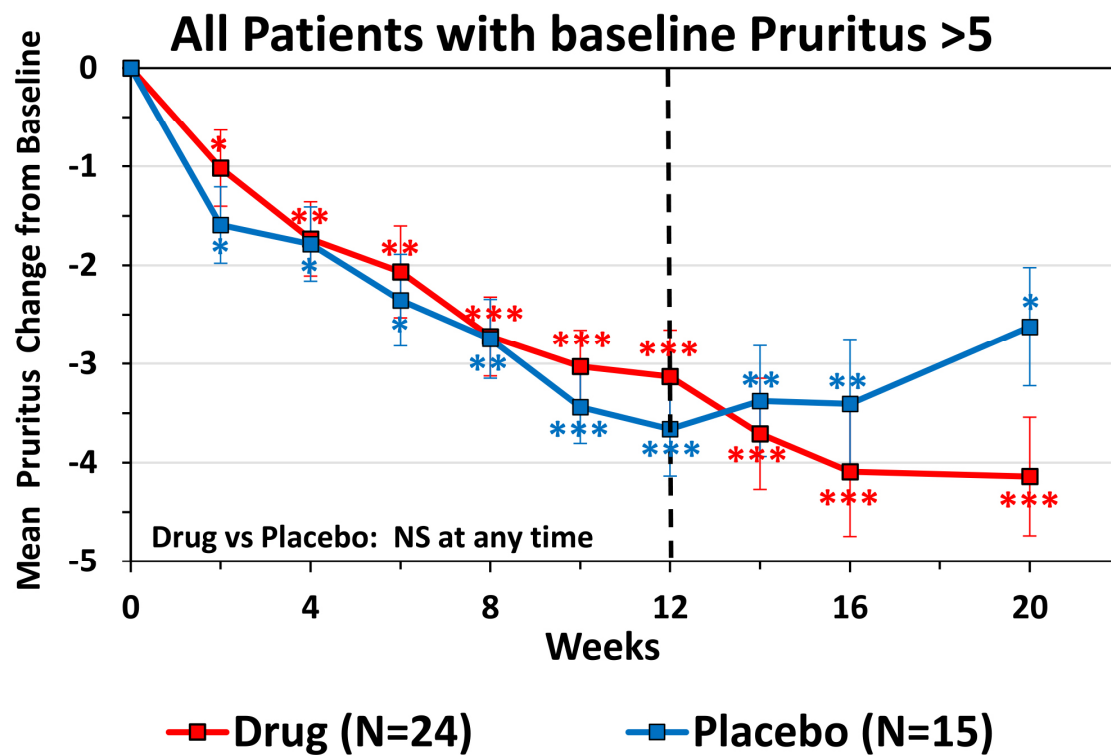


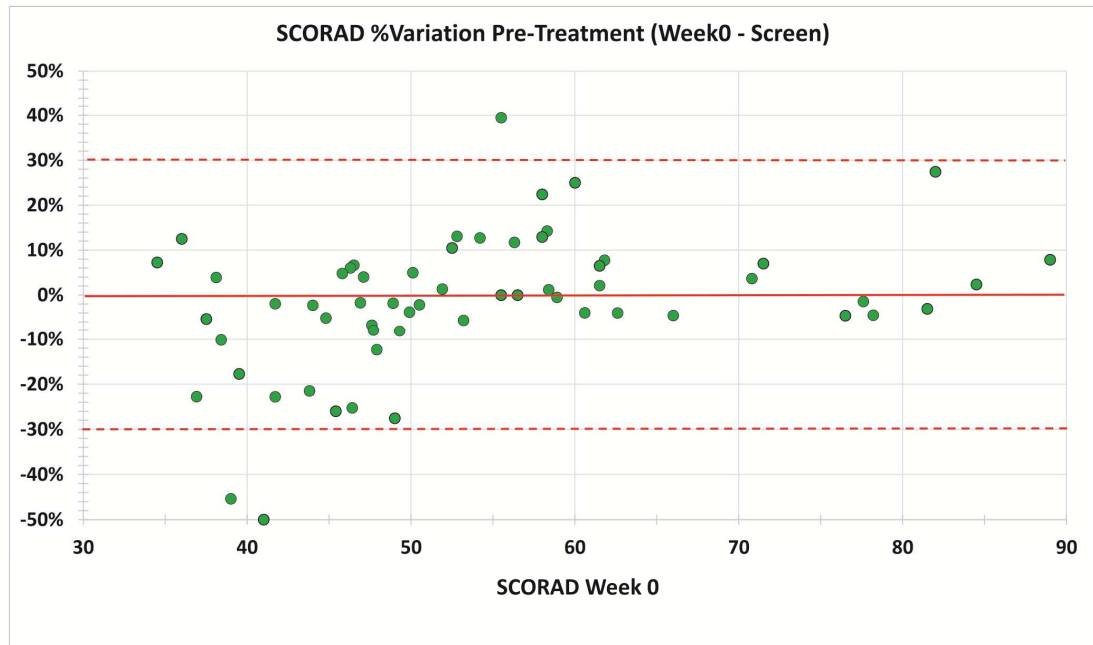
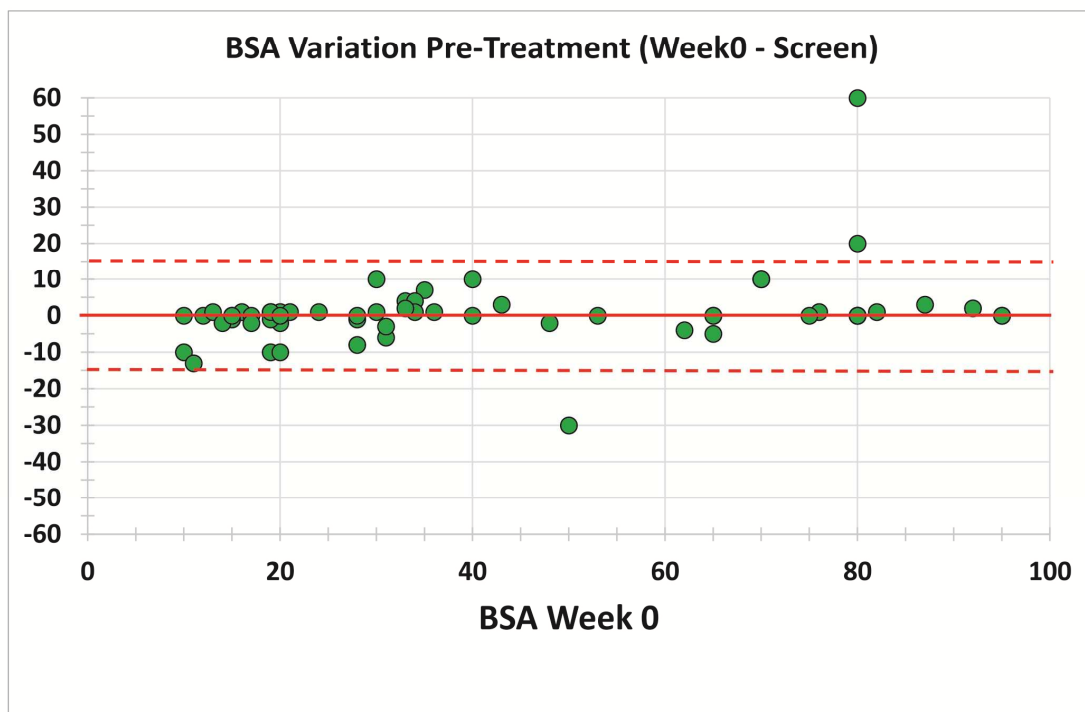
Figure S2**A****B**

Figure S3