

Efficacy and safety of subcutaneous allergen-specific immunotherapy with depigmented polymerized mite extract in atopic dermatitis

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Background: Exposure to house dust mites (HDMs) aggravates the course of atopic dermatitis (AD) in patients sensitized to HDMs.

Objectives: This study investigated the efficacy and safety of subcutaneous allergen-specific immunotherapy with the use of depigmented polymerized mite extract as an add-on therapy to basic (ie, topical and, as necessary, systemic) medication.

Methods: Patients (n = 168) were recruited in a randomized, double-blind, placebo-controlled parallel group phase III study conducted in Germany (21 sites), in adult patients with AD aggravated by HDMs. The primary end points of the study were the assessments of the area under the curves of the total Severity Scoring Atopic Dermatitis (SCORAD) score and of the use of basic medication during the 18-month treatment period. *Post hoc* subgroup analyses were also performed.

Results: Overall efficacy analysis of the intention-to-treat and per-protocol study populations showed no statistically significant differences between the active treatment and placebo groups. However, the subgroup of patients with severe AD (SCORAD > 50) showed a statistically significant reduction of

the median total SCORAD by 18% ($P = .02$) compared with placebo. The frequency of adverse reactions was similar in both groups, suggesting the safety of the active treatment.

Conclusion: Although subcutaneous allergen-specific immunotherapy showed no statistically significant difference in the overall population of patients with AD, statistically significant reduction of the total SCORAD could be achieved in a subgroup of patients with severe AD. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Allergy, atopic dermatitis, house dust mites, specific immunotherapy

Aeroallergens, such as house dust mite (HDM) and birch or grass pollen allergens can, among other exogenous and endogenous triggers, aggravate the course of atopic dermatitis (AD) in sensitized patients.¹ Treatment of clinical symptoms of AD caused by sensitization, such as acute flare-ups and exacerbation of the disease, has been limited to symptomatic therapy with anti-inflammatory and antipruritic drugs. Allergen avoidance and encasing strategies as additional therapeutic measures are difficult to implement into everyday life, particularly for perennial allergens such as HDMs that are present not only at home but also at day care centers, at schools, and in the workplace.²

Two routes exist for HDM allergens to enter the body: via the skin and via the airways. Contact of HDM allergens with the epidermis can provoke AD lesions, revealed, for example, by the atopy patch test.³ In sensitized persons, HDM allergens applied under occlusion during atopy patch test induce an eczematous skin reaction within 24 to 48 hours.⁴ Bronchial challenge with HDM allergens also elicits skin lesions in patients with AD, indicating that allergen uptake not only via the skin but also via the respiratory tract plays a role in AD.^{4,5} HDM-specific T cells are present in the skin lesions induced by HDM patch testing.⁶ HDM allergens aggravate the disease, particularly during autumn and winter when indoor heating is in use. Follow-up studies found that sensitization to HDM allergens in patients with AD increases the risk both of persistence of AD and of concomitant development of asthma and other allergic disorders of the respiratory tract.⁷ Thus, sensitization to HDM allergens underlies both the acute flare-ups of AD and the development of a severe, persistent course of the disease, aggravated by cofactors that might together promote the so-called atopic march.⁸

There are many other triggers of AD apart from allergens. Complex genetic modifications and certain combinations of environmental and endogenous factors can direct the course of the disease.¹ In this context it has been found that genetically predetermined skin barrier impairment, caused in part by

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Abbreviations used

AD:	Atopic dermatitis
AUC:	Area under the curve
CONSORT:	Consolidated Standards of Reporting Trials
<i>Der f</i> :	<i>Dermatophagoides farinae</i>
<i>Der p</i> :	<i>Dermatophagoides pteronyssinus</i>
DLQI:	Dermatology Life Quality Index
DPP:	Depigmenting and polymerizing
HDM:	House dust mites
ITT:	Intention to treat
PP:	Per protocol
SCIT:	Subcutaneous allergen-specific immunotherapy
SCORAD:	Severity Scoring of Atopic Dermatitis
V0:	Screening visit

loss-of-function mutations in the filaggrin gene, promote sensitization to HDM allergens as well as AD exacerbation after cutaneous contact to HDM allergens.^{9,10}

Subcutaneous allergen-specific immunotherapy (SCIT) is well established as a long-term treatment of sensitization to HDM in patients with allergic rhinitis or mild asthma.¹¹ The main advantages of SCIT encompass both reduction of symptoms caused by specific sensitization during allergen exposure and prevention of additional sensitization or worsening of asthma.¹² SCIT has shown satisfactory results in individual patients with AD in small uncontrolled studies and in initial controlled studies.^{13,14} However, the value of SCIT for patients with AD remains unclear because only a few well-controlled studies have been performed.¹⁵ More controlled studies are required to evaluate efficacy and safety of SCIT in AD and to identify those patients with AD who might best benefit from SCIT. We therefore performed a double-blind, placebo-controlled, phase III study in 168 adult patients with AD with exacerbated disease, who had been sensitized to HDM. They were treated with SCIT in the form of a depigmented, polymerized mite extract as add-on therapy to basic (ie, topical and, as necessary, systemic) medication.

METHODS

Patients and study design

This was a randomized, double-blind, placebo-controlled, parallel group study. One hundred sixty-eight adult patients (18–66 years of age) with moderate-to-severe AD were recruited at 21 centers in Germany from March 2007 to January 2009 and were randomly assigned to add-on therapy with SCIT treatment or to placebo, in addition to their basic medication, in an allocation ratio of 2:1 (Fig 1). A simple randomization procedure (computerized random numbers) was used. AD was diagnosed according to the criteria of Hanifin and Rajka¹⁶; disease severity was assessed with Severity Scoring Atopic Dermatitis (SCORAD).

A sample size of 150 patients (100 in the SCIT group and 50 in the placebo group) was calculated as being required to show efficacy at a 1-sided significance level of 2.5% with a power of 80%.

Demographic data for the overall population and for the subpopulation of patients with severe AD (SCORAD > 50) at study onset are shown in Table E1 (in this article's Online Repository at www.jacionline.org). Patients with AD were included who had disease duration >2 years, at least 2 exacerbations of eczema or permanent skin lesions during the past 2 months, aggravation of eczema by exposure to HDM during the heating period (September to February), a positive skin prick test to *Dermatophagoides pteronyssinus* (*Der p*) and *Dermatophagoides farinae* (*Der f*) with a wheal diameter of ≥4 mm, a negative

control reaction, and specific IgE for *Der p* or *Der f* in a RAST class of ≥3. Patients were to have implemented encasing strategies for bedding and mattresses for >6 months (stable environmental control). Inclusion and exclusion criteria were comparable with those in a previous study on patients with AD treated with SCIT in the form of polymerized depigmented HDM allergen.¹⁷ Written informed consent was obtained from all patients; the study was approved by the ethics committee and was conducted in accordance with the latest version of the Declaration of Helsinki 2008 and the Good Clinical Practice guidelines (ICH E6/GCP). The EudraCT number of the study was 2006-003066-34. The trial report was written according to the guidance provided in the CONSORT (Consolidated Standards of Reporting Trials) statement.¹⁸

Immunotherapy

SCIT was divided into 2 periods: an initial up-dosing period and a maintenance treatment period. Overall treatment duration per patient was 18 months. The initial up-dosing period during the first 4 weeks after the screening visit (V0) consisted of weekly administration of gradually increasing amounts of placebo or allergen extract. Allergen extract was expressed in "DPP" units, whereby 1 DPP is the result of depigmenting and polymerizing 1 Histamine Equivalent Prick Leti of allergenic extract. Two vials of extract were provided: vial 1 with allergen extract at a concentration of 10 DPP/mL and vial 2 with allergen extract at a concentration of 100 DPP/mL. During the up-dosing period, single-dose treatment was given at 1-week intervals up to the maximum recommended dose as follows: 0.2-mL vial 1, 0.5-mL vial 1, 0.2-mL vial 2, 0.5-mL vial 2. The highest dose was then repeated at 6-week intervals during the maintenance period.

Basic medication provided for all patients is summarized in Table I.

Assessment of efficacy and quality of life

The primary efficacy end points were the total SCORAD scores and the use of basic medication (ie, cumulative application of topical medication and overall consumption of systemic medication), both over the 18-month treatment period. Secondary efficacy was provided by quality-of-life questionnaires with the use of the Dermatology Life Quality Index (DLQI), evaluated for the whole treatment period and for the heating period from September to February.

Measurement of IgE and IgG in the sera

Total serum IgE and allergen-specific IgE was quantified in the sera of subjects with AD with an Immulite 2000 system (Siemens AG, Eschborn, Germany). IgG antibody titres in the sera were analyzed by ELISA (Dr. Focke Laboratorien GmbH, Neuss, Germany).

Assessment of safety

Adverse reactions reported by the patient or noted by the investigator were documented during the whole study according to the European Academy of Allergy and Clinical Immunology scale.¹⁹ Standard hematology, blood chemistry, vital signs, and global safety were evaluated.

Statistics

The primary analysis variables were the area under the curve (AUC) values for both the total SCORAD and the use of basic medication (the "medication score") over the 18-month treatment period. For patients who had discontinued treatment for medical reasons, the worst case was assumed; that is, maximal total SCORAD and use of basic medication were carried forward to the end of the study for analysis purposes. For patients who had discontinued treatment for nonmedical reasons, the total SCORAD and use of basic medication were not carried forward. The 1-sided or Wilcoxon rank-sum test was used for all primary analysis variables to show superiority or inferiority of the SCIT-treated group compared with the placebo-treated group. The 2-sided Wilcoxon rank-sum test was used for some of the secondary analysis variables to show differences between the actively treated and the placebo-treated

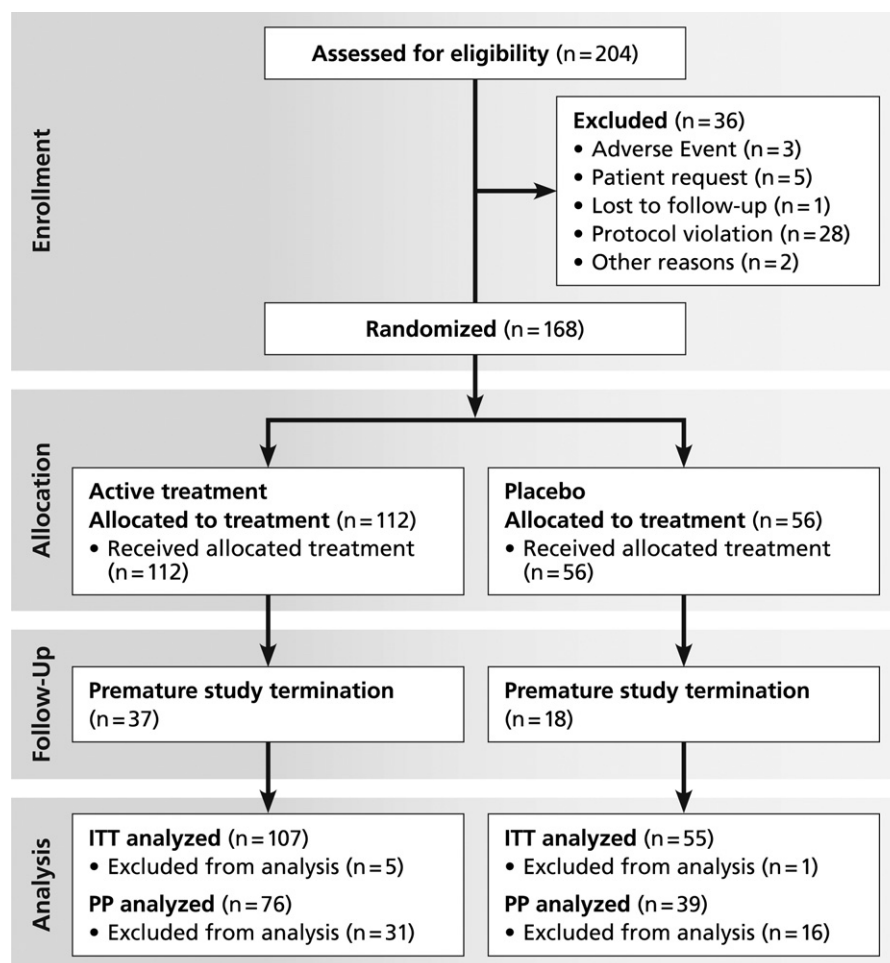


FIG 1. CONSORT chart and summary of the study population.

groups. Subgroups were specified after the primary analysis in an exploratory analysis. The time-weighted SCORAD (total AUC/number of days per patient) was used only for the subgroup analyses. The following subgroups were defined: patients with a SCORAD > 50 at V0; patients with a SCORAD > 50 at V0 during the time period September to February; and patients with a SCORAD > 50 at V0 during the last 12, 6, and 3 months of treatment. Cutoff point of SCORAD > 50 was used on the basis of data of previous studies on SCIT in AD.¹⁷

RESULTS

AUC of the total SCORAD and use of basic medication

The AUCs of the total SCORAD and use of basic medication over the 18-month treatment period were compared between the 2 treatment groups for both the intention-to-treat (ITT) and per-protocol (PP) study populations.

No statistically significant difference was observed between the actively treated and placebo-treated groups for either AUC variable (Fig 2; see Tables E2 and E3 in this article's Online Repository at www.jacionline.org). Median improvement of the AUC of the SCORAD over 18 months was 6% in the actively treated group versus the placebo-treated group, and median improvement of the AUC of the medication score over 18 months of treatment was 32% in the actively treated group versus the placebo-treated group in the ITT set.

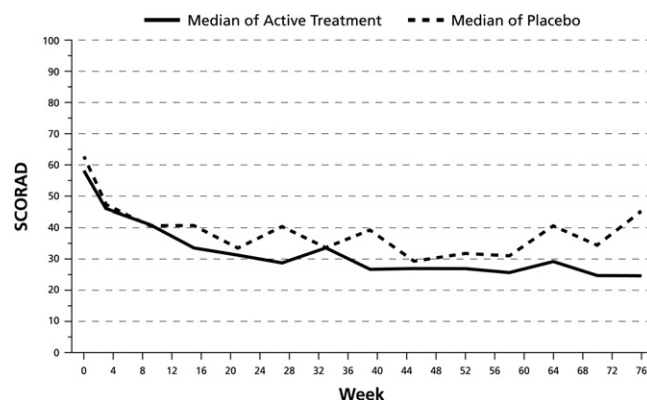
Post hoc analyses of primary end points

Post hoc subgroup analyses were performed on patients with severe AD (SCORAD > 50) at V0 (demographic data in Table E1), referred to as the SCORAD > 50 subgroup. In this subgroup, the time-weighted AUC of the total SCORAD was lower in actively treated patients than in the placebo-treated group, indicating a statistically significant improvement in patients with AD on active treatment with a $P = .02$ for the ITT set (median improvement of the AUC of the SCORAD of 21% in the actively treated groups compared with the placebo-treated group) and a trend for a greater improvement in the PP set (median improvement of 22% in the actively treated group compared with the placebo-treated group) with a P value of .09, which did not reach statistical significance (Table II).

Unlike other allergens, HDM is particularly clinically relevant when indoor heating is in use. A subgroup analysis of the total SCORAD for the period September to February was therefore performed. As shown in Table III, total SCORAD was statistically significantly lower ($P = .02$) for the ITT study population, with a median reduction of the AUC of the total SCORAD of 18% in the actively treated group versus the placebo-treated group. This effect was also seen in the PP study population, although it did not reach statistical significance ($P = .03$).

TABLE I. Basic medication

Active component	Pharmaceutical form	Dose
Desloratadine	Tablet	5 mg
Pimecrolimus	Cream	1%
Prednicarbate (betamethasone)	Cream	0.25% (0.1%)
Eucerin cum aqua	Ointment	—
Glycerolmonostearate 60, cetyl alcohol, medium chain triglycerides, white Vaseline, Macrogol-1000-glycerolmonostearate, propylene glycol, purified water	Cream	—
Methylprednisolone	Tablet	40 mg
Fusidic acid	Cream	0.2%
Mometasone	Spray	50 µg
Levocabastin	Drops	0.5 mg

**FIG 2.** Total SCORAD in the group of patients treated with a depigmented polymerized mite extract and in the placebo-treated group.

In a further *post hoc* analysis, the time-weighted AUC of the total SCORAD was evaluated for the last 12, 6, and 3 months of treatment in the SCORAD > 50 subgroup. The median total SCORAD in actively treated patients was reduced by 25% during the last 12 months, by 30% during the last 6 months, and by 32% during the last 3 months of treatment (Table IV, percentage reductions for the ITT study population). These data indicated that the effect of treatment depended on its duration.

Lower medication scores were consistently observed in the actively treated group than in the placebo-treated group in the SCORAD > 50 subgroup, indicating a greater AD improvement with active treatment. However, this difference was not statistically significant in either the ITT or the PP study population (Table E3).

Quality of life

Although before and after differences in the DLQI sum score indicated greater improvement of quality of life in the actively treated group than in the placebo-treated group, none of the differences were statistically significant.

Post hoc analyses of the DLQI score were performed, analyzing the results during the indoor heating period for the overall study population and for the SCORAD > 50 subgroup. For the overall study population, no statistically significant differences between

active treatment and placebo were seen. For the SCORAD > 50 group, a greater improvement was seen for the actively treated group, with median improvement of 60% in the actively treated group of the ITT set and median improvement of 51% in the actively treated group of the PP set (Table V), although the results were only statistically significant in the PP set but not in the ITT set.

Immunonologic markers

Der p-specific, *Der f*-specific, and total serum IgE levels were measured before and at the end of the study. Overall (ITT set), a statistically significant difference in the before and after total IgE serum level was observed (Wilcoxon rank-sum test 2-sided, $P = .02$; data not shown). For the overall PP set, these before and after differences were also statistically significant ($P = .04$; data not shown). Within the subpopulation of patients with total SCORAD > 50 at V0, a statistically significant difference in the total IgE was found between the treatment groups as well (ITT set, $P = .02$; PP set, $P = .04$; data not shown). *Der p*-specific and *Der f*-specific IgE levels both decreased significantly in the overall ITT and PP set (Table VI). A significant increase of *Der p*-specific IgG₄ on active treatment was observed in the overall population (ITT and PP set) as well as in the subgroup of patients with AD and SCORAD > 50 at V0 (Table VI).

Safety

Eight percent of actively treated patients and 10.7% of placebo-treated patients had systemic adverse reactions of grade 1 or 2, such as flare-ups of eczematous and urticarial lesions, symptoms of rhinitis, pruritus, transient headache, and asthma. We found that 39.3% of actively treated patients and 35.7% of placebo-treated patients developed local reactions of mild intensity (Table E4 in this article's Online Repository at www.jacionline.org). No differences in standard hematology, blood chemistry, or vital signs were observed.

DISCUSSION

In this study we show that SCIT with a depigmented polymerized mite extract is effective as an add-on therapy in patients with severe AD, whereas no significant effect was seen in the overall study population. *Post hoc* analyses found that patients with severe AD at initiation showed significant improvement over placebo of the time-weighted total SCORAD score. Best efficacy was achieved during September to February, characterized by high HDM exposure because of the use of indoor heating.^{20,21} Moreover, this effect was more pronounced the longer the SCIT treatment was given. Reduction in the use of basic medication, as an indicator of efficacy, showed a similar clear trend, although not statistically significant. This was true for both the overall study population and the SCORAD > 50 subgroup.

Because exposure to aeroallergens acts as a trigger in sensitized patients with AD, the value of SCIT as a rationale-based long-term treatment in such patients is of major interest.²² Several uncontrolled studies were performed with different allergens, allergen preparations, and application schedules in individual patients with AD and in small uncontrolled and controlled studies.^{14,15} A controlled study in adult patients with

TABLE II. AUC of the total SCORAD in patients with a baseline SCORAD > 50 over 18 months of treatment

	ITT set (n = 80)			PP set (n = 52)		
	No.	Mean (SD)	Median (lower; upper quartile)	No.	Mean (SD)	Median (lower; upper quartile)
Active treatment	52	19452.0 (8397.0)	17820.9 (14086.1; 23385.8)	36	17818.1 (7404.1)	16131.0 (13290.3; 21636.4)
Placebo	28	23215.6 (8954.8)	22443.8 (16707.8; 26828.2)	16	20317.9 (6615.6)	20726.8 (16257.1; 23832.9)
Improvement, %		16	21		12	22
P value*			.02			.09

*Wilcoxon rank-sum test 1-sided on an α level of 2.5%.**TABLE III.** Time-weighted AUC of the total SCORAD during winter season for the subpopulation of patients with a total SCORAD > 50 at V0

	ITT set (n = 80)			PP set (n = 52)		
	No.	Mean (SD)	Median (lower; upper quartile)	No.	Mean (SD)	Median (lower; upper quartile)
Active treatment	49	39.0 (15.5)	36.5 (28.3; 49.6)	35	34.8 (13.5)	34.4 (26.2; 39.3)
Placebo	27	46.4 (14.8)	44.4 (36.5; 56.6)	16	41.9 (12.9)	41.7 (31.6; 47.4)
Improvement, %		16	18		17	17
P value*			.02			.03

*Wilcoxon rank-sum test 1-sided on an α level of 2.5%.**TABLE IV.** Time weighted AUC of the total SCORAD during the last 12, 6, and 3 months of the treatment period for the subpopulation of patients with a total SCORAD > 50 at V0

	ITT set (n = 80)			PP set (n = 52)		
	No.	Mean (SD)	Median (lower; upper quartile)	No.	Mean (SD)	Median (lower; upper quartile)
Last 12 mo						
Depigoid Mite Mix	51	37.3 (31.1)	31.1 (24.3; 42.1)	35	28.5 (12.2)	27.6 (21.7; 34.2)
Placebo	28	43.8 (19.9)	41.7 (32.4; 57.4)	16	36.6 (15.2)	37.1 (26.3; 43.4)
Improvement, %*		15	25		22	26
P value†			<.01			.02
Last 6 mo						
Depigoid Mite Mix	51	31.5 (18.1)	28.0 (20.6; 39.0)	35	27.3 (15.2)	26.2 (17.2; 35.6)
Placebo	28	45.0 (25.3)	39.7 (28.7; 53.4)	16	37.1 (16.7)	37.6 (25.7; 47.6)
Improvement, %*		30	30		26	30
P value†			<.01			.02
Last 3 mo						
Depigoid Mite Mix	51	30.8 (18.6)	28.1 (18.5; 39.5)	35	26.7 (16.4)	23.4 (16.4; 36.6)
Placebo	28	41.3 (21.3)	41.3 (27.3; 52.0)	16	37.3 (18.2)	38.8 (22.6; 50.3)
Improvement, %*		26	32		28	40
P value†			<.01			.01

*Reduction in active treatment group compared with placebo group.

†Wilcoxon rank-sum test 1-sided on an α level of 2.5%.**TABLE V.** Median DLQI score during winter season for the subpopulation of patients with a total SCORAD > 50 at V0

	ITT set (n = 80)			PP set (n = 52)		
	No.	Mean (SD)	Median (lower; upper quartile)	No.	Mean (SD)	Median (lower; upper quartile)
Active treatment	47	5.7 (5.2)	4.0 (1.5; 9.0)	33	6.0 (5.0)	5.0 (2.0; 9.0)
Placebo	27	8.4 (6.2)	10.0 (2.0; 13.0)	16	9.4 (5.9)	10.3 (4.3; 13.0)
Improvement, %		32	60		36	51
P value*			.06			.04

*Wilcoxon rank-sum test 1-sided on an α level of 5%.

AD sensitized to HDM allergens, using active placebo and 2 different doses of HDM allergen extract, showed improvement of AD and reduction in the use of both topical and systemic medications.¹³

AD improvement was also seen in an uncontrolled study in which adult patients with AD sensitized to HDM allergen were treated with a depigmented polymerized mite extract¹⁷ and in a

further study in which patients with AD sensitized to birch pollen allergen were treated with a depigmented polymerized allergoid to birch pollen allergen.²³

Results of the study presented here show that patients with severe AD (ie, the SCORAD > 50 subgroup) benefitted from SCIT as add-on therapy to basic medication, an effect not seen in the overall study population. This finding is consistent with

TABLE VI. Changes in immunologic parameters

	ITT set (n = 162)			PP set (n = 115)		
	No.	Mean (SD)	Median (lower; upper quartile)	No.	Mean (SD)	Median (lower; upper quartile)
IgE <i>Der p</i> (mg/L)						
Active treatment	77	−8.46 (18.84)	0.00 (−13.90; 0.00)	73	−8.64 (19.30)	0.00 (−13.90; 0.00)
Placebo	45	0.69 (18.52)	0.00 (0.00; 0.90)	38	1.57 (19.77)	0.00 (0.00; 5.30)
<i>P</i> value*			<.01			<.01
IgE <i>Der f</i> (mg/L)						
Active treatment	77	−11.20 (18.42)	−3.03 (−15.20; 0.00)	73	−11.39 (18.86)	−3.00 (−15.20; 0.00)
Placebo	45	−0.77 (19.33)	0.00 (−4.00; 0.00)	38	−0.39 (20.88)	0.00 (−5.92; 0.99)
<i>P</i> value*			≤.01			.01
IgG ₄ <i>Der p</i> (mg/L)						
Active treatment	76	140.50 (354.95)	117.50 (31.00; 245.00)	72	144.99 (363.98)	132.00 (32.00; 248.50)
Placebo	44	−8.95 (140.07)	2.50 (−21.50; 16.50)	37	−9.73 (152.63)	1.00 (−15.00; 17.00)
<i>P</i> value*			<.0001			<.0001
IgG ₄ <i>Der f</i> (mg/L)						
Active treatment	76	−8.70 (103.57)	2.65 (−16.50; 18.00)	72	−9.71 (106.35)	2.00 (−17.50; 20.50)
Placebo	44	−8.63 (77.16)	3.00 (−10.00; 12.00)	37	−12.21 (83.03)	3.00 (−11.00; 11.00)
<i>P</i> value*			.72			.72
Total SCORAD > 50						
IgE <i>Der p</i> (mg/L)						
Active treatment	36	−11.90 (22.40)	0.00 (−20.50; 0.00)	35	−12.24 (22.64)	0.00 (−22.30; 0.00)
Placebo	20	−3.10 (25.32)	0.00 (−10.10; 0.00)	16	−2.47 (28.01)	0.00 (−10.10; 0.00)
<i>P</i> value*			.27			.26
IgE <i>Der f</i> (mg/L)						
Active treatment	36	−11.34 (19.31)	−1.05 (−15.50; 0.00)	35	−11.67 (19.50)	−2.10 (−15.50; 0.00)
Placebo	20	−2.11 (25.46)	0.00 (−15.50; 0.00)	16	−1.51 (28.34)	0.00 (−15.50; 0.00)
<i>P</i> value*			.19			.20
IgG ₄ <i>Der p</i> (mg/L)						
Active treatment	36	182.31 (182.20)	168.50 (38.00; 146.50)	35	184.34 (184.44)	172.00 (36.00; 250.00)
Placebo	20	−25.55 (193.38)	6.50 (−34.50; 22.00)	16	−30.63 (216.75)	6.50 (−76.50; 21.50)
<i>P</i> value*			<.0001			<.0001
IgG ₄ <i>Der f</i> (mg/L)						
Active treatment	36	−37.25 (133.08)	2.00 (−30.00; 16.05)	35	−38.40 (134.85)	2.00 (−32.00; 21.00)
Placebo	20	0.45 (81.90)	0.00 (−12.50; 14.00)	16	−0.25 (91.99)	1.50 (−14.00; 14.00)
<i>P</i> value*			.63			.67

*Wilcoxon rank-sum test 1-sided on an α level of 5%.

immunologic results from an uncontrolled study conducted with a depigmented polymerized mite extract.¹⁷ In that study, immunologic changes such as a decrease of TARC/CCL17 and MDC/CCL22 levels were only statistically significant in patients with AD with a SCORAD > 30 at study onset.¹⁷ These findings suggest that a future SCIT study exclusively in patients with severe AD (SCORAD > 50) might lead to clearer statistical results for treatment efficacy.

Another interesting aspect observed in the present study was the more pronounced improvement of AD during the period of indoor heating. Note that most of the patients were multiply sensitized, including to aeroallergens such as birch or grass pollen. Thus, it is to be expected that the efficacy of SCIT with respect to HDM will be most clearly seen during the time of year characterized by relatively high HDM exposure and concomitant absence of birch and grass pollen. In contrast, birch or grass pollen exposure during spring and summer can lead to exacerbation of AD in sensitized patients. Such an independent “bystander effect” would undoubtedly compromise the effect of SCIT seen in this study and may account for the observed lack of a statistically significant difference between treatment groups for most of the efficacy analyses. Unfortunately, performing a study only in HDM-monosensitized adult patients with AD would not be feasible because of the rarity of such patients. A further factor

that may have compromised the efficacy findings in this study was that patients were included throughout the whole of a 2-year period. Thus, some patients began treatment after the pollen season and ended treatment during the pollen season and vice versa for other patients.

Another limitation of this study was the relatively low power of the subgroups defined in the *post hoc* analyses, which is mirrored by a clinically meaningful reduction of the total SCORAD, DLQI, or medication score, which did not always reach statistical significance.

In this study, SCIT was given as an add-on therapy, with all patients being treated with topical and, as necessary, systemic medications during the whole study. Regular and consistent treatment of AD in a study setting with multiple routine visits to a dermatologist is likely to improve patient compliance and adherence to therapy.²⁴ This may explain why AD improved in placebo-treated patients, as shown by both the SCORAD score and the use of basic medication. Such an effect in placebo-treated patients as well as actively treated patients would also contribute to the observed lack of statistically significant differences between the 2 treatment groups.

Regarding safety, no relevant differences were observed in the frequency of local or systemic adverse reactions between the actively treated and the placebo-treated groups. The

observed frequencies were similar to those seen in other studies.²⁵ Treatment of AD with HDM allergens was also shown to be safe in an uncontrolled study that used a rush protocol (3-day protocol) in contrast to a ultra-rush build-up protocol (1-day protocol).²⁶

In conclusion, this study shows the treatment of patients with AD with depigmented polymerized mite extract is effective and safe and should be considered as a valuable add-on treatment especially in severely affected patients sensitized to HDM.

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Clinical implication: Subcutaneous allergen-specific immunotherapy is effective in a subgroup of patients with atopic dermatitis.

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TABLE E1. Demographic data (overall safety set, n = 168; subpopulation safety set, n = 85)

Demographic variable	Active treatment	Placebo
Overall	n = 112	n = 56
Sex		
Male, no. (%)	62 (55.4)	28 (50.0)
Female, no. (%)	50 (44.6)	28 (50.0)
Age (y), mean (SD)	34.2 (11.9)	32.9 (11.0)
Height (cm), mean (SD)	174.9 (9.1)	172.7 (9.5)
Weight (kg), mean (SD)	76.6 (15.7)	76.8 (16.3)
BMI, mean (SD)	25 (4.5)	25.7 (5.2)
Ethnic group		
White, no. (%)	110 (98.2)	56 (100)
Other, no. (%)	2 (1.8)	—
Smoking habit		
Nonsmoker, no. (%)	76 (67.9)	31 (55.4)
Occasional smoker, no. (%)	14 (12.5)	12 (21.4)
Regular smoker, no. (%)	22 (19.6)	13 (23.2)
Alcohol consumption (n)		
Never/occasionally, no. (%)	111 (99.1)	56 (100)
Daily, no. (%)	1 (0.9)	—
Total SCORAD > 50 at V0	n = 6	n = 29
Sex		
Male, no. (%)	31 (55.4)	17 (58.6)
Female, no. (%)	25 (44.6)	12 (41.4)
Age (y), mean (SD)	35.7 (13.5)	34.4 (12.4)
Height (cm), mean (SD)	175.8 (10.2)	172.8 (9.8)
Weight (kg), mean (SD)	77.9 (17.5)	78.5 (16.5)
BMI, mean (SD)	25.1 (5.0)	26.3 (5.5)
Ethnic group (n)		
White, no. (%)	56 (100)	29 (100)
Other	—	—
Smoking habit		
Nonsmoker, no. (%)	37 (66.1)	16 (55.2)
Occasional smoker, no. (%)	6 (10.7)	3 (10.3)
Regular smoker, no. (%)	13 (23.2)	10 (34.5)

BMI, Body mass index, calculated as weight divided by height (kg/m^2).

TABLE E2. AUC of the total SCORAD over 18 months of treatment overall

	ITT set (n = 162)			PP set (n = 115)		
	No.	Mean (SD)	Median (lower; upper quartile)	No.	Mean (SD)	Median (lower; upper quartile)
Active treatment	107	17,802.7 (7,752.4)	15,990.2 (13,131.2; 22,303.7)	76	16,469.4 (6,877.8)	14,731.3 (12,548.1; 19,705.6)
Placebo	55	19,093.1 (8,635.0)	16,971.3 (11,674.3; 24,910.8)	39	17,149.5 (6,864.8)	16,138.4 (11,254.8; 21,867.4)
<i>P</i> value*			.24			.33

*Wilcoxon rank-sum test 1-sided on an α level of 2.5%.

TABLE E3. AUC of the medication score over 18 months of treatment

	ITT set (n = 162)			PP set (n = 115)		
	No.	Mean (SD)	Median (lower; upper quartile)	No.	Mean (SD)	Median (lower; upper quartile)
Overall	162					
Active treatment	105	31,648.0 (36,887.1)	19,330.0 (5,774.6; 45,849.9)	76	38,503.1 (43,568.8)	25,131.3 (9,851.1; 52,101.9)
Placebo	55	41,828.7 (46,236.2)	28,422.0 (11,852.5; 50,229.9)	39	52,396.9 (50,291.0)	38,490.8 (14,955.0; 70,296.6)
<i>P</i> value*			.08			.06
Total SCORAD > 50 at V0	80			52		
Active treatment	52	37,489.9 (48,687.5)	21,515.6 (6,343.1; 50,819.1)	36	46,409.6 (54,688.3)	37,017.0 (9,279.5; 66,089.4)
Placebo	28	42,601.2 (46,287.2)	30,294.8 (11,316.7; 51,038.6)	16	61,480.6 (51,873.8)	45,094.0 (26,316.9; 83,889.7)
<i>P</i> value*			.03			.06

*Wilcoxon rank-sum test 1-sided on an α level of 2.5%.

TABLE E4. Adverse drug reactions

ADR	Active treatment (n = 112)	Placebo (n = 56)
Local reactions, no. of patients (%) / no. of reactions	44 (39.3) / 229	20 (35.7) / 87
Systemic reactions, no. of patients (%) / no. of reactions	9 (8) / 14	6 (10.7) / 6
Atopic dermatitis, no. of patients / no. of reactions	8 / 8	6 / 6
Asthma, no. of patients / no. of reactions	—	1 / 1
Dry eye, no. of patients / no. of reactions	1 / 1	—
Rhinitis, no. of patients / no. of reactions	1 / 1	—
Throat irritation, no. of patients / no. of reactions	1 / 1	—
Headache, no. of patients / no. of reactions	1 / 1	—
Vesicular eczema, no. of patients / no. of reactions	1 / 1	—
Erythema, no. of patients / no. of reactions	1 / 1	—
Generalized pruritus, no. of patients / no. of reactions	1 / 1	—
Skin lesion, no. of patients / no. of reactions	1 / 1	—
Flatulence, no. of patients / no. of reactions	1 / 1	—
Sensation of foreign body, no. of patients / no. of reactions	—	1 / 1

ADR, Adverse drug reaction.