

REVIEW ARTICLE

Placebo response in phase 2 and 3 trials of systemic and biological therapies for atopic dermatitis—a systematic review and meta-analysis

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Abstract

A growing number of clinical trials of biological and systemic therapies have been conducted within adult atopic dermatitis (AD). No study has yet examined and meta-analysed the pooled placebo response in AD. We performed a systematic review and meta-analysis to examine the placebo response in clinical trials evaluating the effect of systemic and biological therapies in adult AD and compared it to results from clinical trials in psoriasis. Two screeners independently searched the databases ClinicalTrials.gov, Embase, Pubmed and Web of Science. A total of 2058 articles were identified, of which 78 were full-text reviewed. Overall, 25 trials were included in the qualitative analysis, of which 24 were further included in the quantitative analysis. At 12-week follow-up, EASI50, EASI75 and EASI90 placebo responses were 39.9% [95% confidence interval (CI), 36.7–43.2], 20.9% (95% CI, 18.2–23.8) and 9.0% (95% CI, 6.7–11.6), respectively. At week 12, the pooled proportion of placebo-treated AD patients that obtained EASI50, EASI75 and EASI90 was significantly higher than the pooled proportion of placebo-treated psoriasis patients obtaining PASI50, PASI75 and PASI90 ($P < 0.05$). Our findings emphasize the fluctuating nature of AD and show that correct and consistent use of topical treatments strongly reduces disease severity.

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Conflicts of interest

Dr. Thyssen has attended advisory boards for Eli Lilly, Abbvie, Pfizer and Sanofi-Genzyme, received speaker honorarium from LEO Pharma and Sanofi-Genzyme and been an investigator for Abbvie, Eli Lilly & CO, LEO Pharma and Sanofi-Genzyme. Dr. Egeberg has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation, and the Kgl. Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from Abbvie, Ammirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly, Novartis, Galderma and Janssen Pharmaceuticals. Andreassen, Christensen and Halling have no relevant interests to declare.

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin condition that causes intense pruritus, sleep disturbance and a decreased quality of life.^{1,2} For many patients, the disease course is fluctuating and characterized by periods of partial or complete remission as well as periods with acute flares and worsening.³ For example, patients with AD who live in the northern hemisphere tend to have worsening of their disease during the winter leading to increased healthcare consumption and use of AD medication.⁴

A subgroup of AD patients has moderate-to-severe disease where they cannot control their disease with topical medication only. Few systemic drugs have historically been available to treat AD, but, in 2017, dupilumab was the first biological to be approved for the treatment of moderate-to-severe AD.⁵ Additionally, an unprecedented high number of phase 2 placebo-controlled trials have been conducted in recent years.^{6–8} These controlled studies provide unique insight into the course of AD in patients with moderate-to-severe disease, who were not in the active treatment arm.

We, and others, have examined the placebo response in patients with moderate-to-severe psoriasis who participated clinical trials with systemic therapy.⁹ We recently found that the 12-week placebo responses of a 75% and 90% reduction in Psoriasis Area and Severity Index (PASI), i.e. PASI75 and PASI90, were 5.2% and 2.1%, respectively, in phase 3 studies with systemic therapy (D. Ambikaibalan, AS. Quaade, A-S. Halling-Overgaard, JP. Thyssen, A. Egeberg, Unpublished data). However, since psoriasis has a much less fluctuating course than AD, we would expect the placebo response in AD to be much higher.^{1,10} Through analysis of differences and similarities between psoriasis and AD, we may ultimately better understand these conditions.

In this systematic review and meta-analysis, we investigated the placebo response in clinical phase 2 and 3 trials for systemic and biological therapy for AD. We then compared the pooled placebo response with that of psoriasis patients from the recent review and examined the effects of topical corticosteroid (TCS) use in clinical trials in AD (D. Ambikaibalan, AS. Quaade, A-S. Halling-Overgaard, JP. Thyssen, A. Egeberg, Unpublished data).

Materials and methods

Literature search

A study protocol describing aim, search strategy and analysis plan was developed prior to study start and published on Copenhagen Research Group for Inflammatory Skin's (CORGIS) webpage.¹¹ Two authors (T.H.A. and M.O.C.) independently searched three medical databases, Embase, PubMed and Web of Science using the search terms: (*atopic dermatitis* OR *atopic eczema*) AND (*phase 2* OR *phase II* OR *phase 3* OR *phase III*). The search strategy was similar to the one performed for the systematic review on psoriasis (D. Ambikaibalan, AS. Quaade, A-S. Halling-Overgaard, JP. Thyssen, A. Egeberg, Unpublished data). Additionally, a search on ClinicalTrials.gov was conducted, and reference lists of key articles and relevant reviews were screened. No limit was set regarding study size, publication year, age of study participants or country of origin. The literature search was completed on 27 March 2019, and the full search and exclusion process is outlined in the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) flow diagram (Fig. S1, Supporting Information).¹²

Selection criteria

All published phase 2 and 3 clinical trials for systemic or biological therapy in AD were included if the placebo response among patients with AD was investigated. Placebo response had to be measured by Eczema Area and Severity Index (EASI) or SCORing Atopic Dermatitis (SCORAD) between baseline and follow-up at week 12, 16 and/or 52. Publications not written in English were excluded. Clinical trials on topical treatments were also excluded.

The placebo group was defined as patients who did not receive active treatment with systemic or biological treatment. Patients in the placebo arm of included studies were allowed to use emollients.

Data extraction

All data were extracted independently by two of the authors (T.H.A. and M.O.C.) from all included trials. Specifically, data from AD patients with 25%, 50%, 75% and 90% improvement in EASI (i.e. EASI25, EASI50, EASI75 and EASI90) and SCORAD (i.e. SCORAD25, SCORAD50, SCORAD75 and SCORAD90) scores at various time points were extracted. In addition, mean change in points for EASI and SCORAD was extracted. If data from a trial were presented both in a published article and at ClinicalTrials.gov, and the presented data differed, we used the data from the published article. In articles with relevant data only presented in graphs, we used digitizing software (Engauge Digitizer version 11.1 Mark Mitchell, Torrance, CA, USA) to extract data from these graphs.

For comparison, we used data from a recent meta-analysis and systematic review by Ambikaibalan *et al.*, investigating pooled placebo responses in phase 3 clinical trials of systemic therapies for moderate-to-severe plaque psoriasis (D. Ambikaibalan, AS. Quaade, A-S. Halling-Overgaard, JP. Thyssen, A. Egeberg, Unpublished data). We extracted the pooled proportion of patients in the placebo arm who achieved PASI75 and PASI90, respectively, at 12-week follow-up from this review. Data extraction and calculation for PASI50 placebo response was not performed in the review article by D. Ambikaibalan, AS. Quaade, A-S. Halling-Overgaard, JP. Thyssen, A. Egeberg (Unpublished data).¹⁰ Therefore, data were extracted and analysed from included articles by one of the authors (T.H.A.) in a *post hoc* analysis.

Statistical analysis

StatsDirect software (version 3.1.22, StatsDirect Ltd, Cambridge, UK) was used to calculate the pooled placebo response by the weighted proportion of the included trials. Hereby, it was possible to calculate a mean placebo response based on data from all included studies. These were presented with 95% confidence intervals (CIs) in individual proportion meta-analysis. Sub-analyses were conducted to make a distinction between trials allowing concurrent TCS and those that prohibited concurrent TCS use. For this, we used chi-squared test and Student's *t*-test to evaluate the statistical difference between studies.¹³ We used the Freeman–Tukey double arcsine transformation to find the weighted proportions of all included trials.¹⁴ For the pooled meta-analysis, fixed effect (inverse variance) method was chosen, due to all included trials being randomized phase 2 or 3 trials with comparable study populations. Funnel plots were made to evaluate publication bias. Results were presented in individual forest plots. Cochran's *Q* test and *I*² statistics were used to evaluate heterogeneity of included trials.

Results

In total, 2032 articles were identified during the screening process. After removal of duplicates, 1636 articles were identified, of which 78 were retrieved for full-text review. Of these, 53 articles were excluded due to reasons listed in PRISMA flow chart (Fig. S1, Supporting Information).

A total of 25 trials^{8,15–37} were included in the qualitative analysis, of which 24^{8,15–29,31–37} were also included in the quantitative analysis (Tables S3–S5, Supporting Information). One publication contained data from two individual phase 3 trials (SOLO1 and SOLO2).⁸ Due to few available data, no quantitative analyses could be performed for the placebo response in trials with 52-week follow-up, or in patients obtaining EASI25, SCORAD25 and SCORAD90. In two trials, data presented in the published article and ClinicalTrials.gov differed in the number of patients analysed at follow-up.^{21,34} In these cases, data from the published articles were extracted. Thirteen trials required that patients had moderate-to-severe AD with an EASI score above 12 (Tables S3–S5, Supporting Information).

Twenty trials^{8,15–22,24,25,28,29,32–37} demanded that patient had a history of inadequate response to topical treatment with TCS or topical calcineurin inhibitors. The remaining 5 trials^{23,26,27,30,31} did not state this as an inclusion criterium. In the article by D. Ambikaibalan, AS. Quaade, A-S. Halling-Overgaard, JP. Thyssen, A. Egeberg (Unpublished data) none of the included psoriasis trials required concurrent topical therapy and were therefore monotherapy studies. In comparison, 6 of the included AD trials allowed concomitant topical therapy in addition to systemic therapy (Tables S3–S5, Supporting Information). Importantly, all included publications discontinued assessment of patients who during the study period received rescue treatment.

The level of heterogeneity differed widely in our individual sub-analyses. The highest registered I^2 statistics was 81%, indicating considerable heterogeneity. Notably, the majority of analyses had I^2 statistics below 60%, which suggest moderate heterogeneity in the pooled data (Table S1, Supporting Information). Evaluation of funnel plots for each analysis gave no reason to suspect publication bias (Fig. S2, Supporting Information).

Quantitative analysis

EASI50, EASI75 and EASI90 placebo responses at week 12 and 16 The 12-week pooled EASI50 response among placebo-treated patients was 39.9% (95% CI, 36.7–43.2) based on data from 12 clinical trials ($n = 882$ patients). The pooled EASI75 and EASI90 response was 20.9% (95% CI, 18.2–23.8) and 9.0% (95% CI, 6.7–11.6), respectively, based on 11 ($n = 818$ patients) and five clinical trials ($n = 534$ patients), respectively (Figs 1,2).

When we examined the effect of TCS use on the placebo response, a significantly higher proportion of placebo-treated patients with concurrent use of TCS achieved EASI50 (43.6%, 95% CI, 39.6–47.6) at week 12, compared with placebo-treated

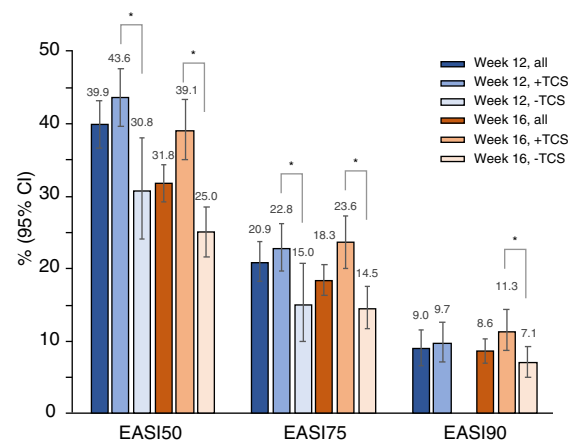


Figure 1 EASI placebo responses at week 12 and 16. *Significant difference, $P < 0.05$. TCS, Topical corticosteroids.

patients who were prohibited to use TCS (30.8%, 95% CI, 24.1–38.0) ($P < 0.05$) (Fig. 1, Table S2, Supporting Information). The same trend was observed for pooled EASI75 placebo response (chi-squared test, $P < 0.05$).

At week 16, the overall pooled EASI50, EASI75 and EASI90 responses among placebo-treated patients were comparable to the results of week 12 (Figs 1,2). Similar to week 12 data, a significant difference ($P < 0.05$) was observed between studies where patients used concurrent TCS and studies where TCS use was prohibited regarding EASI50, EASI75 and EASI90 scores at 16-week follow-up (Fig. 1, Table S2, Supporting Information).

Mean EASI and EASI placebo reductions at week 12 and week 16 The mean baseline EASI score for placebo-treated patients was 30.9 points (95% CI, 27.6–34.2), and at 12-week follow-up, EASI score was reduced to 20.1 points (95% CI, 7.4–32.8). For data at week 16, the mean baseline EASI score was 32.6 points (95% CI, 29.9–35.4) for patients receiving placebo and was reduced to 21.1 points (95% CI, 13.2–29.0) at 16-week follow-up.

A statistical significant greater mean reduction in EASI score was observed at week 12 and 16 among placebo-treated patients with concurrent use of TCS compared with patients that were not allowed to use TCS (Student's t -test, $P < 0.05$) (Table S6, Supporting Information).

SCORAD50 and SCORAD75 placebo response at week 12 At 12-week follow-up, pooled placebo responses measured as SCORAD50 and SCORAD75 were 21.8% (95% CI, 17.2–26.7) and 5.3% (95% CI, 2.3–9.4), respectively (Table S2 and Fig. S3, Supporting Information). Due to few available data, it was

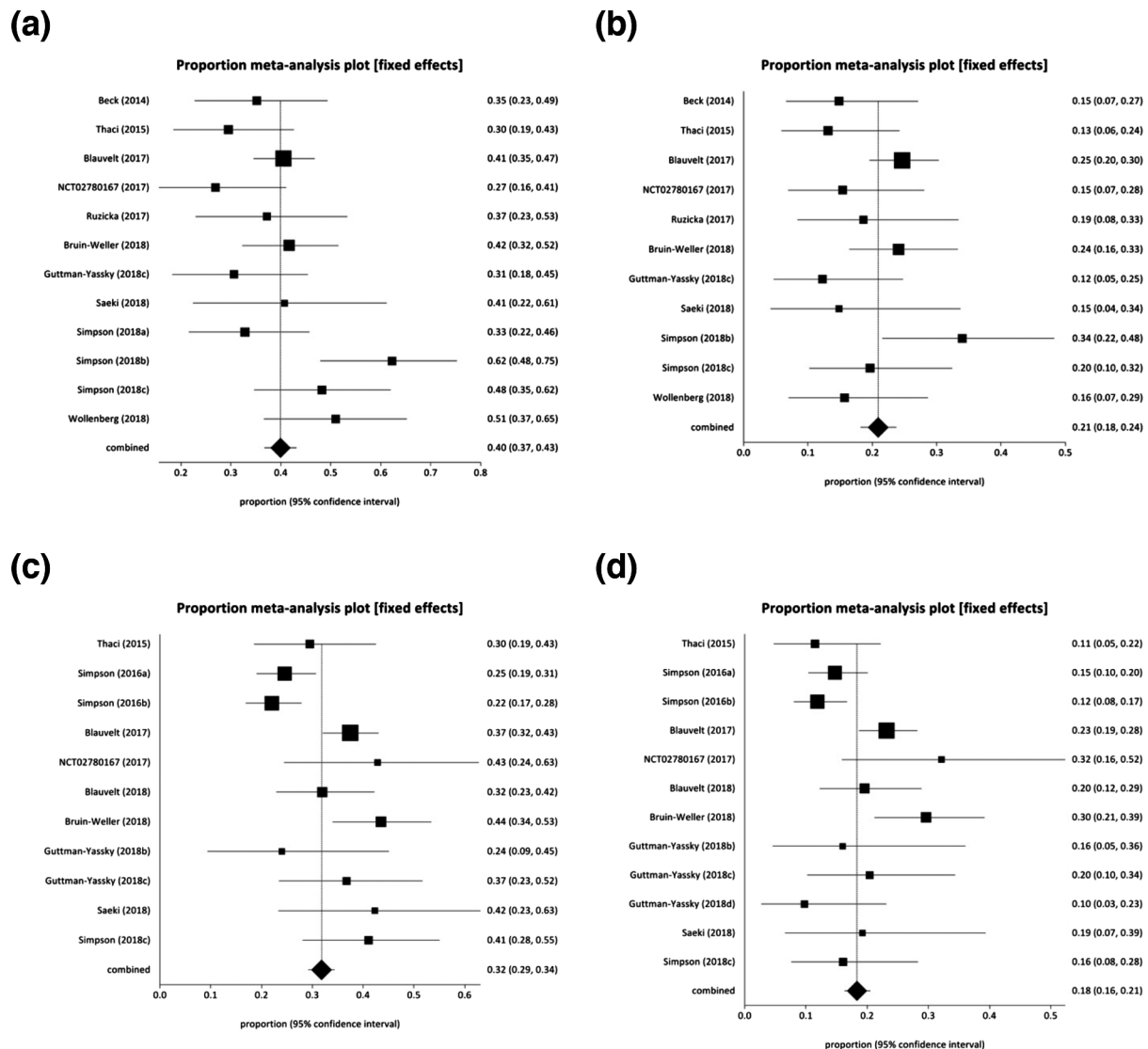


Figure 2 Proportion meta-analysis of the atopic dermatitis placebo responses at week 12 and 16. a: EASI50 placebo response at week 12, b: EASI75 placebo response at week 12, c: EASI50 placebo response at week 16, d: EASI75 placebo response at week 16.

impossible to conduct quantitative analyses comparing SCORAD scores from studies with and without concurrent use of TCS.

Comparing placebo responses among AD (EASI) and psoriasis (PASI) patients The pooled proportion of placebo-treated psoriasis patients who obtained PASI50, PASI75 and PASI90 at 12-week follow-up in phase 3 studies was, respectively, 14.5% (95% CI, 13.3–15.7), 5.2% (95% CI, 4.7–5.7) and 2.1% (95% CI, 1.7–2.4) based on a *post hoc* systematic review and results from a recent systematic review article (D. Ambikaibalan, AS. Quaade, A-S. Halling-Overgaard, JP. Thyssen, A. Egeberg, Unpublished

data). At week 12, the pooled proportion of placebo-treated AD patients that obtained EASI50, EASI75 and EASI90 was significantly higher than the pooled proportion of placebo-treated psoriasis patients obtaining PASI50, PASI75 and PASI90 ($P < 0.05$) (Fig. 3).

Qualitative analysis

Few data from 52-week studies were available. In a study with dupilumab and concomitant TCS use, 30% achieved EASI50, 21.6% achieved EASI75 and 16% achieved EASI90 in the placebo group at week 52.³⁴ An immunotherapy study found a median

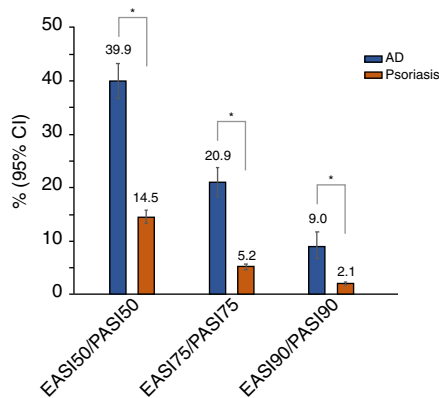


Figure 3 Placebo response in atopic dermatitis and psoriasis at week 12. *Significant difference, $P < 0.05$. EASI, Eczema Area and Severity Index; PASI, Psoriasis Area and Severity Index.

improvement in SCORAD score at 30.8 points (baseline SCORAD: 62.5 points), at 52-week follow-up in the placebo arm.³⁰ Patients were allowed to use concurrent TCS (Table S5, Supporting Information).

Discussion

Main findings

This study showed that relatively large proportions of patients with moderate-to-severe AD who were managed in the placebo arm of phase 2 and 3 clinical trial, achieved EASI50 and EASI75, respectively, over 12-week and 16-week observation periods. Placebo responses were overall higher in placebo arms where TCS was used compared with emollients only, particularly for EASI50 and EASI75, where responses were significantly higher at both week 12 and 16. Significantly higher proportions of AD patients achieved 50%, 75% and 90% disease improvement compared with psoriasis patients.

Interpretation

This study not only contains important information for scientists who plan and interpret results from clinical trials in AD, but also for clinicians who care for these patients. EASI50 and EASI75 placebo responses were identified in relatively high proportions of patients with moderate-to-severe disease emphasizing that AD patients who are closely monitored and consistently apply topical treatments may experience significant disease reductions. Participation in a clinical trial leads to improved adherence, and the consistent emollient use in itself, or in combination with TCS, will lead to improved skin barrier functions, reduced clinical severity of AD and increased time to next disease flare.³ Furthermore, more regular bathing during clinical trial participation may reduce colonization with *Staphylococcus aureus*, further improving skin symptoms of patients with AD.³⁹

These are likely central explanations for the substantial placebo responses that we observed in the large amount of data. While real-world management of AD patients cannot offer the same close monitoring and patient care, the findings emphasize the benefits of inexpensive emollients and TCS when used continuously even in patients with moderate-to-severe disease.^{40,41} However, patients with AD, and in particularly those with severe AD, high itch scores and facial AD, have a desire to obtain complete resolution of their disease, indicating that clinicians also should remain vigilant and attempt to identify effective treatments.⁴²

Stress and psychological factors can influence the disease course and risk of flares in AD.⁴³ It is possible that the expectations of disease reduction when participating in a clinical trial may have positive effects on AD in itself. However, based on a large amount of published data, the placebo response in clinical trials is not expected to influence objective continuous outcomes, e.g. blood pressure, but indeed psychological outcomes.⁴⁴ Consequently, the observed improvement in AD disease severity measured by EASI is unlikely to be explained by a placebo effect to a higher degree, but rather represents the effects of topical treatments and the natural course of AD as proposed above.

Recent clinical trials have chosen to either prohibit TCS use in both treatment arms, e.g. SOLO1 and SOLO2 trial for dupilumab, or require all patients to use TCS consistently through the trials, e.g. TREBLE trial using lebrikizumab.^{8,22} It can be argued that the inclusion of TCS as adjunct therapy mimics real-world activities better since no drugs so far have shown efficacy levels that may allow exclusion of TCS, whereas monotherapy studies can improve insight in the relative effect difference of the studied drug. The significant difference in EASI scores that we observed between studies that dictated concurrent TCS use and those that prohibited TCS use shows the relative effect of TCS. Of interest, since TCS in clinical trials is often provided by the investigators, this tends to increase adherence to TCS use.³⁴ Importantly, the use of placebo in clinical AD trials was recently discussed by members of the International Eczema Council,⁴⁵ who concluded that several considerations should be made when designing an AD placebo-controlled clinical trial and that monotherapy should be used in proof-of-concept studies.⁴⁵

The comparison of our study results with similar data from clinical trials of psoriasis patients with moderate-to-severe disease highlights important differences between these two inflammatory skin diseases. Psoriasis patients experience fewer disease flares and have a more stable disease, whereas AD patients, in particular those with moderate-to-severe disease, have a strongly fluctuating disease with frequent flares.^{1,10} The typical long wash-out phase in clinical trials normally leads to 'artificial' disease worsening, perhaps in particular in AD patients. Our analysis suggests that in subgroups, management with emollients can

lead to improvement of skin disease along with the natural waxing and waning nature of the disease.

We welcome the recent development of new systemic and biological treatments in AD. While the forthcoming place in the treatment landscape of these expensive future drugs has not been established, clinicians should remain aware of the benefits of patient education and topical treatments as well as the inherent cyclic nature of the skin disease. Although a large number of patients with AD need prolonged and continuous treatment, other patients may benefit from shorter treatment periods in case of worsening due to seasonal changes, stress or other factors. Moreover, patient education is key in AD management, which also includes instruction in correct TCS use.⁴⁶

Strengths and limitations

Certain study limitations should be mentioned. We did not collect information about the amount and potency of TCS that were used, nor the kind of emollient and its lipid content. Other important factors that in theory might have affected the placebo response were as follows: time of year that the trial was conducted, geographic setting, comorbidities, previous treatment of AD and differences in age. Also, patients in placebo arms might have used topical anti-inflammatory treatment despite instruction not to use these, which may falsely have improved the placebo response.

The use of rescue medication and the number of patients who dropped out from the placebo arm, e.g. due to lack of efficacy, could be relevant measurements of the placebo effect, but we did not collect such data. Importantly, all included trials chose to discontinue assessments of patients who received rescue medication.

Upon estimation of the placebo treatment response, this review focused on EASI and SCORAD. We did not include global assessment tools, e.g. IGA or PGA. Patient reported outcomes including severity scales that measure sleep problems and itch are important factors when assessing the severity of AD. These symptoms are included in SCORAD; however, it would have been preferable to also show the placebo effect solely on subjective symptoms, e.g. change on the numeric rating scale for pruritus.¹⁵ Notably, assessment of the frequency and severity of disease flares in AD is of strong clinical relevance for patients and physicians. However, this was not examined.³

There were few data from follow-up at week 52. Such data would be important to better assess the long-term placebo response. The comparison of placebo responses in AD and psoriasis was assessed via relative improvements in EASI and PASI scores. While these indexes are very similar and combine the severity of skin disease with surface area involvement, it is unknown whether they can be directly compared. Notably, the clinical assessment of disease severity in AD and psoriasis differ due to psoriasis lesions being characteristically more well defined, while chronic AD lesions are poorly demarcated. This

further limits the comparison between the placebo response in AD and psoriasis.⁴⁵

Conclusion

Data from phase 2 and 3 clinical trials showed high placebo responses in moderate-to-severe AD patients at 12-week and 16-week follow-up. We conclude that clinicians should continue to encourage their AD patients to adhere to topical treatments and be aware of the fluctuating nature of the disease.

Acknowledgement

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Author contributions

Andreasen and Christensen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Andreasen, Halling and Thyssen studied the concept and designed the manuscript. All authors involved in acquisition, analysis and interpretation of data. Andreasen, Halling and Thyssen involved in drafting of the manuscript. All authors involved in critical revision of the manuscript for important intellectual content. Andreasen and Egeberg involved in statistical analysis. All authors received administrative, technical or material support. Halling and Thyssen involved in study supervision.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. PRISMA flow diagram.

Fig. S2. Funnel plots for EASI50, EASI75 and EASI90 at week 12 and 16.

Fig. S3. Placebo-responses at week 12 (respectively, SCORAD50 and SCORAD75) in clinical trials of systemic or biologic therapy.

Table S1. Results from the heterogeneity assessment analysis.

Table S2. Placebo-responses in clinical trials with systemic or biologic therapy, with or without concurrent topical corticosteroid use.

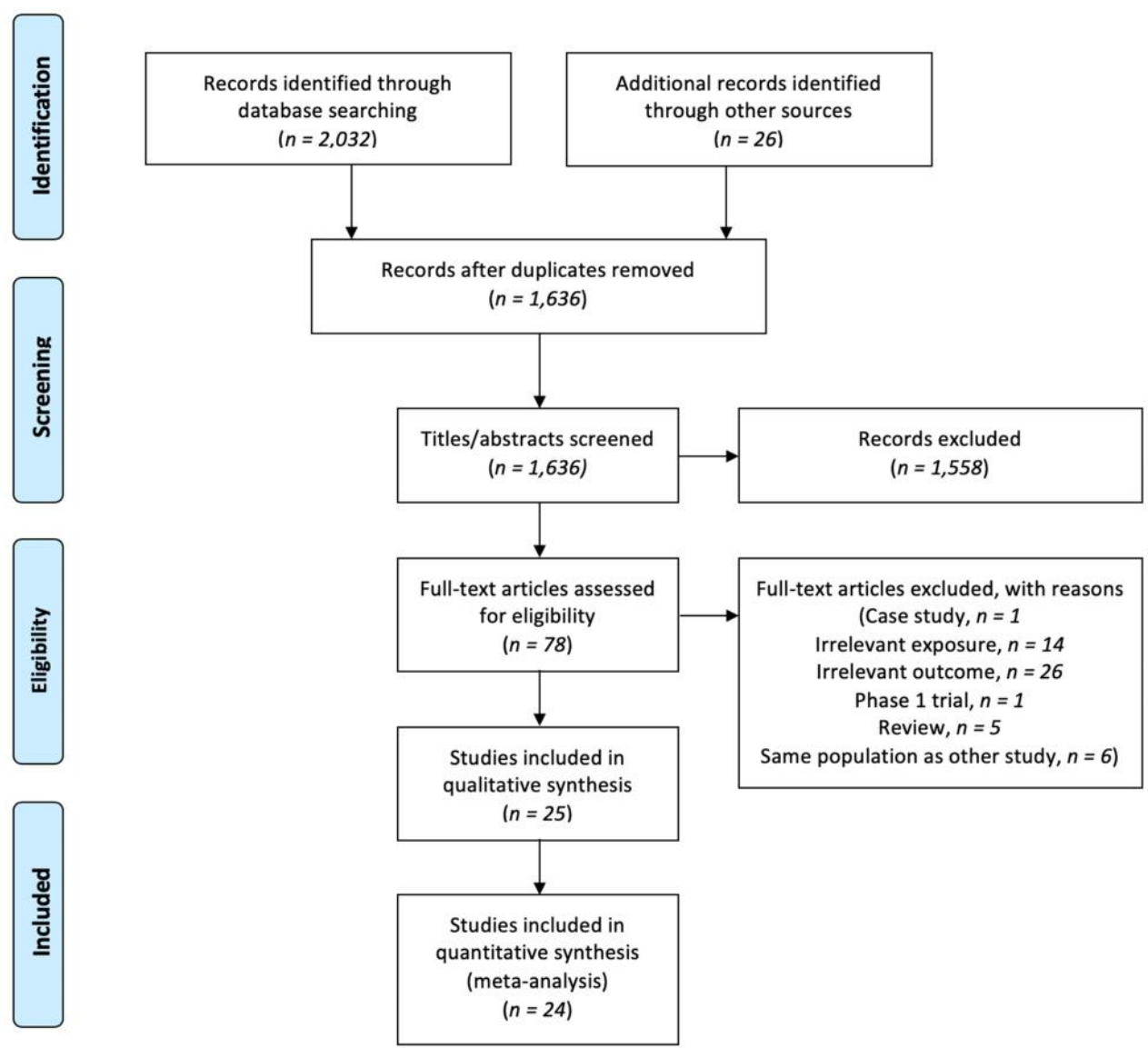
Table S3. Clinical trials that contain placebo response data at week 12.

Table S4. Clinical trials that contain placebo response data at week 16.

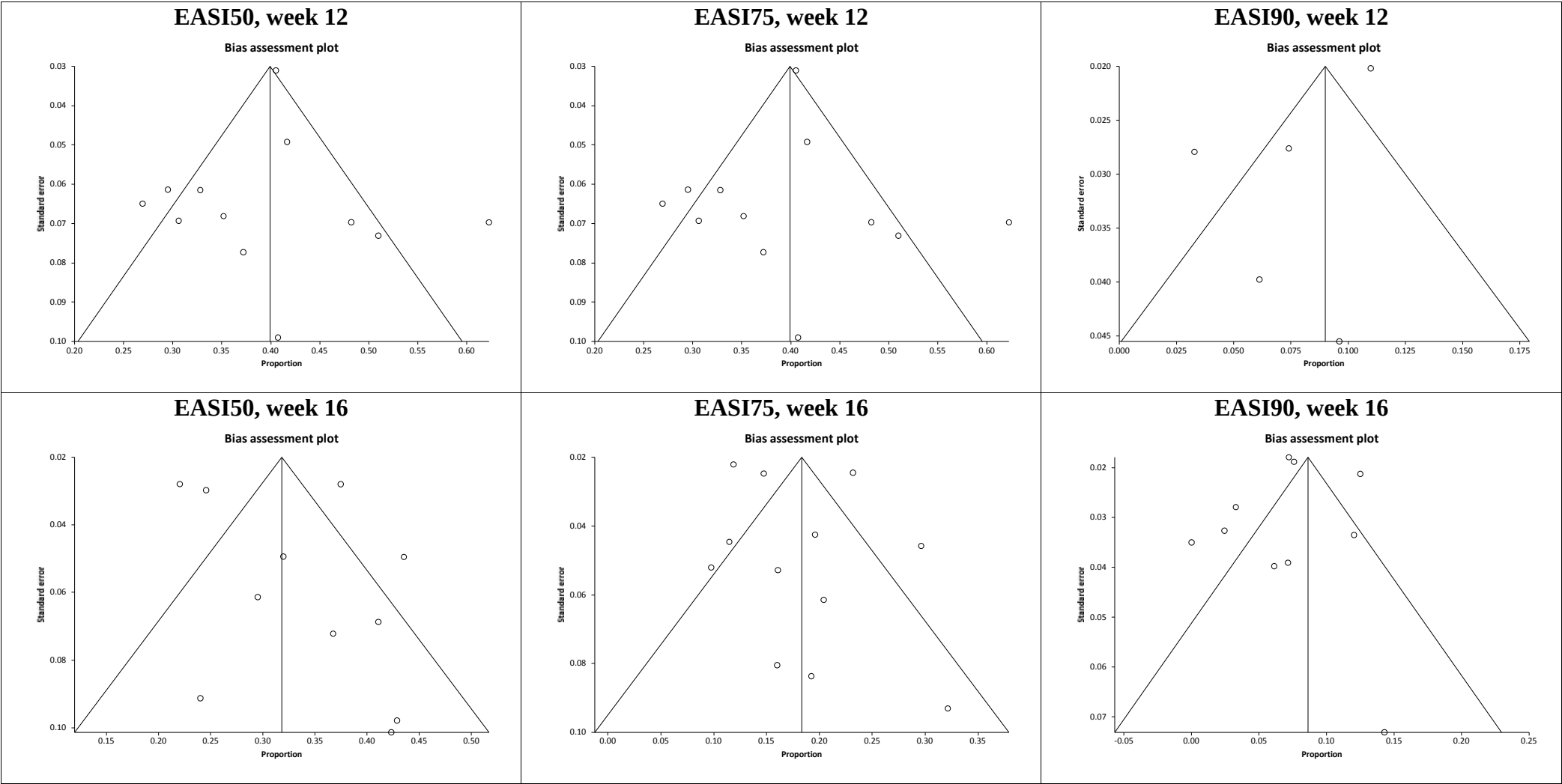
Table S5. Clinical trials that contain placebo response data at week 52.

Table S6. Mean change in placebo-response measured with EASI score.

Supplemental Fig. S1 – PRISMA Flow Diagram



Supplemental Fig. S2 – Funnel plots for EASI50, EASI75 and EASI90 at week 12 and 16



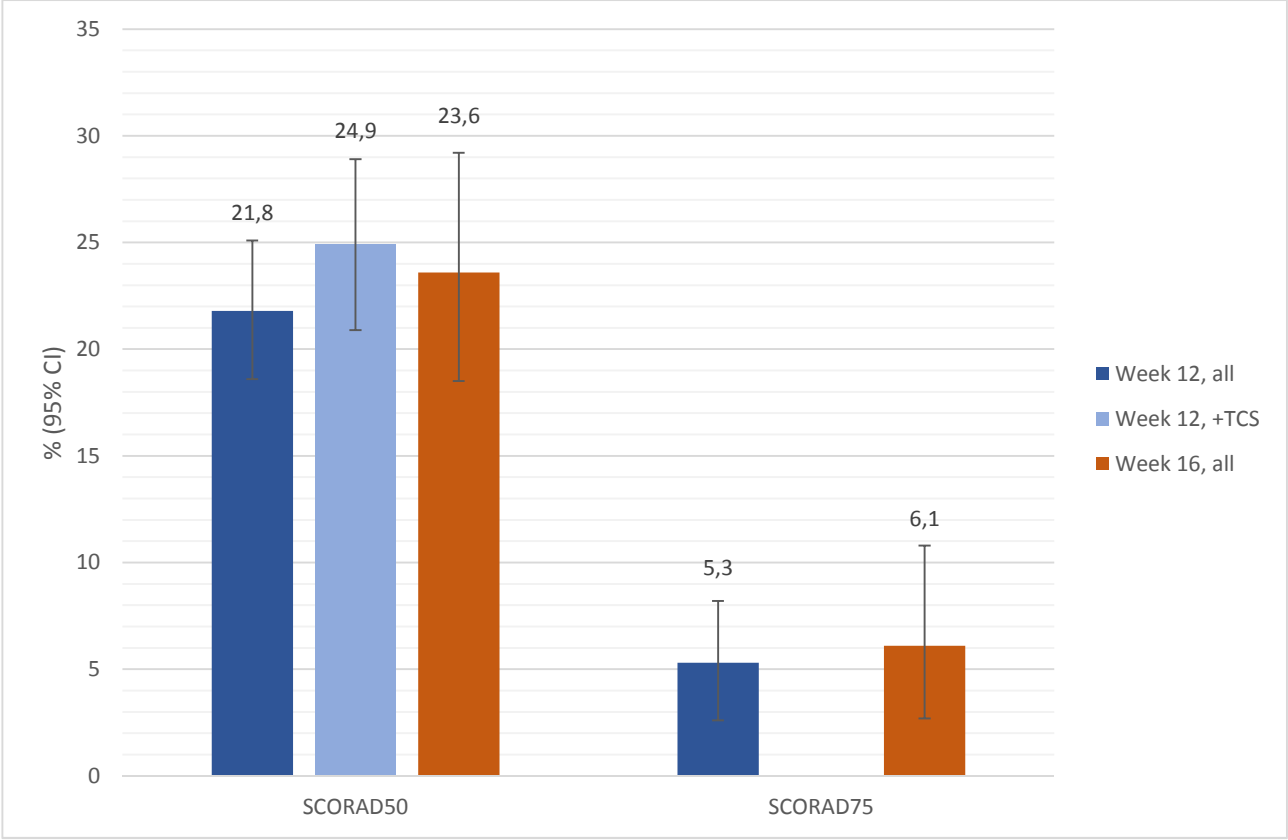
EASI: Eczema Area and Severity Index

Supplemental table S1 - Results from the heterogeneity assessment analysis

Week	EASI score	Egger test	Begg-Mazumdar	Cochran Q	I ² (inconsistency)
12	EASI50	0.030737 (95% CI, -3.2 – 3.3) P=0.9836	Kendall's tau = 0.242424 P=0.3108	25.114595 (df=11) P=0.0088	56.5% (95% CI, 0-75.5)
	EASI75	-1.582527 (95% CI, -4.4 – 1.3) P=0.2384	Kendall's tau = 0.2 P=0.4454	15.401557 (df=10) P=0.1181	35.1% (95% CI, 0-66.9)
	EASI90	-1.482193 (95% CI, -7.8 – 4.9) P=0.5125	Kendall's tau = -0.2 P=0.4833	4.563139 (df=4) P=0.3351	12.3% (95% CI, 0-68.3)
16	EASI50	1.678225 (95% CI, -1.0-4.4) P=0.1952	Kendall's tau = 0.127273 P=0.6481	34.255762 (df=10) P=0.00002	70.8% (95% CI, 37.1-82.8)
	EASI75	0.86807 (95% CI, -1.5-3.2) P=0.43	Kendall's tau = 0.212121 P=0.3807	29.517201 (df=11) P=0.0019	62.7% (95% CI, 16-78.5)
	EASI90	-0.576934 (95% CI, -3.7-2.5) P=0.6781	Kendall's tau = -0.066667 P=0.7275	16.795183 (df=9) P=0.052	46.4% (95% CI, 0-76.6%)

EASI: Eczema Area and Severity Index

Supplemental Fig. S3 – Placebo-responses at week 12 (respectively, SCORAD50 and SCORAD75) in clinical trials of systemic or biologic therapy.



SCORAD: Scoring Atopic Dermatitis
TCS: Topical corticosteroid

Supplemental table S2 – Placebo-responses in clinical trials with systemic or biologic therapy, with or without concurrent topical corticosteroid use

Week	Therapy	Score	Severity reduction in % (95% confidence interval)
12	All	EASI50	39.9 (36.7-43.2)
		EASI75	20.9 (18.2-23.8)
		EASI90	9.0 (6.7-11.6)
		SCORAD50	21.8 (17.2-26.7)
		SCORAD75	5.3 (2.3-9.4)
	-TCS	EASI50	30.8 (24.1-38.0)
		EASI75	15.0 (10.0-20.7)
	+TCS	EASI50	43.6 (39.6-47.6)
		EASI75	22.8 (19.6-26.2)
		EASI90	9.7 (7.1-12.7)
		SCORAD50	24.9 (18.8-31.5)
16	All	EASI50	31.8 (29.2-34.4)
		EASI75	18.3 (16.3-20.5)
		EASI90	8.6 (7.0-10.4)
		SCORAD50	23.6 (18.5-29.2)
		SCORAD75	6.1 (2.7-10.8)
	-TCS	EASI50	25.0 (21.6-28.6)
		EASI75	14.5 (11.7-17.5)
		EASI90	7.1 (5.1-9.3)
	+TCS	EASI50	39.1 (35.0-43.3)
		EASI75	23.6 (20.1-27.3)
		EASI90	11.3 (8.7-14.3)

EASI: Eczema Area and Severity Index

TCS: Topical corticosteroid

Supplemental table S3 – Clinical trials that contain placebo response data at week 12

Reference	Study type, period (and name)	Mean age of patients or range, baseline (SD)	Sex, baseline (Female/Male)	AD severity for eligibility	Medication and dose	n total (number analyzed)	Mean DLQI % or points change from baseline to week 12	n PGA/IGA score 0/1 at week 12	n EASI25 at week 12	n EASI50 at week 12	n EASI75 at week 12	n EASI90 at week 12	n SCORAD25 at week 12	n SCORAD50 at week 12	n SCORAD75 at week 12	n SCORAD90 at week 12	Mean EASI, baseline	Mean EASI change from baseline to week 12, points and/or % (SD)	Mean SCORAD, baseline	Mean SCORAD change from baseline to week 12, points and/or % (SD)
Beck et al, 2014 ¹ NCT01548404 ²	Phase IIa 2012-2013 M12	39.4 (1.7)	27/27	Moderate to severe AD EASI≥16 IGA 3-4 BSA≥10% Prohibited concurrent TCS use EASI≥15	Placebo QW through 12 weeks	54	-	4 (7.4%)	-	19 (35%)	8 (15%)	-	-	-	-	-	30.8 (13.6)	-6.4 (14.9)	69.1 (13.4)	-9.8 (20.5)
		33.7 (1.4)	24/31		Dupilumab 300 mg QW through 12 weeks	55	-	22 (40.0%)	-	47 (85%)	34 (62%)	-	-	-	-	-	28.4 (13.6)	-19.9 (11.5)	66.7 (13.8)	-35.0 (19.4)
NCT01785602 ³	Phase II 2013-2014	38.7 (10.0)	12/15		Placebo QD orally	27	-	-	-	-	-	-	-	-	-	-	-	-7.0 (0.0)	-	-
		35.5 (13.1)	27/49		Fevipirant 450 mg orally QD	76	-	-	-	-	-	-	-	-	-	-	-	-8.7 (0.0)	-	-
NCT02324972 ⁴	Phase II 2014-2015 KINSHIP	18-65 years	14/14	Mild to moderate AD IGA 2 or 3 BSA≥1%	Placebo QD orally through 12 weeks	24	-	-	-	-	-	-	-	-	-	-	5.4 (2.2)	-2.1 (3.2)	37.2 (6.4)	-11.5 (11.5)
		18-65 years	18/8		Aquinox 450 mg QD orally through 12 weeks	20	-	-	-	-	-	-	-	-	-	-	5.6 (3.3)	-2.8 (1.6)	36.2 (8.7)	-12.1 (11.2)
Thaçi et al, 2015 ⁵ NCT01859988 ⁶	Phase IIb 2013-2014	37.2 (13.1)	21/40	EASI≥16 IGA≥3 BSA≥10% Prohibited concurrent TCS use	Placebo QW through 15 weeks	61	-	-	-	18 (29.2%)§	8 (13.2%)§	2 (3.9%)§	-	-	-	-	32.9 (13.8)	-6.7 -20.4%§	67.1 (13.6)	-9.5 -14.2%§
		36.2 (10.7)	20/43		Dupilumab 300 mg QW (loading dose 600 mg) through 15 weeks	63	-	-	-	54 (85.7%)§	38 (60.2%)§	23 (36.8%)§	-	-	-	-	30.1 (11.2)	-21.5 -71.3%§	65.0 (12.2)	-36.9 -56.8%§
		39.4 (12.06)	23/41		Dupilumab 300 mg Q2W (loading dose 600 mg) through 15 weeks	64	-	-	-	52 (81.4%)§	35 (54.9%)§	19 (30.1%)§	-	-	-	-	33.8 (14.5)	-22.5 -66.5%§	68.5 (12.6)	-33.8 -49.3%§
		35.8 (14.90)	25/36		Dupilumab 200 mg Q2W (loading dose 400 mg) through 15 weeks	61	-	-	-	39 (64.1%)§	32 (51.9%)§	16 (26.5%)§	-	-	-	-	32.9 (15.5)	-21.1 -64%§	68.3 (14.0)	-31.1 -45.5%
		36.8 (10.8)	25/40		Dupilumab 300 mg Q4W (loading dose 600 mg) through 15 weeks	65	-	-	-	48 (73.8%)§	34 (51.9%)§	17 (26.5%)§	-	-	-	-	29.4 (11.5)	-18.3 -62.4%§	67.2 (12.3)	-31.9 -47.4%§
		36.6 (11.6)	31/34		Dupilumab 100 mg Q4W (loading dose 400 mg) through 15 weeks	65	-	-	-	31 (47.8%)§	20 (31.0%)§	14 (21.5%)§	-	-	-	-	32.2 (13.5)	-15.0 -46.5%§	68.2 (15.0)	-19.3 -28.3%§
Khattri et al, 2016 ⁷ NCT01806662 ⁸	Phase II 2013-2015 Crossover design	40	6/10	Moderate to severe AD SCORAD≥15	Placebo Q4W first for 16 weeks, then Ustekinumab for 16 weeks + TCS (class VI)	16	-5.9	-	-	-	-	-	-	3 (19%)	-	-	-	-	69.7§	-19.6§
		37	6/10		Ustekinumab 45/90 mg Q4W first for 16 weeks, then placebo for 16 weeks + TCS (class VI)	16	-4.7	-	-	-	-	-	-	6 (38%)	-	-	-	-	65.4§	-20.8§

Simpson et al, 2016a ⁹ NCT02277743 ¹⁰	Phase III SOLO1 2014-2016	39.0 (median)	106/118	Moderate to severe AD EAS≥16 IGA≥3 BSA≥10% Prohibited concurrent TCS use	Placebo Q2W through 16 weeks	224	-	-	-	-	-	-	-	-	-	-	34.5	-11.1 -32.2%§	68.3	-
		38.0 (median)	94/130		Dupilumab 300 mg Q2W through 16 weeks	224	-	-	-	-	-	-	-	-	-	-	33.0	-23.4 -71.0%§	66.9	-
		39.0 (median)	81/142		Dupilumab 300 mg QW through 16 weeks	223	-	-	-	-	-	-	-	-	-	-	33.2	-23.8 -71.8%§	67.5	-
Simpson et al, 2016b ⁹ NCT02277769 ¹¹	Phase III SOLO2 2014-2016	35.0 (median)	104/132	Moderate to severe AD EAS≥16 IGA≥3 BSA≥10% Prohibited concurrent TCS use	Placebo Q2W through 16 weeks	236	-	-	-	-	-	-	-	-	-	-	33.6	-10.8 -32.1%§	69.2	-
		34.0 (median)	96/137		Dupilumab 300 mg Q2W through 16 weeks	233	-	-	-	-	-	-	-	-	-	-	31.8	-21.5 -67.5%§	67.2	-
		35.0 (median)	100/139		Dupilumab 300 mg QW through 16 weeks	239	-	-	-	-	-	-	-	-	-	-	31.9	-22.3 -69.8%§	67.5	-
Blauvelt et al, 2017 ¹² NCT02260986 ¹³	Phase III 2014-2016 CHRONOS	36.6 (13.0)	122/193	EAS≥16 IGA≥3	Placebo + TCS (medium-low potency) through 52 weeks	264	-	33	-	107	65	29	-	-	-	-	32.6 (12.9)	-14.7§ -45.0%§	66.0 (13.5) (analyzed, n = 313)	-21.5§ -32.6%§
		39.6 (14.0)	44/62		Dupilumab 300 mg Q2W (loading dose 600 mg) + TCS (medium-low potency) through 52 weeks	89	-	33	-	71	58	37	-	-	-	-	33.6 (13.3)	-24.7§ -76.9%§	69.3 (15.2) (analyzed, n = 105)	-44.0§ -63.5%§
		36.9 (13.7)	128/191		Dupilumab 300 mg QW (loading dose 600 mg) + TCS (medium-low potency) through 52 weeks	270	-	105	-	217	171	105	-	-	-	-	32.1 (12.8)	-24.1§ -76.9%§	65.9 (13.6) (analyzed, n = 316)	-41.6§ -63.2%§
NCT02780167 ¹⁴	Phase IIb 2016-2017	42.6 (15.1)	35/21	EAS≥12 IGA≥3 BSA≥10% Prohibited concurrent TCS use	Placebo QD through 12 weeks	52	-4.6 (analyzed, n = 36)	4 (6.3%)*	-	14 (26.9%)	8 (15.4%)	5 (9.6%)	-	10 (19.2%)	2 (3.8%)	-	-	-35.2% (6.6) (analyzed, n = 56)	-	-18.6 (20.0) -29.4% (analyzed, n = 35)
		44.3 (15.9)	28/21		Abrocitinib 10 mg QD through 12 weeks	46	-4.5 (analyzed, n = 31)	4 (8.2%)*	-	12 (26.1%)	8 (17.4%)	5 (10.9%)	-	6 (13.0%)	5 (10.9%)	-	-	-31.1% (7.1) (analyzed, n = 49)	-	-18.0 (23.1) -27.6% (analyzed, n = 29)
		37.6 (15.9)	29/22		Abrocitinib 30 mg QD through 12 weeks	45	-5.2 (analyzed, n = 33)	6 (12.3%)*	-	15 (33.3%)	6 (13.3%)	0 (0.0%)	-	7 (15.6%)	0 (0.0%)	-	-	-40.7% (6.8) (analyzed, n = 51)	-	-21.2 (17.7) -32.5% (analyzed, n = 30)
		41.1 (15.6)	25/31		Abrocitinib 100 mg QD through 12 weeks	54	-9.8 (analyzed, n = 43)	16 (27.8%)*	-	30 (55.6%)	22 (40.7%)	8 (25.9%)	-	27 (50.0%)	10 (18.5%)	-	-	-59.0% (6.2) (analyzed, n = 56)	-	-33.1 (21.4) -51.6% (analyzed, n = 43)
		38.7 (17.6)	27/28		Abrocitinib 200 mg QD through 12 weeks	48	-9.5 (analyzed, n = 46)	24 (44.5%)*	-	38 (79.2%)	31 (64.6%)	25 (52.1%)	-	35 (72.9%)	18 (37.5%)	-	-	-82.6% (6.2) (analyzed, n = 55)	-	-41.4 (15.4) -68.5% (analyzed, n = 42)
NCT03055195 ¹⁵	Phase II 2017	30.8 (10.0)	7/9	EAS≥16 IGA≥3 BSA≥10%	Placebo, Q4W through week 12	16	-	0 (0%)*	-	-	-	-	-	-	-	-	-	-22.4% (31.7) (analyzed, n = 11)	-	-
		34.6 (14.0)	6/12		Mepolizumab 100 mg Q4W through week	18	-	2 (11.1%)*	-	-	-	-	-	-	-	-	-	-42.5% (49.2)	-	-

					12													(analyzed, n = 11)		
Ruzicka et al, 2017¹⁵ NCT01986933¹⁷	Phase II 2013-2015	37.0 (13.1)	28/25	Moderate to severe AD EAS $\geq$ 10 sIGA $\geq$ 3 Allowed to use concurrent TCS	Placebo Q4W through 12 weeks	43	-	-	30 (70.6%)	16 (36.7%)	8 (18.3%)	-	22 (55.8%) (analyzed, n = 39)	6 (15.3%) (analyzed, n = 39)	1 (3.1%) (analyzed, n = 39)	-	29.0 (14.0)	-10.7 -37.0%	-	-23.6% (analyzed, n = 39)
		33.5 (10.3)	25/28		Nemolizumab 0.1 mg/kg Q4W through 12 weeks	45	-	-	26 (58.2%)	20 (44.3%)	15 (32.3%)	-	24 (61.9%) (analyzed, n = 39)	10 (26.7%) (analyzed, n = 39)	1 (2.5%) (analyzed, n = 39)	-	32.4 (16.1)	-9.7 -29.8%	-	-35.0% (analyzed, n = 39)
		33.7 (11.7)	32/22		Nemolizumab 0.5 mg/kg Q4W through 12 weeks	46	-	-	30 (66.2%)	24 (51.3%)	17 (37.7%)	-	27 (67.2%) (analyzed, n = 40)	15 (37.8%) (analyzed, n = 40)	8 (20.7%) (analyzed, n = 40)	-	28.6 (15.0)	-12.4 -43.5%	-	-39.2% (analyzed, n = 40)
		34.4 (11.9)	21/31		Nemolizumab 2.0 mg/kg Q4W through 12 weeks	46	-	-	34 (73.9%)	21 (46.0%)	10 (22.3%)	-	27.5 (67.0%) (analyzed, n = 41)	15 (37.4%) (analyzed, n = 41)	7 (16.2%) (analyzed, n = 41)	-	28.2 (12.3)	13.1 -46.3%	-	-41.4% (analyzed, n = 41)
Bruin-Weller et al, 2018¹⁸ NCT02755649¹⁹	Phase III CAFÉ 2016-2017	37.5	40/68	EAS $\geq$ 20 IGA $\geq$ 3 BSA $\geq$ 10%	Placebo + TCS (medium potency) through 16 weeks	108	-	-	-	45 (42.0%)§	26 (24.1%)§	8 (7.4%)§	-	-	-	-	31.7 (median)	-44.7%§	67.5 (median)	-29.1%§
		38.0	42/65		Dupilumab Q2W + TCS (medium potency) through 16 weeks	107	-	-	-	94 (87.9%)§	69 (64.5%)§	38 (35.2%)§	-	-	-	-	31.6 (median)	-78.9%§	66.7 (median)	-60.3%§
		38.0	44/66		Dupilumab QW + TCS (medium potency) through 16 weeks	110	-	-	-	93 (84.7%)§	69 (62.7%)§	43 (39.0%)§	-	-	-	-	31.1 (median)	-77.5%§	66.1(median)	-57.4%§
Guttman-Yassky et al, 2018a²¹ NCT01941537²¹	Phase IIa 2014-2016	41.3 (16.3)	11/9	SCORAD $\geq$ 30 IGA $\geq$ 3 Allowed to use class 6 or 7 TCS	Placebo Q2W through 10 weeks	20	-	1 (5%)*	-	-	-	-	-	3 (15%)	-	-	-	-	55.5 (13.4)	-8.0 -14.7%
		40.5 (14.9)	17/23		Fezakinumab 300 mg (loading dose 600 mg) Q2W through 10 weeks	40	-	6 (15%)*	-	-	-	-	-	9 (22.5%)	-	-	-	-	53.4 (13.1)	-13.8 -23.0%
Guttman-Yassky et al, 2018b²² NCT01979016²³	Phase II 2013-2015	43	13/14	Moderate to severe AD EAS $\geq$ 16 Prohibited concurrent TCS use	Placebo QW through 16 weeks	25	-	-	-	-	-	-	-	-	-	-	34 (median)	-9.0%§	-	-
		35	11/16		Dupilumab 200 mg QW (loading dose 400 mg) through 16 weeks	26	-	-	-	-	-	-	-	-	-	-	30 (median)	-73.8%§	-	-
Guttman-Yassky et al, 2018c²⁴ NCT02576938²⁵	Phase II 2016-2017	37.3 (13.5)	25/24	EAS $\geq$ 12 BSA $\geq$ 10%	Placebo QD + TCS (class III) through 16 weeks	49	-	4 (8%)	-	15 (31%)	6 (12%)	3 (6%)	-	-	-	-	22.1 (median)	-38.4%§	55 (median)	-24.9%§
		40.0 (14.4)	15/22		Baricitinib 2 mg QD + TCS (class III) through 16 weeks	37	-	4 (11%)	-	21 (57%)	12 (32%)	4 (11%)	-	-	-	-	22.1 (median)	-55.5%§	53.3 (median)	-37.6%§
		36.4 (14.5)	16/22		Baricitinib 4 mg QD + TCS (class III) through 16 weeks	38	-	9 (24%)	-	24 (63%)	14 (37%)	8 (21%)	-	-	-	-	19.5 (median)	-63.1%§	57.6 (median)	-46.8%§
Sacki et al, 2018²⁶ NCT01945086²⁷	Phase II 2013-2014	32.6 (10.5)	8/19	Severe or very severe AD EAS $\geq$ 12 IGA 4 or 5 Allowed to use concurrent TCS (low potency)	Placebo at week 0 and week 4	27	-0.7	0 (0.0%)	-	11 (41%)	4 (15%)	-	-	-	-	-	37.4 (12.2)	-14.0 -37.5%	-	-
		37.5 (8.8)	7/17		Ustekinumab 45 mg at week 0 and week 4	24	-1.6	0 (0.0%)	-	9 (38%)	2 (8%)	-	-	-	-	-	38.0 (10.9)	-14.5 -38.2%	-	-
		33.0 (8.9)	9/19		Ustekinumab 90 mg at week 0 and week 4	28	-1.7	0 (0.0%)	-	10 (36%)	5 (18%)	-	-	-	-	-	36.5 (12.6)	-14.5 -39.8%	-	-
Simpson et al, 2018a²⁸	Phase II 2014-2016	37.7 (14.7)	39/25	Moderate to severe AD EAS $\geq$ 12	Placebo BID through 12 weeks	64	-	4 (6.3%)	-	21 (32.8%)	-	-	-	-	-	-	24.0	-2.7 -11.0% (6.9)	-	-

NCT02087943 ²⁹				BSA≥10% sPGA-A≥3 Allowed to use concurrent TCS													(analyzed, n = 62)			
	39.2 (15.8)	27/31	Apremilast 30 mg BID through 24 weeks		58	-	2 (3.4%)	-	18 (31.0%)	-	-	-	-	-	24.2	-6.3 -26.0% (7.1)	-	-		
	38.3 (14.7)	32/31	Apremilast 40 mg BID through 24 weeks		63	-	9 (14.3%)	-	27 (42.9%)	-	-	-	-	-	23.6	-7.5 -31.6% (6.8)	-	-		
Simpson et al, 2018b ³⁰ NCT02340234 ³¹	Phase II 2015-2016 TREBLE	38.7 (13.2)	17/36	Moderate to severe AD EASL≥14 IGA≥3 BSA≥10%	Placebo + TCS (class IV) through 12 weeks	53	-33.6%	10 (18.9%)	-	33 (62.3%)	18 (34.0%)	-	-	14 (26.4%)	-	-	23.6 (9.2)	-12.5 -53.1%	59.2 (12.0)	-30.0 -35.4%
		34.9 (12.7)	18/34		Lebrikizumab 125 mg SD + TCS (class IV) through 12 weeks	52	-34.3%	11 (21.2%)	-	36 (69.2%)	20 (38.5%)	-	-	18 (34.6%)	-	-	24.6 (11.1)	-14.4 -58.5%	56.5 (13.4)	-21.9 -38.7%
		34.4 (12.3)	22/31		Lebrikizumab 250 mg SD + TCS (class IV) through 12 weeks	53	-40.7%	15 (28.3%)	-	37 (69.8%)	26 (49.1%)	-	-	25 (47.2%)	-	-	26.3 (12.2)	-15.2 -57.7%	58.9 (13.5)	-25.1 -42.6%
		36.6 (12.3)	16/35		Lebrikizumab 125 mg Q4W + TCS (class IV) through 12 weeks	51	-43.1%	17 (33.3%)	-	42 (82.4%)	28 (54.9%)	-	-	26 (51.0%)	-	-	26.9 (11.7)	-19.0 -70.5%	60.8 (13.6)	-32.5 -53.5%
Simpson et al, 2018c ³² NCT02525094 ³³	Phase IIa ALLEVIAD 2015-2016	38.8 (15.3)	26/30	Moderate to severe AD EASL≥12 SCORAD≥20 IGA≥3 BSA≥10%	Placebo Q2W + TCS (class III) through 10 weeks	56	-	7 (12.8%)*	-	27 (48.2%)	11 (19.8%)	-	-	16 (29.4%)	4 (7.4%)	-	24.5 (11.2)	-11.2 (8.7) (analyzed, n = 50)	58.7 (13.3)	-19.4 (17.5) (analyzed, n = 50)
		38.5 (14.9)	23/32		Tezepelumab 280 mg Q2W + TCS (class III) through 10 weeks	55	-	11 (19.3%)*	-	36§ (64.7%)	13 (24.4%)	-	-	23 (41%)	5 (9.8%)	-	24.1 (12.4)	-12.2 (10.0) (analyzed, n = 49)	57.7 (14.8)	-24.2 (16.9) (analyzed, n = 49)
Wollenberg et al, 2018 ³⁴ NCT02347176 ³⁵	Phase IIb 2015-2016	39.4 (14.5)	29/22	EASL≥12 SCORAD≥25 IGA≥3 BSA≥10%	Placebo Q2W + TCS (class III) through 12 weeks	51	-	6 (11.8%)*	-	26 (51.9%)	8 (15.5%)	-	-	10 (19.5%)	-	-	26.4 (12.6)	-10.8 (1.4)	58.5 (12.9)	-16.7 (2.2)
		39.1 (15.1)	21/29		Tralokinumab 45 mg Q2W + TCS (class III) through 12 weeks	50	-	6 (11.6%)*	-	27 (54.3%)§	16 (32.1%)§	-	-	13 (26.9%)	-	-	24.8 (8.3)	-13.7 (1.4)	57.5 (12.6)	-22.0 (2.2)
		37.1 (14.0)	25/26		Tralokinumab 150 mg Q2W + TCS (class III) through 12 weeks	51	-	10 (19.5%)*	-	34 (67.3%)§	22 (43.6%)§	-	-	23 (44.2%)	-	-	27.1 (11.2)	-15.1 (1.4)	60.8 (11.9)	-26.1 (2.2)
		35.7 (14.6)	19/33		Tralokinumab 300 mg Q2W + TCS (class III) through 12 weeks	52	-	13 (26.7%)*	-	38 (73.4%)	22 (42.5%)	-	-	23 (44.1%)	-	-	27.3 (10.9)	-15.7 (1.3)	60.8 (12.3)	-26.5 (2.1)
Guttman- Yassky et al, 2019 ³⁶ NCT02683928 ³⁷	Phase IIa 2016-2017	40.4 (15.1)	5/11	Moderate to severe AD EASL≥12 SCORAD≥20 IGA≥3 Allowed to use concurrent TCS (class 6 or 7)	Placebo day 1+29	16	-	-	-	-	-	-	-	-	-	23.3 (9.4)	-11.6 -49.8%§	55.5 (10.4)	-	
		36.2 (13.4)	25/21		GBR-830 10mg/kg day 1+29	46	-	-	-	-	-	-	-	-	25.1 (12.3)	-13.4 -53.3%§	61.8 (14.3)	-		

Supplemental table S4 – Clinical trials that contain placebo response data at week 16

Reference	Study type, period (and name)	Mean age of patients or range, baseline (SD)	Sex, baseline (Female/Male)	AD severity for eligibility	Medication, interval and dose	n total (number analyzed)	Mean DLQ1 % or points change from baseline to week 16	n IGA score 0/1 at week 16	n EASI 25 at week 16	n EASI50 at week 16	n EASI75 at week 16	n EASI90 at week 16	n SCORAD25 at week 16	n SCORAD50 at week 16	n SCORAD75 at week 16	n SCORAD90 at week 16	Mean EASI, baseline	Mean EASI change from baseline to week 16, points and/or % (SD)	Mean SCORAD, baseline	Mean SCORAD change from baseline to week 16, points and/or % (SD)
Thaçi et al, 2015 ¹ NCT01859988 ⁶	Phase IIb 2013-2014	37.2 (13.1)	21/40	EASEx16 IGAEx3 BSAEx10% Prohibited concurrent TCS use	Placebo QW through 15 weeks	61	2.6%	1 (2%)	-	18 (29.5%)	7 (11.5%)	2 (3.3%)	-	12 (19.7%)	2 (3.3%)	0 (0.0%)	32.9 (13.8)	-7.3	67.1 (13.6)	-12.4
		36.2 (10.7)	20/43		Dupilumab 300 mg QW (loading dose 600 mg) through 15 weeks	63	-59.0%	21 (33%)	-	52 (82.5%)	38 (60.3%)	23 (36.5%)	-	43 (68.3%)	15 (23.8%)	4 (6.3%)	30.1 (11.2)	-22.9	65.0 (12.2)	-38.9
		39.4 (12.06)	23/41		Dupilumab 300 mg Q2W (loading dose 600 mg) through 15 weeks	64	-39.6%	19 (30%)	-	50 (78.1%)	34 (53.1%)	19 (29.7%)	-	38 (59.4%)	16 (25.0%)	4 (6.3%)	33.8 (14.5)	-23.1	68.5 (12.6)	-36.8
		35.8 (14.90)	25/36		Dupilumab 200 mg Q2W (loading dose 400 mg) through 15 weeks	61	-43.3%	17 (28%)	-	38 (62.3%)	34 (55.7%)	19 (31.1%)	-	32 (52.5%)	10 (16.4%)	3 (4.9%)	32.9 (15.5)	-22.0	68.3 (14.0)	-32.9
		36.8 (10.8)	25/40		Dupilumab 300 mg Q4W (loading dose 600 mg) through 15 weeks	65	-37.4%	14 (22%)	-	46 (70.8%)	32 (49.2%)	19 (29.2%)	-	36 (55.4%)	14 (21.5%)	2 (3.1%)	29.4 (11.5)	-19.6	67.2 (12.3)	-34.6
		36.6 (11.6)	31/34		Dupilumab 100 mg Q4W (loading dose 400 mg) through 15 weeks	65	-11.9%	8 (12%)	-	29 (44.6%)	19 (29.2%)	10 (15.4%)	-	17 (26.2%)	5 (7.7%)	2 (3.1%)	32.2 (13.5)	-14.8	68.2 (15.0)	-20.1
Khattari et al, 2016 ⁷ NCT01806662 ⁸	Phase II 2013-2015 Crossover design	40	6/10	Moderate to severe AD SCORADEx15	Placebo Q4W first for 16 weeks, then Ustekinumab for 16 weeks + TCS (class VI)	16	-6.1	-	-	-	-	-	-	3 (18.8%)	2 (12%)	-	-	-	69.7	-25.9
		37	6/10		Ustekinumab 45/90 mg Q4W first for 16 weeks, then placebo for 16 weeks + TCS (class VI)	16	-4.4	-	-	-	-	-	-	5 (31.3%)	0 (0%)	-	-	-	65.4	-19.8
NCT02002208 ^{9,10}	Phase II 2013-2016	30.9 (8.5)	31/39	Moderate to severe AD	Placebo orally QD	70	-	-	-	-	-	-	-	-	-	-	-	-6.1 (1.7)	-	-
		31.6 (8.4)	29/40		Timapiprant 50 mg orally QD	69	-	-	-	-	-	-	-	-	-	-	-	-3.8 (1.7)	-	-
Simpson et al, 2016a ⁹ NCT02277743 ¹⁰	Phase III SOLO1 2014-2016	39.0 (median)	106/118	Moderate to severe AD EASEx16 IGAEx3 BSAEx10% Prohibited concurrent TCS use	Placebo Q2W through 16 weeks	224	-5.6 (analyzed, n = 97)	23 (10.3%)*	-	55 (24.6%)	33 (14.7%)	17 (7.6%)	-	-	-	-	34.5	-13.0 -37.6% (3.3)	68.3	-19.8 -29.0% (3.2)
		38.0 (median)	94/130		Dupilumab 300 mg Q2W through 16 weeks	224	-9.0 (analyzed, n = 173)	85 (37.9%)*	-	154 (68.8%)	115 (51.3%)	80 (35.7%)	-	-	-	-	33.0	-23.9 -72.3% (2.6)	66.9	-38.6 -57.7% (2.1)
		39.0 (median)	81/142		Dupilumab 300 mg QW through 16 weeks	223	-8.8 (analyzed, n = 162)	83 (37.2%)*	-	136 (61.0%)	117 (52.5%)	74 (33.2%)	-	-	-	-	33.2	-23.9 -72.0% (2.6)	67.5	-38.5 -57.0% (2.1)
Simpson et al, 2016b ⁹ NCT02277769 ¹¹	Phase III SOLO2 2014-2016	35.0 (median)	104/132	Moderate to severe AD EASEx16 IGAEx3 BSAEx10% Prohibited	Placebo Q2W through 16 weeks	236	-4.0 (analyzed, n = 105)	20 (8.5%)*	-	52 (22.0%)	28 (11.9%)	17 (7.2%)	-	-	-	-	33.6	-10.4 -30.9% (3.0)	69.2	-13.6 -19.7% (2.5)
		34.0 (median)	96/137		Dupilumab 300 mg Q2W	233	-9.7	84 (36.1%)*	-	152 (65.2%)	103 (44.2%)	70 (30%)	-	-	-	-	31.8	-21.3 -67.1%	67.2	-34.3 -51.1%

				concurrent TCS use	through 16 weeks		(analyzed, n = 197)											(2.5)		(2.0)
		35.0 (median)	100/139		Dupilumab 300 mg QW through 16 weeks	239	-10.3 (analyzed, n = 191)	87 (36.4%)*	-	146 (61.1%)	115 (48.1%)	73 (30.5%)	-	-	-	-	31.9	-22.0 -69.1% (2.5)	67.5	-36.1 -53.5% (2.0)
Blauvelt et al, 2017¹² NCT02260986¹³	Phase III 2014-2016 CHRONOS	36.6 (13.0)	122/193	IGA≥3 EAS≥16	Placebo + TCS (medium-low potency) through 52 weeks	315	-5.3	39 (12.4%)	-	118 (37%)	73 (23.2%)	33 (11%) (analyzed, n = 264)	-	-	-	-	32.6 (12.9)	-13.7 -43.2% (2.3)	66.0 (13.5) (analyzed, n = 313)	-21.0 -31.8% (1.55)
		39.6 (14.0)	44/62		Dupilumab 300 mg Q2W (loading dose 600 mg) + TCS (medium-low potency) through 52 weeks	106	-9.7	41 (38.7%)	-	85 (80%)	73 (68.9%)	39 (43%) (analyzed, n = 89)	-	-	-	-	33.6 (13.3)	-25.1 -76.7% (3.8)	69.3 (15.2) (analyzed, n = 105)	-43.0 -62.1% (2.61)
		36.9 (13.7)	128/191		Dupilumab 300 mg QW (loading dose 600 mg) + TCS (medium-low potency) through 52 weeks	319	-10.5	125 (39.2%)	-	249 (78%)	204 (63.9%)	124 (40%) (analyzed, n = 270)	-	-	-	-	32.1 (12.8)	-25.2 -77.3% (2.2)	65.9 (13.6) (analyzed, n = 316)	-41.7 -63.3% (1.53)
NCT02780167¹⁴	Phase IIb 2016-2017	42.6 (15.1)	35/21	EAS≥12 IGA≥3 BSA≥10% Prohibited concurrent TCS use	Placebo, QD through 12 weeks	28	-4.5 (analyzed, n = 27)	3 (10.7%)*	-	12 (42.9%)	9 (32.1%)	4 (14.3%)	-	11 (39.3%)	4 (14.3%)	-	-	-35.9% (47.7)	-	-19.4 (22.2)
		44.3 (15.9)	28/21		Abrocitinib 10 mg QD through 12 weeks	26	-4.5 (analyzed, n = 26)	6 (23.1%)*	-	11 (42.3%)	10 (38.5%)	6 (23.1%)	-	8 (30.8%)	3 (11.5%)	-	-	-45.2% (44.6)	-	-18.9 (21.5)
		37.6 (15.9)	29/22		Abrocitinib 30 mg QD through 12 weeks	27	-3.5 (analyzed, n = 26)	2 (7.4%)*	-	9 (33.3%)	1 (3.7%)	1 (3.7%)	-	4 (14.8%)	0 (0.0%)	-	-	-20.8% (47.9)	-	-12.7 (15.9)
		41.1 (15.6)	25/31		Abrocitinib 100 mg QD through 12 weeks	36	-4.6 (analyzed, n = 34)	5 (13.9%)*	-	15 (41.7%)	9 (25.0 %)	3 (8.3%)	-	9 (25.0%)	4 (11.1%)	-	-	-27.7% (54.6)	--	-17.8 (19.2)
		38.7 (17.6)	27/28		Abrocitinib 200 mg QD through 12 weeks	38	-3.6 (analyzed, n = 38)	7 (18.4%)*	-	26 (68.4%)	14 (36.8%)	4 (10.5%)	-	13 (34.2%)	1 (2.6%)	-	-	-55.8% (32.8)	-	-21.0 (18.16)
NCT03055195¹⁵	Phase II 2017	30.8 (10.0)	7/9	EAS≥16 IGA≥3 BSA≥10%	Placebo Q4W through week 12	16	-	0 (0.0%)	-	-	-	-	-	-	-	-	-	-32.3% (27.8) (analyzed, n = 8)	-	-
		34.6 (14.0)	6/12		Mepolizumab 100 mg Q4W through week 12	18	-	2 (11.1%)	-	-	-	-	-	-	-	-	-	-31.9% (50.1) (analyzed, n = 6)	-	-
Blauvelt et al, 2018¹⁹ NCT02210780⁴⁰	Phase II EVALUATE 2014-2015	40 (14)	41/46	Moderate-to-severe AD EAS≥16 IGA≥3 BSA≥10% Allowed to use concurrent TCS	Placebo QW + Tdap (vaccine) + MSPV4 (vaccine)	97	-	10 (10.3%)		31 (32.0%)	19 (19.6%)	-	-	-	-	31 (14)	-	-	-	
		39 (14)	48/49		Dupilumab 300 mg QW (loading dose 600 mg) + Tdap (vaccine) + MSPV4 (vaccine)	97	-	43 (44.3%)		70 (72.2%)	52 (53.6%)	-	-	-	-	29 (13)	-	-	-	
Bruin-Weller et al, 2018¹⁸ NCT02755649¹⁹	Phase III CAFÉ 2016-2017	37.5	40/68	EAS≥20 IGA≥3 BSA≥10%	Placebo + TCS (medium potency) through 16 weeks	108	-4.5%	15 (13.9%)*	-	47 (43.5%)	32 (29.6%)	13 (12.0%)	-	28 (25.9%)	-	-	31.7 (median)	-46.6%	67.5 (median)	-29.5%
		38.0	42/65		Dupilumab Q2W + TCS (medium potency) through 16 weeks	107	-9.5%	43 (40.2%)*	-	91 (85.0%)	67 (62.6%)	49 (45.8%)	-	71 (66.4%)	-	-	31.6 (median)	-79.8%	66.7 (median)	-62.4%

		38.0	44/66		Dupilumab QW + TCS (medium potency) through 16 weeks	110	-8.8%	43 (39.1%)*	-	94 (85.5%)	65 (59.1%)	41 (37.3%)	-	61 (55.5%)	-	-	31.1 (median)	-78.2%	66.1(median)	-58.3%
Guttman-Yassky et al, 2018a ²⁰ NCT01941537 ²¹	Phase IIa 2014-2016	41.3 (16.3)	11/9	SCORAD≤30 IGA≤3 Allowed to use class 6 or 7 TCS	Placebo Q2W through 10 weeks	20	-	-	-	-	-	-	-	-	-	-	-	-	55.5 (13.4)	-11.5§
		40.5 (14.9)	17/23		Fezakinumab 300 mg (loading dose 600 mg) Q2W through 10 weeks	40	-	-	-	-	-	-	-	-	-	-	-	-	53.4 (13.1)	-17.2§
Guttman-Yassky et al, 2018b ²² NCT01979016 ²³	Phase II 2013-2015	43	13/14	Moderate to severe AD EASE16 Prohibited concurrent TCS use	Placebo QW through 16 weeks	25	-	0 (0.0%)	-	6 (22.2%)	4 (14.8%)	0 (0.0%)	-	2 (7.4%)	0 (0.0%)	0 (0.0%)	34 (median)	-3.7 (2.7) -5.8%	64 (median)	-5.1 (3.6)
		35	11/16		Dupilumab 200 mg QW (loading dose 400 mg) through 16 weeks	26	-	10 (37.0%)	-	21 (77.8%)	18 (66.7%)	9 (33.3%)	-	15 (55.6%)	3 (11.1%)	2 (7.4%)	30 (median)	-25.2 (2.7) -75.2%	65 (median)	-36.4 (3.6)
Guttman-Yassky et al, 2018c ²⁴ NCT02576938 ²⁵	Phase II 2016-2017	37.3 (13.5)	25/24	EASI≥ 12 BSA≥10%	Placebo QD + TCS (class III) through 16 weeks	49	-6.27	4 (8%)	-	18 (37%)	10 (20%)	3 (6%)	-	-	-	-	22.1 (median)	-10.8 (1.6) -45.9%	55 (median)	-11.9 (2.9) -21%
		40.0 (14.4)	15/22		Baricitinib 2 mg QD + TCS (class III) through 16 weeks	37	-6.89	8 (22%)	-	21 (57%)	11 (30%)	7 (19%)	-	-	-	-	22.1 (median)	-16.4 (1.7) -64.2%	53.3 (median)	-23.9 (3.0) -41%
		36.4 (14.5)	16/22		Baricitinib 4 mg QD + TCS (class III) through 16 weeks	38	-7.96	8 (21%)	-	23 (61%)	13 (34%)	8 (21%)	-	-	-	-	19.5 (median)	-16.0 (1.7) -64.7%	57.6 (median)	-26.5 (3.0) -47%
Guttman-Yassky et al, 2018d ⁴¹ NCT02925117 ⁴² Conference abstract (AbbVie) – ongoing study	Phase IIb 2016-2019	-	-	Moderate to severe AD EASE16 IGA≥3 BSA≥10%	Placebo QD through 16 weeks	41	-	1 (2%)	-	-	4 (10%)	1 (2%)	-	-	-	-	-	-23%	-	-
		-	-		Upadacitinib 30 mg QD through 16 weeks	42	-	21 (50%)	-	-	29 (69%)	21 (50%)	-	-	-	-	-	(analyzed, n = 39) -74.4%	-	-
		-	-		Upadacitinib 15 mg QD through 16 weeks	42	-	13 (31%)	-	-	22 (52%)	11 (26%)	-	-	-	-	-	-61.7%	-	-
		-	-		Upadacitinib 7.5 mg QD through 16 weeks	41	-	6 (14%)	-	-	12 (29%)	6 (14%)	-	-	-	-	-	-39.4%	-	-
Sacki et al, 2018 ²⁶ NCT01945086 ²⁷	Phase II 2013-2014	30.0	8/19	Severe or very severe AD EASE12 IGA 4 or 5 Allowed to use concurrent TCS (low potency)	Placebo at week 0 and week 4	26	-	2 (7.7%)	-	11 (42.3%)	5 (19.2%)	-	-	-	-	-	37.4 (12.2)	-15.0 -40.0% (40.6)	-	-
		38.5	7/17		Ustekinumab 45 mg at week 0 and week 4	24	-	0 (0.0%)	-	10 (41.7%)	4 (16.7%)	-	-	-	-	-	38.0 (10.9)	-14.6 -38.4% (34.2)	-	-
		34.0	9/19		Ustekinumab 90 mg at week 0 and week 4	27	-	1 (3.7%)	-	12 (44.4%)	3 (11.1%)	-	-	-	-	-	36.5 (12.6)	-16.2 -44.4% (40.2)	-	-
Simpson et al, 2018c ³² NCT02525094 ³³	Phase IIa ALLEVIAD 2015-2016	38.8 (15.3)	26/30	Moderate to severe AD EASE12 SCORAD≤20 IGA≤3 BSA≥10%	Placebo Q2W + TCS (class III) through 10 weeks	56	-	6 (13.0%)§	-	23 (50.3%)§	9 (20.3%)§	4 (8.8%)§	-	-	-	-	24.5 (11.2)	-13.2 -53.8%§	58.7 (13.3)	-22.8 -38.8%§
		38.5 (14.9)	23/32		Tezepelumab 280 mg Q2W + TCS (class III) through 10 weeks	55	-	13 (29.6%)§	-	27 (59.9%)§	16 (34.8%)§	9 (19.4%)§	-	-	-	-	24.1 (12.4)	-15.1 -62.7%§	57.7 (14.8)	-27.6 -47.8%§
Wollenberg et al, 2018 ³⁴ NCT02347176 ³⁵	Phase IIb 2015-2016	39.4 (14.5)	29/22	EASE12 SCORAD≤25 IGA≤3 BSA≥10%	Placebo Q2W + TCS (class III) through 12 weeks	51	-	-	-	-	-	-	-	-	-	-	26.4 (12.6)	-10.3§	58.5 (12.9)	-15.2§
		39.1 (15.1)	21/29		Tralokinumab 45 mg Q2W + TCS (class III) through 12 weeks	50	-	-	-	-	-	-	-	-	-	-	24.8 (8.3)	-14.0§	57.5 (12.6)	(analyzed, n = 38) -23.0§
		37.1 (14.0)	25/26		Tralokinumab 150 mg Q2W +	51	-	-	-	-	-	-	-	-	-	-	27.1 (11.2)	-14.4§	60.8 (11.9)	(analyzed, n = 37) -21.4§

					TCS (class III) through 12 weeks															(analyzed, n = 41)
		35.7 (14.6)	19/33		Tralokinumab 300 mg Q2W + TCS (class III) through 12 weeks	52	-	-	-	-	-	-	-	-	-	-	27.3 (10.9)	-15.7§	60.8 (12.3)	-25.6§ (analyzed, n = 46)

Supplemental table S5 – Clinical trials that contain placebo response data at week 52

Reference	Study type, period (and name)	Mean age of patients or range, baseline (SD)	Sex, baseline (Female/Male)	AD severity for eligibility	Medication and dose	n total (number analyzed)	% or points DLQI change from baseline to week 52	n IGA score 0/1 at week 52	n EASI 25 at week 52	n EASI50 at week 52	n EASI75 at week 52	n EASI90 at week 52	n SCORAD25 at week 52	n SCORAD50 at week 52	n SCORAD75 at week 52	n SCORAD90 at week 52	Mean EASI, baseline	Mean EASI change from baseline to week 52, points and/or % (SD)	Mean SCORAD, baseline	Mean SCORAD change from baseline to week 52, points and/or % (SD)
Novak et al, 2012 ¹¹	Phase III 2007-2009	32.9 (11.0)	28/28	Moderate to severe AD aggravated by house dust mites Allowed to use concurrent TCS	Placebo	56	-	-	-	-	-	-	-	-	-	-	-	-	62.5	-30.8§ (median)
		34.2 (11.9)	50/62		Subcutaneous allergen-specific immunotherapy with depigmented polymerized mite extract	112	-	-	-	-	-	-	-	-	-	-	-	-	58.0	-31.0§ (median)
Blauvelt et al, 2017 ¹² , NCT02260986 ¹³	Phase III 2014-2016 CHRONOS	36.6 (13.0)	122/193	EASIE16 IGA≥3	Placebo + TCS (medium-low potency) through 52 weeks	264	-7.2	33 (12.5%)	-	79 (30%)	57 (21.6%)	41 (16%)	-	-	-	-	32.6 (12.9)	-14.2 -45.8% (2.7)	66.0 (13.5) (analyzed, n = 313)	-22.5 -34.1% (1.9)
		39.6 (14.0)	44/62		Dupilumab 300 mg Q2W (loading dose 600 mg) + TCS (medium-low potency) through 52 weeks	89	-11.4	32 (36.0%)	-	70 (79%)	58 (65.2%)	45 (51%)	-	-	-	-	33.6 (13.3)	-25.9 -78.3% (4.4)	69.3 (15.2) (analyzed, n = 105)	-45.9 -66.2% (3.1)
		36.9 (13.7)	128/191		Dupilumab 300 mg QW (loading dose 600 mg) + TCS (medium-low potency) through 52 weeks	270	-11.1	108 (40.0%)	-	189 (70%)	173 (64.1%)	137 (51%)	-	-	-	-	32.1 (12.8)	-25.9 -80.3% (2.6)	65.9 (13.6) (analyzed, n = 316)	-43.6 -66.1% (1.9)

Abbreviations for table S2-S4

§: Data extraction using Engauge Digitizer version 11.1

-: No data was given

*: n IGA score 0/1 and ≥2 points improvement

AD: Atopic dermatitis

BID: Twice daily

EASI: Eczema Area and Severity Index

MSPV4: Quadrivalent meningococcal polysaccharide vaccine

SCORAD: Scoring atopic dermatitis

QD: Once daily

QW: Once weekly

Q2W: Once every two weeks

Q4W: Once every four weeks

SD: Single dose *or* Standard deviation

TCS: Topical corticosteroid

Supplemental table S6 – Mean change in placebo-response measured with EASI score.

Week	Score	Therapy	Points (95% CI)	% (95% CI)
12	EASI	All	-10.8 (-12.8 - -8.8)	-35.1 (-41.0 - -29.2)
		+TCS	-13.5 (-16.6 - -10.6)	-45.2 (-51.5 - -38.9)
		-TCS	-10.1 (-13.3 - -6.8)	-29.7 (-36.5 - -23.0)
	SCORAD	All	-18.5 (-22.9 - -14.0)	-28.3 (-33.5 - -23.1)
		+TCS	-21.7 (-26.5 - -16.8)	-31.6 (-37.1 - -26.1)
		-TCS	-11.7 (-23.3 - -0.2)	-25.2 (-40.4 - -10.0)
16	EASI	All	-11.5 (-13.5 - -9.6)	-38.6 (-44.5 - -32.6)
		+TCS	-13.0 (-15.3 - -10.6)	-45.3 (-51.3 - -39.3)
		-TCS	-10.8 (-15.2 - -6.4)	-32.9 (-45.6 - -20.2)
	SCORAD	All	-17.5 (-20.5 - -14.6)	-27.9 (-34.2 - -21.5)
		+TCS	-19.9 (-24.6 - -15.2)	-31.1 (-38.5 - -23.6)
		-TCS	-15.6 (-22.8 - -8.3)	-

-: No data was given

CI: Confidence interval

EASI: Eczema Area and Severity Index

SCORAD: Scoring atopic dermatitis

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