SUBLINGUAL ALLERGEN IMMUNOTHERAPY FOR HOUSE DUST MITES

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November 4, 2015

HDM SLIT TABLETS

ALK obtains European approval for its house dust mite sublingual allergy immunotherapy tablet against allergic rhinitis and allergic asthma

August 31, 2015 06:50 ET | **Source:** ALK-Abelló

Copenhagen, 2015-08-31 12:50 CEST (GLOBE NEWSWIRE) --

ALK today announced that it has successfully completed the registration procedure for its house dust mite (HDM) sublingual allergy immunotherapy (SLIT) tablet in 11 European countries[1].

The HDM SLIT-tablet is indicated in adult patients (18-65 years) diagnosed by a clinical history and by a positive test for HDM sensitisation with at least one of the following conditions:

1. Persistent moderate to severe HDM allergic rhinitis despite the use of symptom-relieving medication
2. HDM allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe HDM allergic rhinitis and where patients' asthma status has been carefully evaluated.

HDM SLIT TABLETS

ALK's partner, Torii, obtains approval for the house dust mite SLIT-tablet in Japan

September 28, 2015 03:00 ET | **Source:** ALK-Abelló

Copenhagen, 2015-09-28 09:00 CEST (GLOBE NEWSWIRE) --

ALK (ALKB:DC / OMX: ALK B / AKABY / AKBLF): Approval releases milestone payment to ALK. ALK now expects operating profit (EBITDA before special items), excluding sales royalties and any additional milestone payments from partnerships, to be in the range of DKK 350-400 million (previously DKK 250-300 million).

ALK today announced that the Japanese Ministry of Health, Labour and Welfare has approved the New Drug Application for the house dust mite (HDM) sublingual allergy immunotherapy (SLIT) tablet MITICURE™.

MITICURE™ is the Japanese trade name of the HDM SLIT-tablet licensed by ALK to Torii for Japan. MITICURE™ is indicated in adults and adolescents (12-64 years) as hyposensitisation therapy (allergy immunotherapy) for the treatment of allergic rhinitis caused by house dust mites.

In parallel with the approval, Torii also announced today that it is initiating a new clinical Phase III trial to investigate the safety and efficacy of MITICURE™ in paediatric patients (five-11 years). The trial is expected to enrol approximately 400 subjects.

POLLEN SLIT TABLETS

Oralair®
(Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract)
Tablet For Sublingual Use

GRASTEK®
Timothy Grass Pollen Allergen Extract
Tablet for Sublingual Use 2800 BAU

RAGWITEK®
Short Ragweed Pollen Allergen Extract
Tablet for sublingual use 12 Amb a 1-U

? FOR THE AUDIENCE

- How many of you currently have patients on SLIT drops?
- How many of you currently have patients on SLIT tablets?
- How many of you have patients monosensitized or predominantly sensitized to HDM?
- If there is good evidence of efficacy and mild side effects, and HDM SLIT were approved by the FDA, would you prescribe HDM SLIT?

HDM SLIT

J Allergy Clin Immunol. 2014 Sep;134(3):568-575.e7. doi: 10.1016/j.jaci.2014.03.019. Epub 2014 May 3.

Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial.

Mosbech H[1], Deckelmann R[2], de Blay F[3], Pastorello EA[4], Trebas-Pietras E[5], Andres LP[6], Malcus I[7], Ljørring C[8], Canonica GW[9].

Author information

Abstract

BACKGROUND: Investigations meeting current standards are limited for the effect of house dust mite (HDM) allergy immunotherapy in asthmatic patients.

OBJECTIVE: This trial investigated the efficacy and safety of a standardized quality (SQ; allergen standardization method proprietary to the trial sponsor) HDM SLIT-tablet (ALK, Hørsholm, Denmark) in adults and adolescents with HDM respiratory allergic disease. This publication reports the results of the endpoints related to asthma.

METHODS: Six hundred four subjects 14 years or older with HDM allergic rhinitis and mild-to-moderate asthma were randomized 1:1:1:1 to double-blind daily treatment with one of 3 active doses (1, 3, or 6 SQ-HDM) or placebo. Their use of inhaled corticosteroid (ICS) was standardized and adjusted at baseline and the end of treatment to the lowest dose providing asthma control. The primary end point was a reduction in ICS dose from the individual subject's baseline dose after 1 year of treatment.

RESULTS: The primary analysis revealed a mean difference between 6 SQ-HDM and placebo in the reduction in daily ICS dose of 81 μg (P = .004). Relative mean and median reductions were 42% and 50% for 6 SQ-HDM and 15% and 25% for placebo, respectively. No statistically significant differences were observed for the other assessed asthma parameters, reflecting the intended controlled status of the trial subjects. The most common adverse events were local reactions in the mouth. The rate and severity of adverse events were higher for 3 and 6 SQ-HDM than for 1 SQ-HDM and placebo.

CONCLUSION: Efficacy in mild-to-moderate asthma of 6 SQ-HDM relative to placebo was demonstrated by a moderate statistically significant reduction in the ICS dose required to maintain asthma control. All active doses were well tolerated.

KEYWORDS: Allergy; SLIT-tablet; SQ; allergy immunotherapy; asthma; asthma control; house dust mite; immunotherapy; inhaled corticosteroid; respiratory allergic disease

PMID: 24797423 [PubMed - indexed for MEDLINE]

Medicine (Baltimore). 2015 Jun;94(24):e701. doi: 10.1097/MD.0000000000000701.

Sublingual Immunotherapy for Asthmatic Children Sensitized to House Dust Mite: A Meta-Analysis.

Liao W[1], Hu Q, Shen LL, Hu Y, Tao HF, Li HF, Fan WT.

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Abstract

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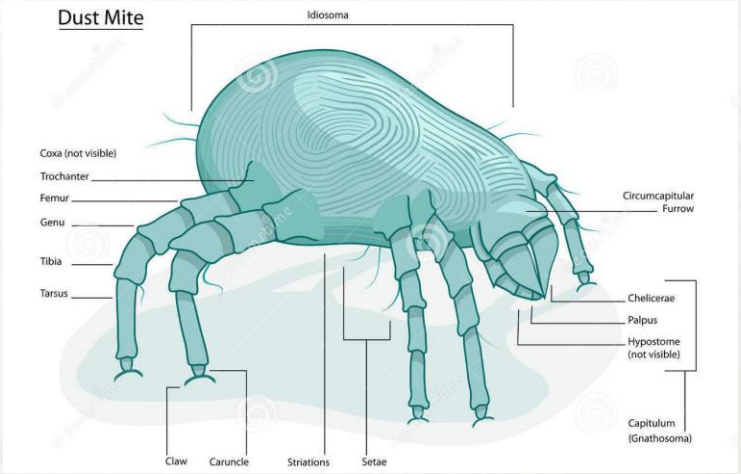
PMID: 26091451 [PubMed - indexed for MEDLINE] PMCID: PMC4616527 Free PMC Article

DUST MITE ALLERGY

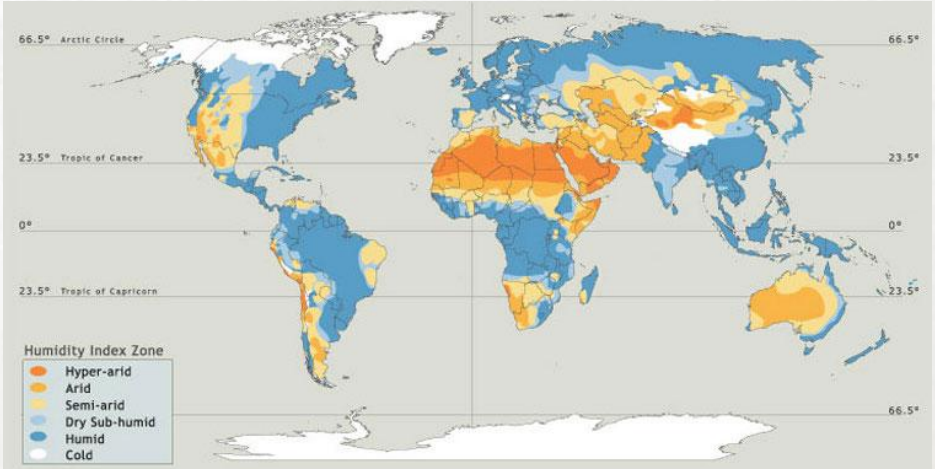
- There are many species of dust mites infested in and around the houses worldwide. The two most common HDMs are *Dermatophagoides pteronyssinus* (Dp) *and Dermatophagoides farinae* (Df). Two common storage mites (SMs) are *Blomia tropicalis* (Bt), *Turophapus puterscentias* (Tp).
- Dust mite allergy is a major cause of respiratory allergic disease (and SM has been reported to induce anaphylaxis through consumption of mite-contaminated food).
- In studies in which Dp-allergic subjects were intranasally challenged with Dp extracts, both the immediate and late phases (with signicant increase in the recruitment of eosinophils, neutrophils, macrophages and lymphocytes) of allergic response were observed.



Yu SJ et al. House dust mite allergy: environment evaluation and disease prevention. Asia Pac Allergy. 2014 Oct;4(4):241-52.

DUST MITE ALLERGY

- The HDM is globally ubiquitous in human habitats and a significant factor underlying allergic rhinitis and allergic asthma.
- Prevalence data for HDM allergen sensitization vary from 65 to 130 million persons in the general population worldwide to as many as 50% among asthmatic patients.
- Among patients from 15 developed countries in the European Community Respiratory Health Survey I, the mean prevalence of sensitization to HDM was 21.7%. Among Latino women in the US of various ages, the prevalence of sensitization to Dp was 37% and to Df was 34%, whereas the prevalence was greater than 80% in a pediatric study in Taiwan.



Calderón MA et al. Respiratory allergy caused by house dust mites: What do we really know? J Allergy Clin Immunol. 2015 Jul;136(1):38-48.

HDM SLIT TABLETS

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CONCLUSION: Efficacy in mild-to-moderate asthma of 6 SQ-HDM relative to placebo was demonstrated by a moderate statistically significant reduction in the ICS dose required to maintain asthma control. All active doses were well tolerated.

KEYWORDS: Allergy; SLIT-tablet; SQ; allergy immunotherapy; asthma; asthma control; house dust mite; immunotherapy; inhaled corticosteroid; respiratory allergic disease

PMID: 24797423 [PubMed - indexed for MEDLINE]

INTRODUCTION

- According to the WHO, the only currently available causal treatment for respiratory allergic disease is allergy immunotherapy (AIT).
- The ARIA guidelines emphasize the link between allergic asthma and allergic rhinitis and consider the available evidence sufficient to recommend AIT for treatment of both disease manifestations, as does the WHO for all allergic rhinitis and at least in cases in which the patient's asthma is clearly related to HDM.
- Thus far, AIT for HDM respiratory allergic disease has primarily been available as SCIT or SLIT-drops. To allow for convenient and reproducible at-home administration with no need for dose adjustment, an SQ HDM SLIT-tablet is currently in development.

INTRODUCTION

- This publication presents the primary result of a phase II/III RDBPC trial of the SQ HDM SLIT tablet in patients with HDM respiratory allergic disease.
- The primary end point was reduction in the individual subject's ICS dose from baseline until the end of treatment, with the ICS dose at both time points being the lowest dose providing symptom control.
- Hence an inclusion criterion was controlled asthma at enrollment (Asthma Control Questionnaire [ACQ] score <1.5).
- Results for all asthma-related secondary end points, as well as safety end points, are also presented, whereas results related to rhinitis and immunology will be reported separately.
- The trial was sponsored by ALK (Hørsholm, Denmark).

METHODS

- This was a multisite, multiple-dose, randomized, double-blind, parallel-group, placebo-controlled trial performed at 81 sites in Denmark, Germany, Italy, Spain, United Kingdom, Sweden, France, and Poland.
- The tablets (active and placebo) provided by the sponsor were oral lyophilisates, either containing standardized extracts of Dp and Df in a 1:1 ratio or a placebo that was similar in appearance, smell, and taste. Three strengths were investigated: 1, 3, and 6 SQ-HDM.
- The aim of the trial population was 14 years of age or older with controlled (based on ACQ score), mild-to-moderate, HDM-allergic asthma requiring ICS use (100-800 mcg/day) and mild-to-severe HDM-allergic rhinitis.
- Randomization was performed according to the sponsor-generated allocation schedule by a trial-independent statistician.

METHODS

- Subjects were randomized (1:1:1:1) to double-blind daily treatment with 1, 3, or 6 SQ-HDM or with placebo, 1 daily tablet administered sublingually. Subjects received intervention treatment for a period of approximately 12 months.

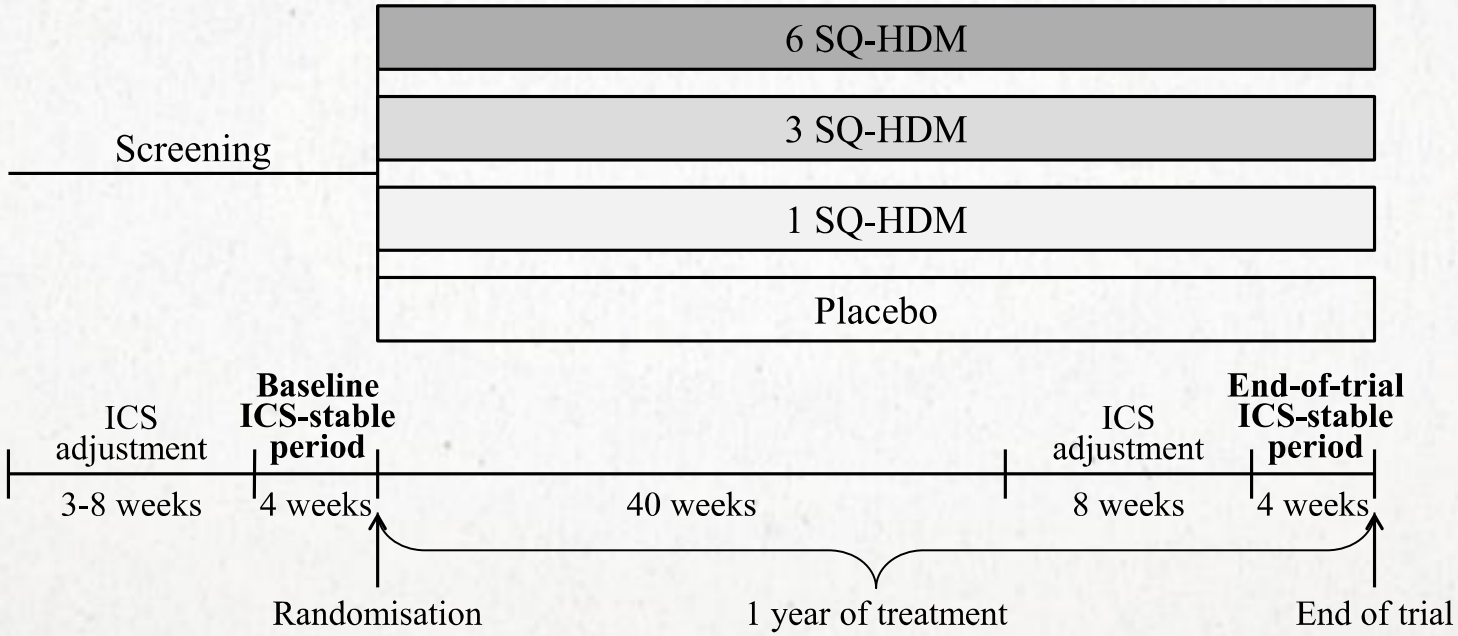


FIG 1. Overall trial design.

METHODS

- Main exclusion criteria: a clinical history of allergy with symptoms to a perennial allergen or a seasonal allergen causing symptoms in the pretreatment ICS adjustment and/or stable periods; FEV1 <70% of predicted value; a clinical history of severe asthma within the last 2 years; AIT with HDM allergen within the previous 5 years; concurrent or previous (within the last 6 months) AIT with other allergens than HDM; and a history of anaphylactic shock or angioedema.
- The power calculation was based on data from a clinical trial on SQ HDM SCIT, as well as on a Cochrane review of omalizumab treatment for 2037 patients with mild-to-severe allergic asthma.
- Inclusion of 180 subjects per treatment arm led to a power of 81% at the 5% level to detect a treatment difference of 20% for 6 SQ-HDM versus placebo. Approximately 10% discontinuations were expected, and hence it was planned to randomize 200 subjects per treatment group.

METHODS

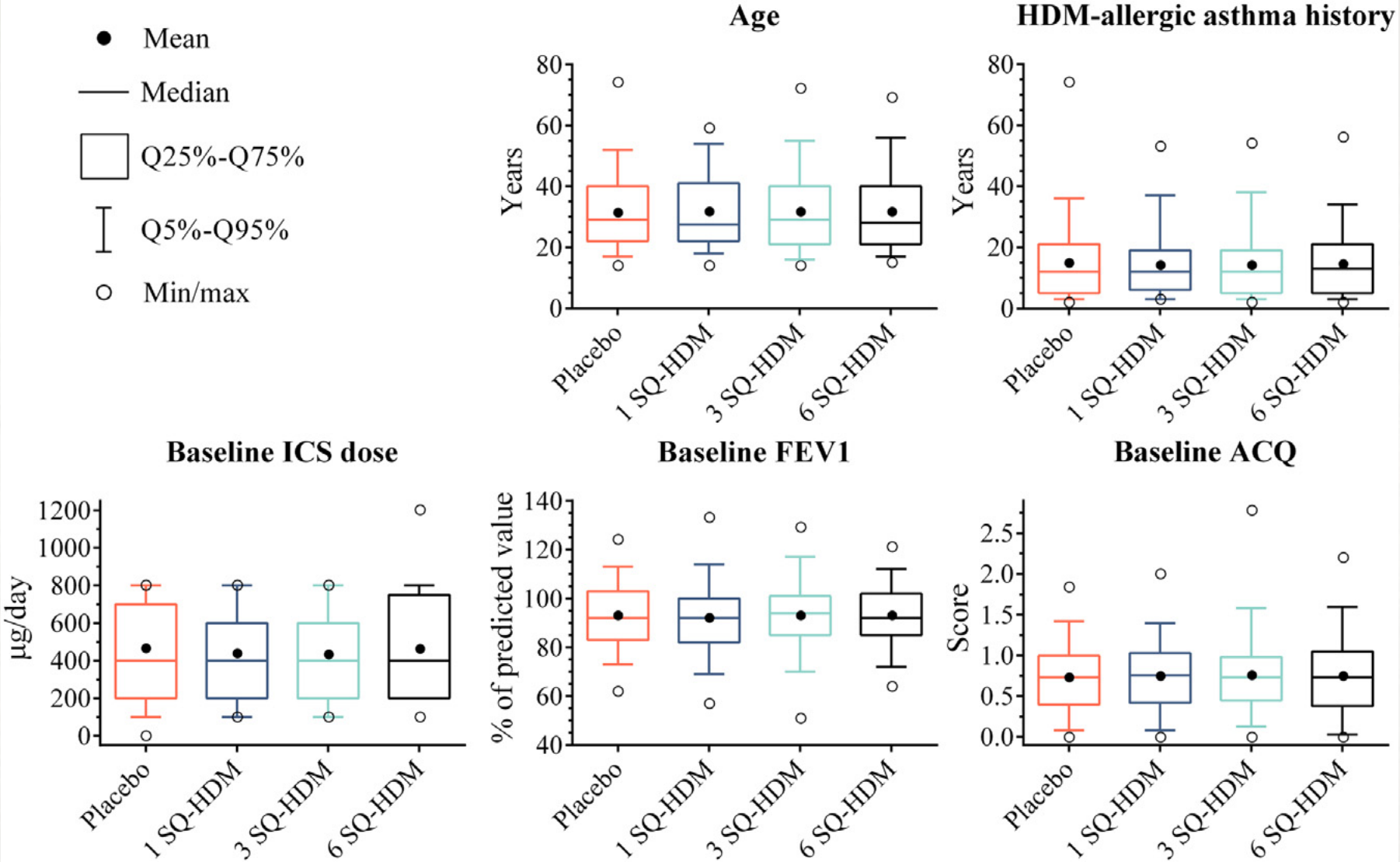
- The primary analysis compared treatment groups by using a linear mixed model by using data from all 4 treatment groups. The model included treatment and baseline ICS dose as fixed effects and site as a random effect.
- Multiplicity was addressed by using hierarchic testing, with 6 SQ-HDM versus placebo as the highest-ranking test.
- Imputation for prematurely discontinued subjects was done by using the last-observation-carried-forward method (the last recorded ICS dose was carried forward for subjects who discontinued the trial prematurely), and the analysis thus followed the ICH intent-to-treat principle.
- Two-sided 95% CIs for the adjusted mean differences are presented, as well as the corresponding *P* values.

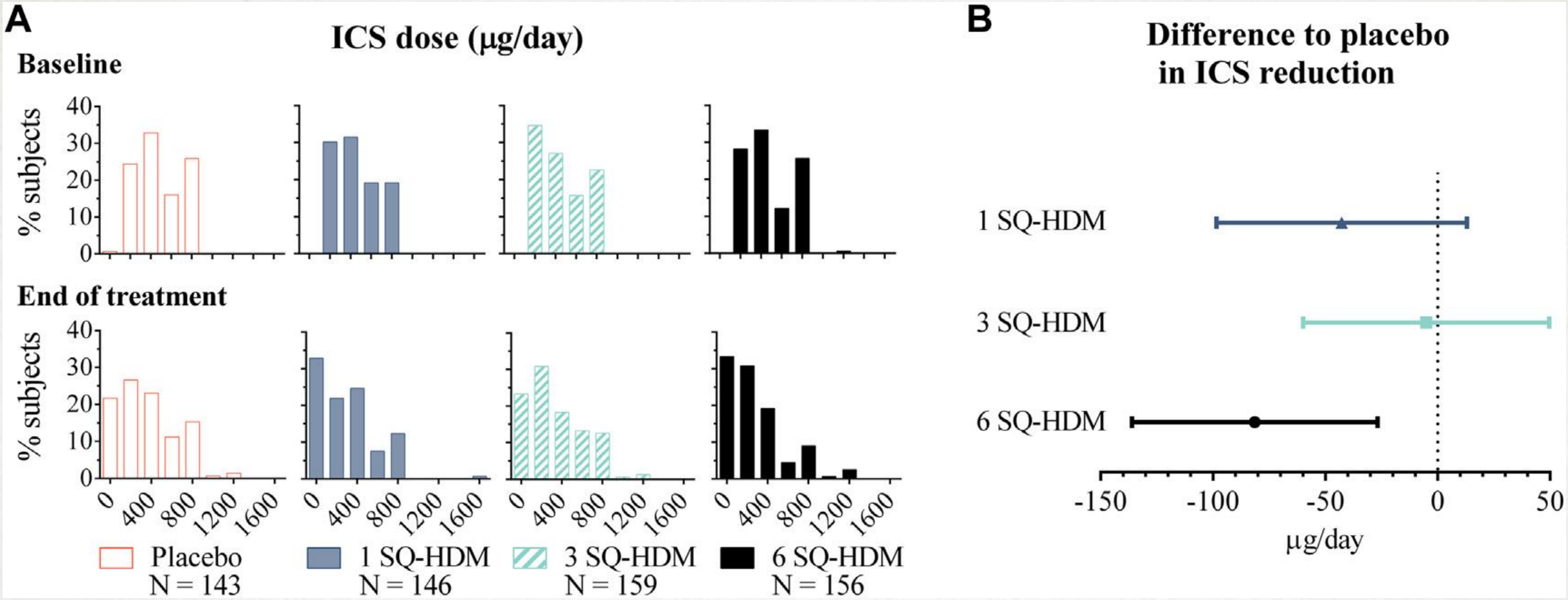
TABLE I. Subject disposition

	Placebo	1 SQ-HDM	3 SQ-HDM	6 SQ-HDM	Active all	Overall
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Screened						1063
Excluded						459
Failure to meet selection criteria						350
Other						109
Randomized (FAS)	143 (100)	146 (100)	159 (100)	156 (100)	461 (100)	604 (100)
Withdrawn	17 (12)	14 (10)	25 (16)	16 (10)	55 (12)	72 (12)
Withdrawal of consent	3 (2)	3 (2)	6 (4)	3 (2)	12 (3)	15 (2)
Pregnancy	2 (1)	1 (<1)	2 (1)		3 (<1)	5 (<1)
Lost to follow-up	5 (3)	2 (1)	4 (3)	3 (2)	9 (2)	14 (2)
Noncompliance	3 (2)	3 (2)	3 (2)	5 (3)	11 (2)	14 (2)
AE	1 (<1)	2 (1)	8 (5)	4 (3)	14 (3)	15 (2)
Other	3 (2)	3 (2)	2 (1)	1 (<1)	6 (1)	9 (1)
Completed	126 (88)	132 (90)	134 (84)	140 (90)	406 (88)	532 (88)
PP analysis set	92 (64)	95 (65)	99 (62)	101 (65)	295 (64)	387 (64)

All randomized subjects were treated with investigational medicinal product.

FAS, Full analysis set after the ICH intent-to-treat principle; *No.*, number of subjects; *PP*, per protocol (ie, all subjects with no major protocol deviations assessed as capable of affecting the trial results); %, percent of subjects in treatment group having the event.


Mean
Median
Q25%-Q75%
Q5%-Q95%
Min/max
Age
Years
HDM-allergic asthma history
Years
Baseline ICS dose
µg/day
Baseline FEV1
% of predicted value
Baseline ACQ
Score
Placebo
1 SQ-HDM
3 SQ-HDM
6 SQ-HDM


A
ICS dose (µg/day)
Baseline
% subjects
40
30
20
10
0
End of treatment
% subjects
0
400
800
1200
1600
Placebo
N = 143
1 SQ-HDM
N = 146
3 SQ-HDM
N = 159
6 SQ-HDM
N = 156
B
Difference to placebo
in ICS reduction
1 SQ-HDM
3 SQ-HDM
6 SQ-HDM
-150
-100
-50
0
50
µg/day

	Placebo N=143	1 SQ-HDM N=146	3 SQ-HDM N=159	6 SQ-HDM N=156
Mean	15%	35%	27%	42%
Median	25%	33%	25%	50%
Odds ratio*		1.63	1.02	1.98
p-value		0.023	0.91	0.0011

* Odds ratio for ICS reduction, active over placebo

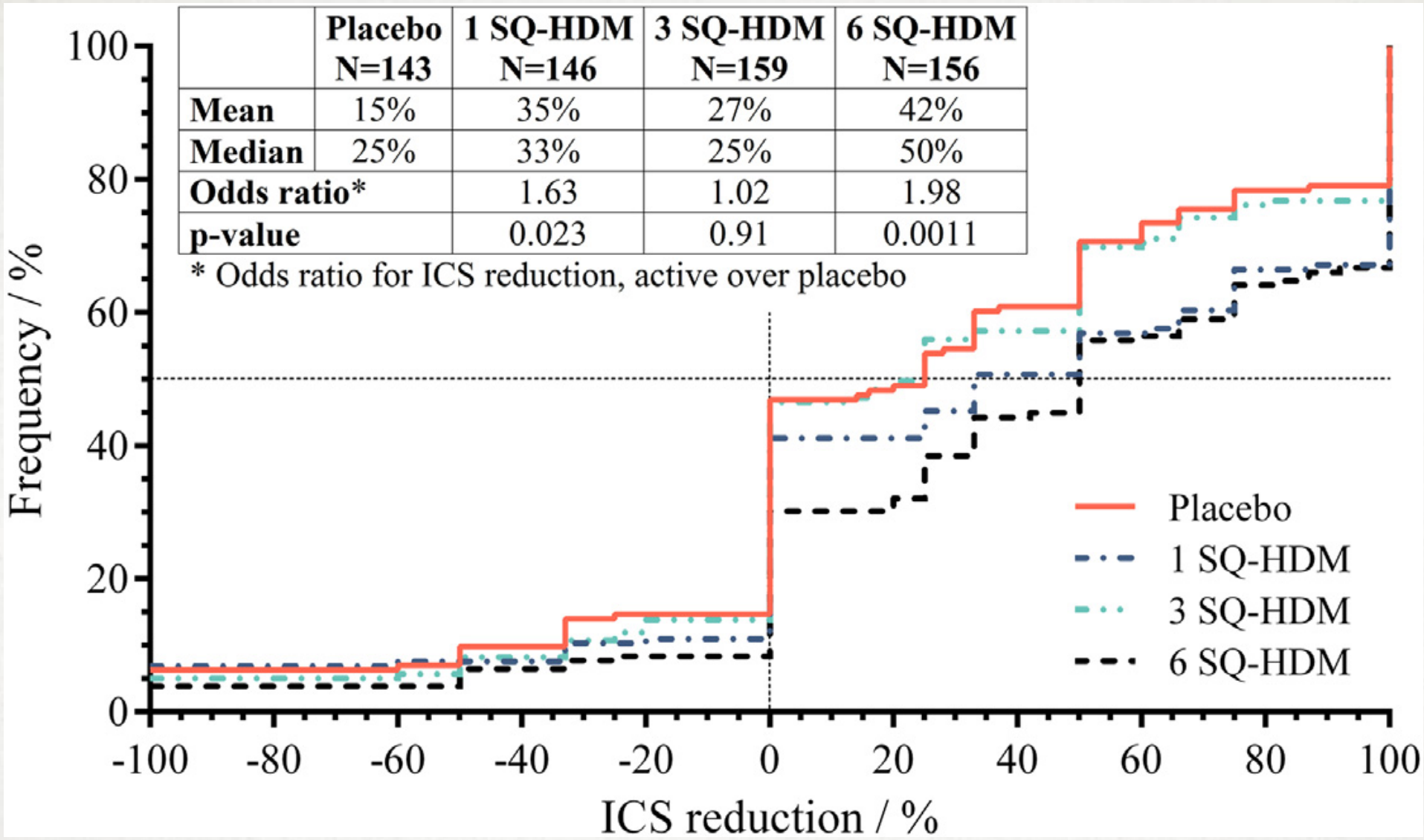


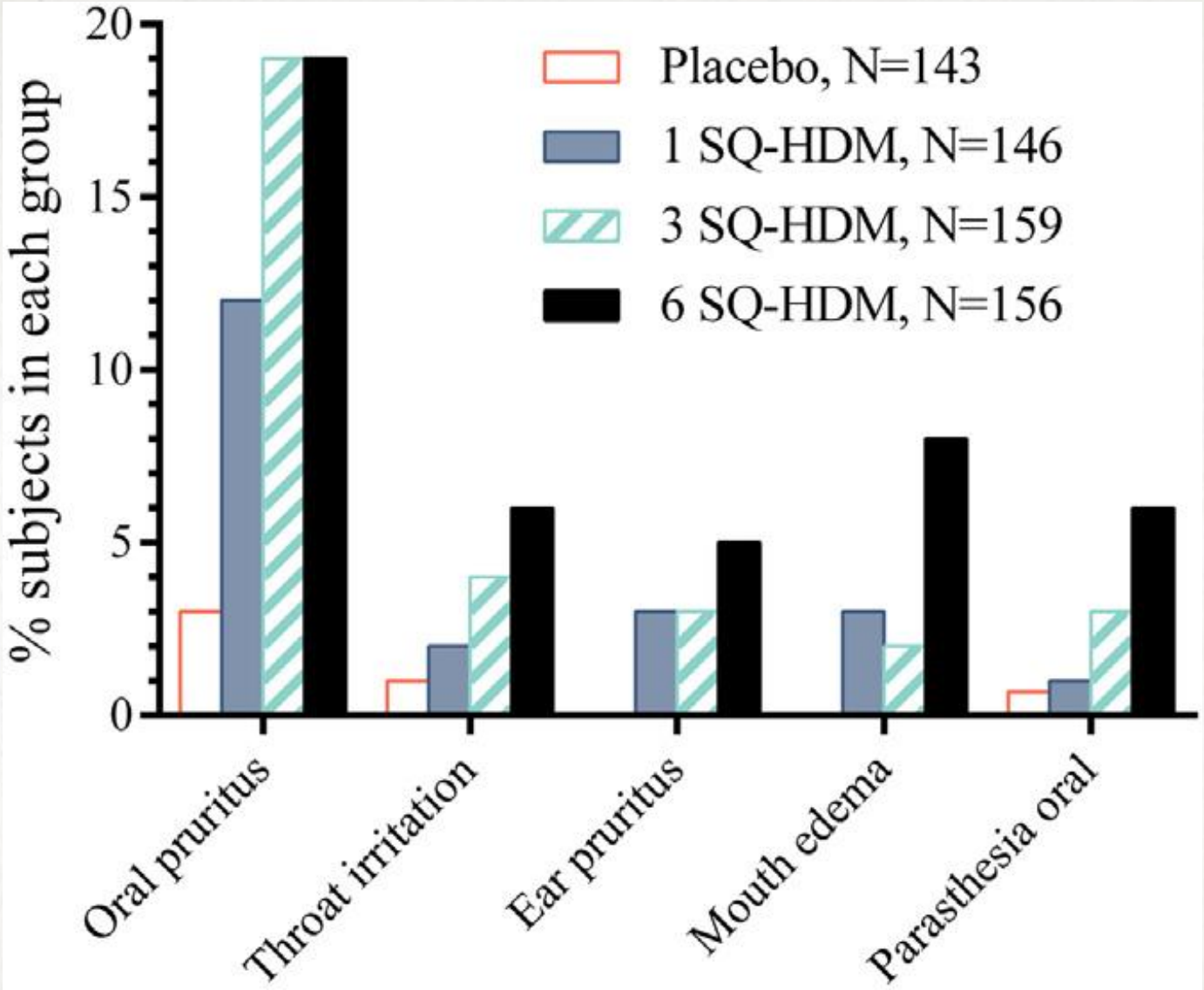
TABLE II. Summary of all AEs occurring after first tablet intake by causality and severity

	Placebo (n = 143)	1 SQ-HDM (n = 146)	3 SQ-HDM (n = 159)	6 SQ-HDM (n = 156)	Active all (n = 461)	Overall (n = 604)
	No. (%); E	No. (%); E	No. (%); E	No. (%); E	No. (%); E	No. (%); E
All AEs	77 (54); 198	81 (55); 217	106 (67); 364	103 (66); 334	290 (63); 915	367 (61); 1113
Causality						
Probable	9 (6); 14	27 (18); 47	48 (30); 113	47 (30); 94	122 (26); 254	131 (22); 268
Possible	12 (8); 18	9 (6); 12	23 (14); 29	21 (13); 39	53 (11); 80	65 (11); 98
Unlikely	71 (50); 166	70 (48); 158	82 (52); 222	81 (52); 201	233 (51); 581	304 (50); 747
Severity						
Mild	65 (45); 122	63 (43); 131	84 (53); 247	85 (54); 212	232 (50); 590	297 (49); 712
Moderate	35 (24); 68	39 (27); 78	51 (32); 104	49 (31); 118	139 (30); 300	174 (29); 368
Severe	5 (3); 8	6 (4); 8	9 (6); 13	3 (2); 4	18 (4); 25	23 (4); 33
Seriousness						
Nonserious	76 (53); 193	80 (55); 210	105 (66); 361	102 (65); 327	287 (62); 898	363 (60); 1091
Serious	4 (3); 5	6 (4); 7	3 (2); 3	6 (4); 7	15 (3); 17	19 (3); 22

E, Number of events; *No.*, number of subjects; %, percent of subjects in treatment group having the event.

TABLE III. AEs leading to discontinuation and assessed as possibly or probably related to the investigational medicinal product

Group	MedDRA preferred term	Causality	Severity	Serious
Placebo	Asthma, myalgia, fatigue, depression	Possible	Moderate	No
1 SQ-HDM	Migraine	Possible	Severe	Yes
1 SQ-HDM	Rhinitis allergic	Possible	Moderate	No
	Rhinitis allergic, pharyngeal edema	Probable	Moderate	No
	Face edema	Probable	Severe	No
3 SQ-HDM	Stomatitis	Probable	Moderate	No
3 SQ-HDM	Asthma	Probable	Mild	No
3 SQ-HDM	Chest discomfort	Probable	Moderate	No
3 SQ-HDM	Face edema	Probable	Moderate	No
3 SQ-HDM	Swollen tongue	Probable	Moderate	No
	Paresthesia oral, chest discomfort	Probable	Mild	No
3 SQ-HDM	Edema mucosal	Probable	Moderate	No
3 SQ-HDM	Somnolescence	Possible	Mild	No
6 SQ-HDM	Edema mucosal	Probable	Mild	No


% subjects in each group
20
15
10
5
0
Placebo, N=143
1 SQ-HDM, N=146
3 SQ-HDM, N=159
6 SQ-HDM, N=156
Oral pruritus
Throat irritation
Ear pruritus
Mouth edema
Parasthesia oral

DISCUSSION

- All in all, the trial design and conduct provide a valid basis for conclusion on the results.
- The objective of 800 randomized subjects based on the power calculation was not met; 604 subjects were randomized, decreasing the power of the trial to detect a difference between treatment groups.
- No statistically significant differences from placebo were observed for the lower dose groups, and the dose response for the 2 lower doses is not clear. Possibly, the end point of ICS reduction is not sensitive enough, particularly with the power to detect a difference being reduced because of the failure to meet the recruitment target. However, the results most likely imply that 1 and 3 SQ-HDM are below the effective dose range.

DISCUSSION

- The statistically significant treatment effect on ICS use in favor of 6 SQ-HDM was consistently observed from all analyses.
- The relative reductions from baseline to the end of treatment were **42%** for 6 SQ-HDM and **15%** for placebo. For comparison, a recent randomized controlled but open trial of the ICS-reducing effect of HDM SCIT in children resulted in relative reductions of **54%** in the actively treated group and **29%** in the control group after 2 years of treatment.
- The results of the presently reported 1-year RDBPC trial are thus comparable with observations from positive 2-year trials of HDM SCIT, and the trial constitutes confirmatory proof that the investigated 6 SQ-HDM SLIT tablet provides maintained asthma control at a reduced dose of ICS or in some cases even with no need for ICS.

DISCUSSION

- There has previously been debate on the effect of AIT in polysensitized patients, but in this trial there was no difference in effect for subjects with additional indoor sensitizations compared with the FAS.
- It is not clear from this trial whether the SQ HDM SLIT-tablet affects only the HDM-induced asthma symptoms or whether an additional, more general effect based on the concept of minimal persistent inflammation, for example, can be expected.
- The posttreatment effect has not been investigated in this trial, but the immunologic observations (to be published separately) are similar to those observed for the corresponding SQ grass SLIT-tablet, studies of which have confirmatively established the posttreatment effect in the treatment of allergic rhinoconjunctivitis.

DISCUSSION

- Most adverse reactions were mild local reactions that resolved spontaneously after a few weeks or months. Neither severe systemic adverse reactions nor any life-threatening adverse reactions (including anaphylactic shock) were reported.
- The observed safety profile does merit investigation of a higher dose that might also lead to a higher observed difference between active and placebo treatment, particularly in a population with more room for improvement.
- For comparison, doses of up to 32 SQ-HDM were investigated in the phase I trials, and a dose of 16 SQ-HDM was found to be the highest tolerable dose in the short term but with a tolerability profile that could potentially impair compliance in a setting of daily use over a period of several years.

DISCUSSION

- With the demonstration of comparable efficacy and improved safety relative to what is usually observed for SCIT, the trial provides new information to be included in the benefit/risk evaluation of different classes of AIT in asthmatic patients.
- The rhinitis results will be reported separately, and taken together, the 2 publications will provide proof of concept for treatment of HDM respiratory allergic disease with the SQ HDM SLIT-tablet.
- For asthma, the currently reported results have led to investigations with the SQ HDM SLIT-tablet in a population with higher ICS requirements and lower levels of asthma control at inclusion, with a focus on the aspect of future risk and including an additional higher dose (12 SQ-HDM).

HDM SLIT

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PMID: 26091451 [PubMed - indexed for MEDLINE] PMCID: PMC4616527 **Free PMC Article**

INTRODUCTION

- SCIT and SLIT show efficacy in treating allergies in children.
- SCIT has been validated for the treatment of asthma and rhinitis, using standardized house dust mite extracts. However, in the pediatric age group, SCIT has some limitations due to the discomfort of repeated injections and side effects.
- There is growing evidence that SLIT therapy is associated with a lower incidence of systemic reactions compared with control and that it reduces the durations and dose of inhaled corticosteroids used and improves lung function in children with asthma.
- House dust mites are the most common allergens worldwide and are the most prevalent allergen in Chinese children with asthma and/or rhinitis.
- Sensitization to house dust mites is one of the key risk factors associated with increase in wheeze in secondary school children in Guangzhou, China.

INTRODUCTION

- A number of studies focused on house dust mite SCIT and house dust mite SLIT in treating asthma or rhinitis in general but not for a particular antigen. However, many of these studies were small and used variable doses of antigen.
- There is good evidence that house dust mite SCIT is efficacious and has long-term benefit in children. However, the evidence of the benefit of house dust mite SLIT is less convincing.
- The objective of this current meta-analysis was to further evaluate the efficacy and safety of dust mite SLIT in children with asthma.

METHODS

- Medical Literature Analysis and Retrieval System Online, ISI Web of Knowledge, and Cochrane Central Register of Controlled Trials databases until February 2014 were searched for randomized controlled trials that investigated the efficacy of SLIT in children with asthma.
- Search terms included asthma, sublingual, immunotherapy, mite allergen, and house dust mite.
- Included studies were randomized, controlled, and prospective studies published in English that evaluated children (<18 years of age) with asthma who were treated with SLIT or control and must have reported clinical efficacy outcome, Dp immunoglobulin E (IgE) levels, serum IgG4 levels, and safety.
- Studies with children with rhinitis only or in which subjects received SCIT were excluded, as well as letters, comments, editorials, and case reports.

METHODS

- Two independent reviewers extracted the data from the eligible studies, and a third reviewer was consulted to resolve any disagreement(s).
- The included studies were assessed for risk bias using the "Risk of Bias" assessment tool, Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, and recommendations for judging risk of bias provided in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.

METHODS

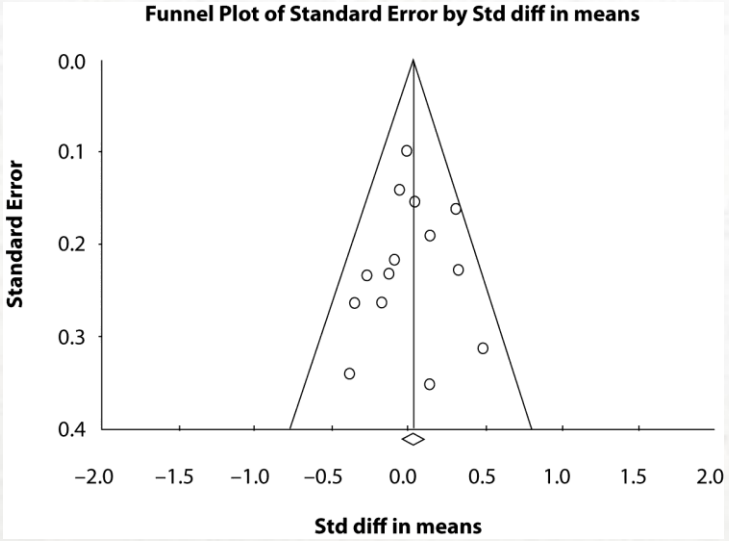
- The primary outcome was mean change in asthma symptom score.
- Secondary outcomes included mean change in medication score, specific Dp IgE levels, and sIgG4 levels. Safety was also assessed.
- The standardized differences in mean changes with 95% confidence intervals (CIs) were calculated.
- The odds ratio (OR) with 95% CI between SLIT and control groups was calculated for the occurrence of adverse event among children treated with SLIT compared with the control group.

METHODS

- Heterogeneity among the studies was assessed by calculating Cochran Q and the I^2 statistic. For the Q statistic, $P<0.10$ indicated statistically significant heterogeneity. I^2 statistics indicate the percentage of the observed between-study variability caused by heterogeneity.
- Heterogeneity was determined using I^2 statistics and was defined as follows: 0% to 24% = no heterogeneity, 25% to 49% = moderate heterogeneity, 50% to 74% = large heterogeneity, and 75% to 100% = extreme heterogeneity.
- The random effects model (DerSimonian-Laird method) was adopted for the current study because it assumes that different studies may have different underlying effects, and it also takes into consideration both within and between-study variations.
- A two-sided $P<0.05$ was considered to indicate statistical significance.

METHODS

- Sensitivity analysis was performed for efficacy outcomes based on the leave-one-out approach.
- When at least 5 studies had sufficient data for the outcome, funnel plot analysis with one-sided Egger tests were performed to evaluate the publication bias for the meta-analyses.



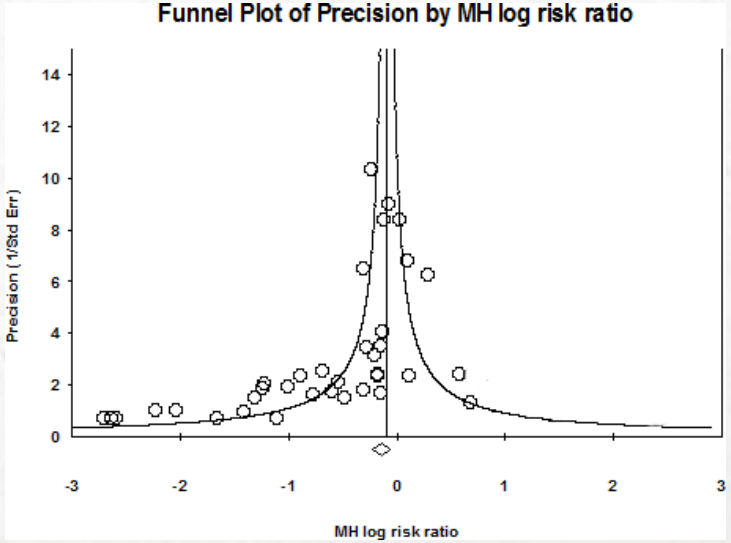


TABLE 1. Summary of Basic Characteristics of Included Studies

Study	Type of Patients	Comparison	Number of Patient	Treatment Duration	Cumulative Dose	Males	Age, y (mean ± SD)
Yukselen (2012)	Rhinitis with asthma related to HDM symptoms	SLIT	10	1 y	86866.5 TU Der p1	50%	9.2 (3.4)
		Placebo	10		86866.5 TU Der f1	60%	10.1 (2.7)
Keles (2011)	Mild persistent/moderate asthma/ rhinitis according to GINA guidelines, monosensitized to HDM	SLIT	13	1 y	54.3 g Der p1	46%	8.55 (2.1)
		Pharmacotherapy	12		54.3 g Der f1	58%	7.9 (2.8)
Eifan (2010)	Mild persistent asthma/rhinitis according to GINA guidelines, having HDM-related asthma/ rhinitis symptoms	SLIT	16	1 y	295.5 g Der p1	44%	6.5 (1.6)
		Pharmacotherapy	16		295.5 g Der f1	44%	7.57 (1.98)
Pham-Thi (2007)	HDM-induced allergic asthma	SLIT	54	18 mo	6.9 mg Der p1	72%	9.6 (5, 14)†
		Placebo	55		14.7 mg Der f1	71%	9.5 (5, 16)†
Lue (2006)	Mild-to-moderate asthma, with single sensitization to HDM	SLIT	10	24 wk	1.7 mg Der p1	40%	7.7 (1.8)
		Placebo	10		3.0 mg Der f1	40%	8.6 (1.80
Niu (2006)	Mild-to-moderate asthma with a single sensitization to HDM	SLIT	49	24 wk	1.7 mg Der p1	62%	7.9 (1.6)
		Placebo	48		3.0 mg Der f1	58%	8.2 (1.7)
Marcucci (2005)	Rhinitis with/without asthma related symptoms to HDM	SLIT	13	3 y	110 or 55 g of mite allergen	NR	8.5 (4–15)
		Placebo	11			NR	
Bahçeciler (2001)	Asthma and rhinitis allergic to HDM	SLIT	8	4 mo	0.56 mg Der p1	50%	12.4 (7.8, 18)*
		Placebo	7		0.98 mg Der f1	57%	12 (7.3, 15)*
Pajno (2000)	Mild-to-moderate asthma, with single sensitization to HDM	SLIT	12	2 y	NR	58%	11 (8, 14)†
		Placebo	12			50%	12 (8,15)†
Hirsch (1997)	Mild-to-moderate asthma, allergic rhinitis or both	SLIT	15	12 mo	570 µg Der p1	66.7%	6–15
		Placebo	15			66.7%	6–14
Tari (1990)	Asthma and rhinitis allergic to HDM	SLIT	30	18 mo	NA	NA	NA
		Placebo	28			NA	NA

GINA = Global Initiative for Asthma, HMD = house mite dust, NA = not available, SLIT = sublingual immunotherapy.
* Median (range).
† Mean (range).

TABLE 2. Summary of Treatment and Evaluation Tools of Included Studies

Study	Immunotherapy Regimen	Tools for Evaluating Symptom Score	Tools for Evaluating Medication Score
Yukselen (2012)	12-week build-up phase: 1 drop of 10 TU/mL daily increasing to 28 drops on day 28, 1–28 drops of 100 TU/mL on days 29–56 and 1–28 drops of 1,000 TU/mL on days 57–84 Maintenance phase: 3 times per week as 28 drops of 1,000 TU/mL	Self-assessment diary: 0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms; asthma symptoms (wheezing, breathlessness, dyspnoea, and cough)	1 point: β2-agonist rescue drug was taken on that day, and 0 if not. Inhaled budesonide (μg/day): 0:0; 1:0–200; 2:200–400; 3:400–800; 4:800–1,000. Intranasal mometasone (μg/day): 0:0; 1:50; 2:100; 3:200
Keles (2011)	1-mo build-up phase followed by maintenance of 5 drops 3 times a week. The dose of Der p 1 that was given in the build-up and maintenance phases was 1.5 and 52.8 mg of Der p 1 and 1.5 and 52.8 mg of Der f 1	NA	NA
Eifan (2010)	1-mo build-up phase followed by a maintenance phase of 5 drops 3 times a week	A daily evaluation of symptoms according to a 4-point scoring system: 0 (no symptoms) to 3 (severe symptoms); asthma symptoms (wheezing, breathlessness, dyspnoea, and cough)	Diary card recorded medications use: 1 point: for β2-agonists and antihistamines, 2 points: inhaled/intranasal steroids, 3 points: one tablet of corticosteroid
Pham-Thi (2007)	A tablet at a concentration of 100 IR contained 9 μg Der p1 and 19 μg Der f 1, which is the major *Dermatophagoides farinae* allergen. Four concentrations were used: 10, 30, 100, and 300 IR	Daytime and nighttime asthma symptoms were recorded using a 4-point scale (0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms)	NA
Lue (2006)	Build-up phase: 1 drop from the 10 IR/mL vial and increasing to 10 drops on day 7, and then stepped up to the 100 IR/mL vial, with 1 drop on day 8 and increasing to 20 drops on day 14. On day 15, 7 drops from the 300 IR/mL vial and increasing doses to 20 drops on day 19 Maintenance phase: Once the 20-drop dose of 300 IR/mL was reached; maintained the same dose for the following 21 weeks.	Daytime and nighttime asthma symptoms were recorded using a 4-point scale (0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms)	Patients were allowed to take the following medications if needed: inhaled corticosteroids [Pulmicort Turbuhaler (AstraZeneca AB, Södertälje, Sweden)], inhaled β2-agonist [Bricanyl Turbuhaler (AstraZeneca AB, Södertälje, Sweden)], and oral corticosteroids (prednisolone, 5 mg). The numbers of puffs and/or tables were also recorded
Niu (2006)	3-week build-up phase: one drop from the 10 IR/mL and increasing to 10 drops on day 7, then one drop from 100 IR/mL vial on day 8 and the dose was increased to 20 drops on day 14. On day 15, 7 drops from the 300 IR/mL vial and increasing to 20 drops on day 19. Maintenance phase: once the 20-drop 300 IR/mL was reached, maintained the same dose for the following 21 weeks	Daytime and nighttime asthma symptoms were recorded using a 4-point scale (0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms)	Patients were allowed to take the following rescue medications if needed: inhaled corticosteroids (budesonide turbuhaler), inhaled β2-agonist (terbutaline aerosol), and oral corticosteroids (pre dnisolone 5 mg). The number of puffs and/or tablets was recorded

Study	Immunotherapy Regimen	Tools for Evaluating Symptom Score	Tools for Evaluating Medication Score
Marcucci (2005)	30-day build-up phase Maintenance phase: 5 drops of the top-dose vial) corresponded to 0.8 and 0.4 μg of mite allergen groups 1 and 2, respectively, and were administered daily for 3 y	Yearly cumulative asthma symptom scores: 0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms; asthma symptoms (breathlessness and cough)	Diary card recorded medications use: 1 point for each application of nasal and/or ocular cromoglycate drops in both nostrils or eyes; 2 points for every inhalation of β2-agonist; 3 points for every antihistamine taken
Bahçeciler (2001)	Build-up phase: 1 drop from the 0.1 IR/mL vial and increasing to 10 drops on day 7. This process was repeated with the 1 IR/mL (for days 8 ± 14) and 10 IR/mL (for days 15 ± 21) vials. On days 22 ± 28, 1 ± 20 drops were given from the fourth vial (100 IR/mL) Maintenance phase: once the 20-drop 100 IR/mL was reached, maintained the same dose daily for 4 wk and then 2 times a week for the following 4 mo	0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms; asthma symptoms (wheezing, dyspnoea, and cough)	NA
Pajno (2000)	Build-up phase: 1 drop from the first vial daily and increasing by 1 drop every day up to 5 drops. The procedure was then repeated with each of the following vials until the maximum dose (5 drops from vial 4, 10 BU/mL) was reached. Maintenance phase: 5 drops from vial 4, 10 BU/mL, corresponding to 2.4 mg Der p 1 and 1.2 mg Der p 2/wk for 3 times a week until the end of the trial	NA	Each drug was scored as follows: score 1: bronchodilators; score 2: inhaled corticosteroids (cromoglycate only during 1993); score 4: oral steroids (7-day course)
Hirsch (1997)	3-week build-up phase: daily increasing doses from 1–7 drops of a 1:100 dilution of the final preparation in the first week, 1–7 drops of a 1:10 dilution in the second week, and 1–7 drops of the final preparation in the third week Maintenance phase: 7 drops on 3 days/wk	0–3 points separately for different organs and symptom types (eyes: itching, secretion, reddening; nose: sneezing, secretion, nasal blockage; lower airways: cough, wheeze, shortness of breath)	NA
Tari (1990)	Build-up phase: 1 drop from the first vial daily and increasing by 1 drop every day up to 15 drops. The procedure was then repeated with each of the following vials until the maximum dose (15 drops from 500 STU/mL vial) was reached Maintenance phase: 15 drops from 500 STU/mL vial 3 times a week for 18 mo	0–3 points of such symptoms as sneezing, nasal discharge, nasal congestion and pruritus, itching and running eyes, and difficulty in breathing	Daily medication was recorded for each day

NA = not available.

TABLE 3. Summary of Primary and Secondary Outcomes and Adverse Event

		SLIT Group			Control Group		
			Baseline	Post-Treatment		Baseline	Post-Treatment
Outcome	Study	Sample Size	Mean (SD)	Mean (SD)	Sample Size	Mean (SD)	Mean (SD)
Asthma symptom score	Bahçeciler (2001)	8	0.64 (0.475)	0.3 (0.358)	7	0.33 (0.29)	0.26 (0.175)
	Eifan (2010)	16	1.4 (1.5)	0.2 (0.4)	16	0.95 (0.62)	2.5 (1.6)
	Lue (2006)	10	0.42 (0.23)	0.13 (0.19)	10	0.42 (0.34)	0.49 (0.38)
	Marcucci (2005)	13	0.121 (0.189)	0.022 (0.059)	11	0.096 (0.185)	0.022 (0.059)
	Niu (2006)	49	0.14 (0.05)	0.07 (0.03)	48	0.04 (0.01)	0.05 (0.02)
	Pham-Thi (2007)	54	0.19 (0.3)	0.15 (0.26)	55	0.17 (0.24)	0.08 (0.17)
	Hirsch (1997)	11	0.36 (0.04–1.3)*	0.07 (0–1.00)*	15	0.07 (0–1.4)*	0.28 (0–1.9)*
	Tari (1990)	30	9.69 (1.59)†	5.71 (1.71)†	28	9.83 (1.57)†	9.33 (1.01)†
Medication score	Eifan (2010)	16	2.8 (1.2)	1.2 (0.9)	16	2.5 (1.5)	2.8 (1.1)
	Lue (2006)	10	1.7 (1.08)	1 (0.94)	10	1.25 (0.72)	1.1 (1.15)
	Marcucci (2005)	13	14 (17.037)	0 (13.333)	11	35 (49.259)	4 (25.185)
Specific IgE *Dermatophagoides pteronyssinus* (IU/mL)	Eifan (2010)	16	98.6 (1.4)	77.4 (24.3)	16	94.3 (5.7)	77.1 (22.9)
	Keles (2011)	13	62 (52)	61 (53)	12	73 (37)	75 (41)
	Lue (2006)	10	3.93 (0.09)	3.95 (0.06)	10	3.86 (0.12)	3.84 (0.14)
	Niu (2006)	49	3.9 (0.37)	3.92 (0.28)	48	3.92 (0.35)	3.75 (0.81)
	Pajno (2000)	12	45.4 (12.6)‡	42 (10.4)‡	12	52.2 (11.2)‡	48 (7.2)‡
	Pham-Thi (2007)	54	208 (279.242)	250 (264.545)	55	197 (222.486)	135 (155.74)
	Hirsch (1997)	15	39.1 (3.5 to >100)	78.9 (20.4 to >100)	15	33.3 (2.7 to >100)	47.4 (1.8 to >100)
	Tari (1990)	30	9.59 (3.13)§	10.58 (3.68)§	28	8.61 (3.25)§	15.71 (2.84)§
sIgG4 (IU/mL)	Keles (2011)	13	0.21 (0.37)	0.22 (0.41)	12	0.11 (0.11)	0.09 (0.08)
	Lue (2006)	10	0.7 (0.1)	2.7 (0.8)	10	0.7 (0.1)	0.6 (0.1)
	Pham-Thi (2007)	54	489.72 (580.235)‖	1874.04 (2654.27)‖	55	319.62 (227.381)‖	273 (158.855)‖
	Yukselen (2012)	10	210 (217.778)‖	273 (497.778)‖	10	42 (77.778)‖	42 (62.222)‖
	Tari (1990)	30	2.49 (1.10)¶	10.71 (3.81)¶	28	2.04 (1.03)¶	2.78 (2.02)¶

		SLIT Group			Control Group		
			Baseline	Post-Treatment		Baseline	Post-Treatment
Outcome	Study	Sample Size	Mean (SD)	Mean (SD)	Sample Size	Mean (SD)	Mean (SD)
		Sample Size	Number of Adverse Events		Sample Size	Number of Adverse Event	
Adverse event	Yüksel et (2012)	10	1		10	4	
	Eifan (2010)	16	0		16	0	
	Pham-Thi (2007)	54	39		55	37	
	Niu (2006)	49	6		48	7	
	Bahçeciler (2001)	8	0		7	0	
	Pajno (2000)	12	6		12	1	
	Tari (1999)	30	15		28	0	

IgE = immunoglobulin E, IgG4 = serum immunoglobulin G4, SLIT = sublingual immunotherapy.

* Median (minimum–maximum).

† Weekly score.

‡ SU/mL.

§ PRU/mL.

‖ µg/L.

¶ µg/mL.

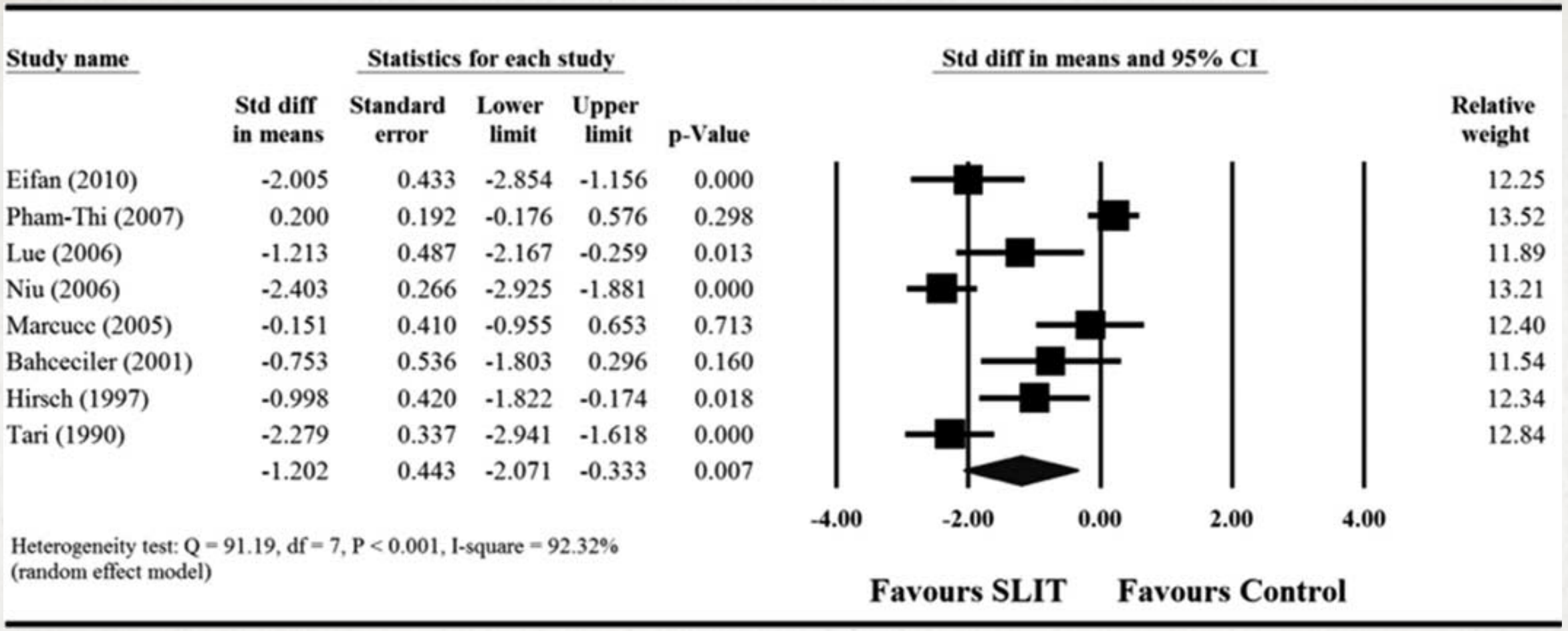
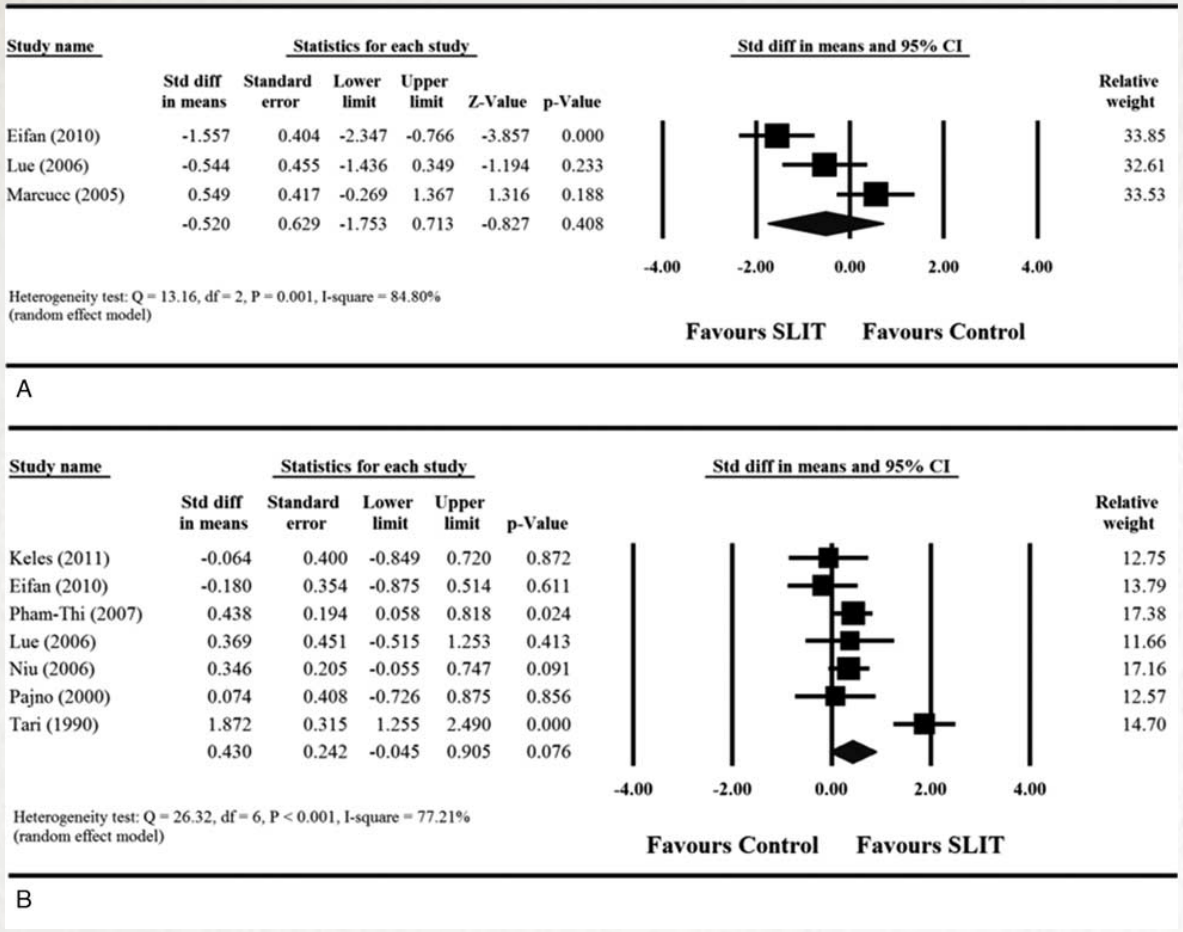


FIGURE 2. Meta-analyses for the comparisons of asthma symptom score between 2 treatment groups. CI = confidence interval.



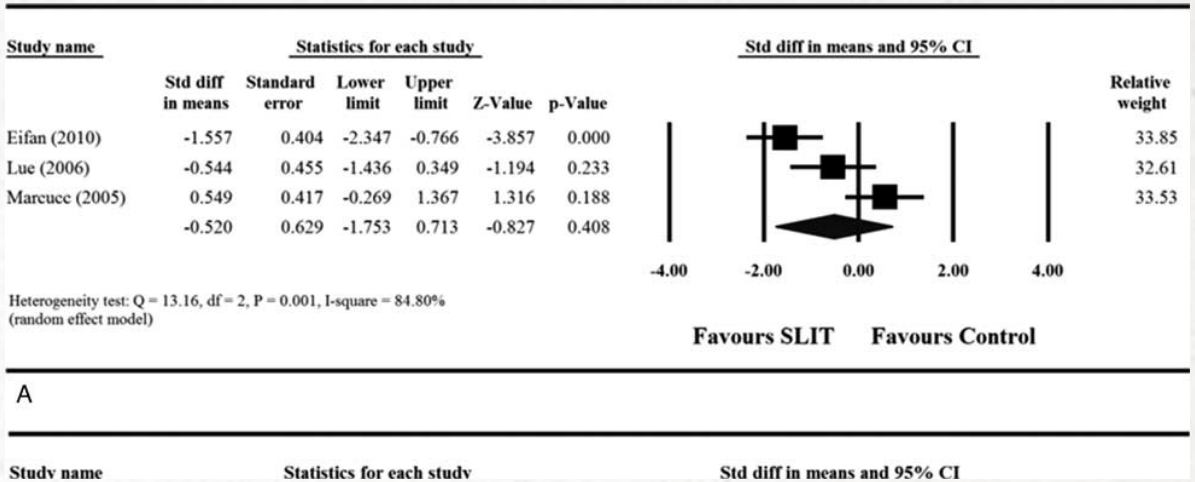


FIGURE 3. Meta-analyses for the comparisons of (A) medication score, (B) specific *Dermatophagoides pteronyssinus* IgE levels, and (C) sIgG4 levels between 2 treatment groups. CI = confidence interval, IgE = immunoglobulin E, sIgG4 = serum immunoglobulin G4.

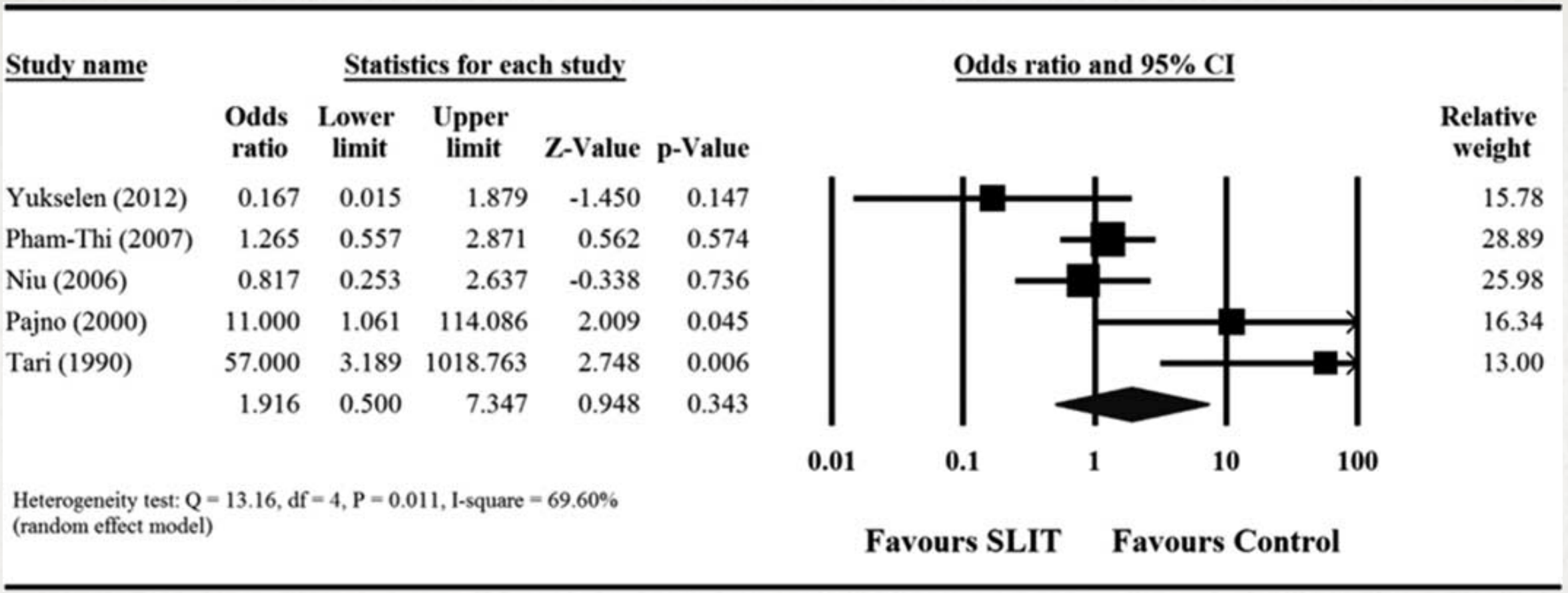
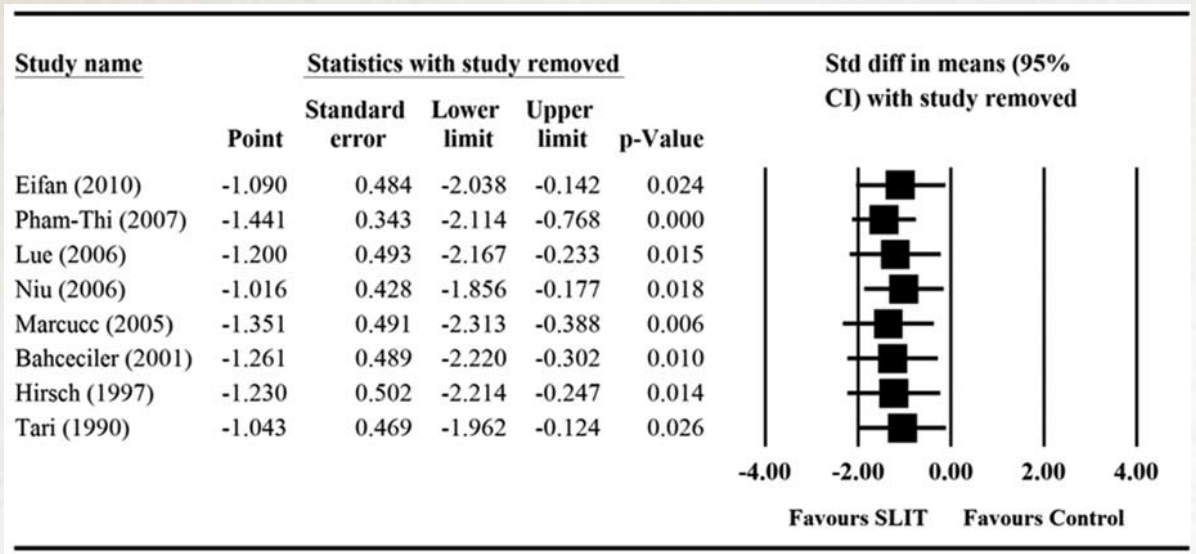


FIGURE 4. Meta-analyses for comparison of the safety outcome (adverse event) between 2 treatment groups. CI = confidence interval.



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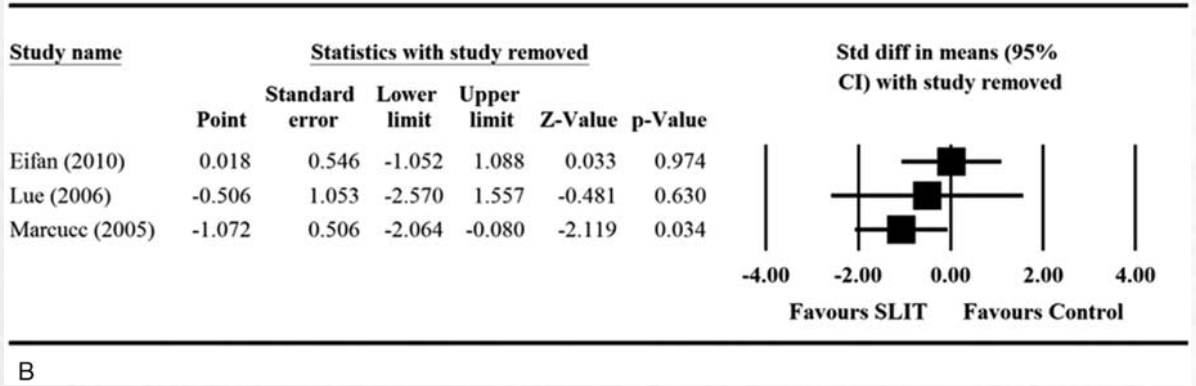

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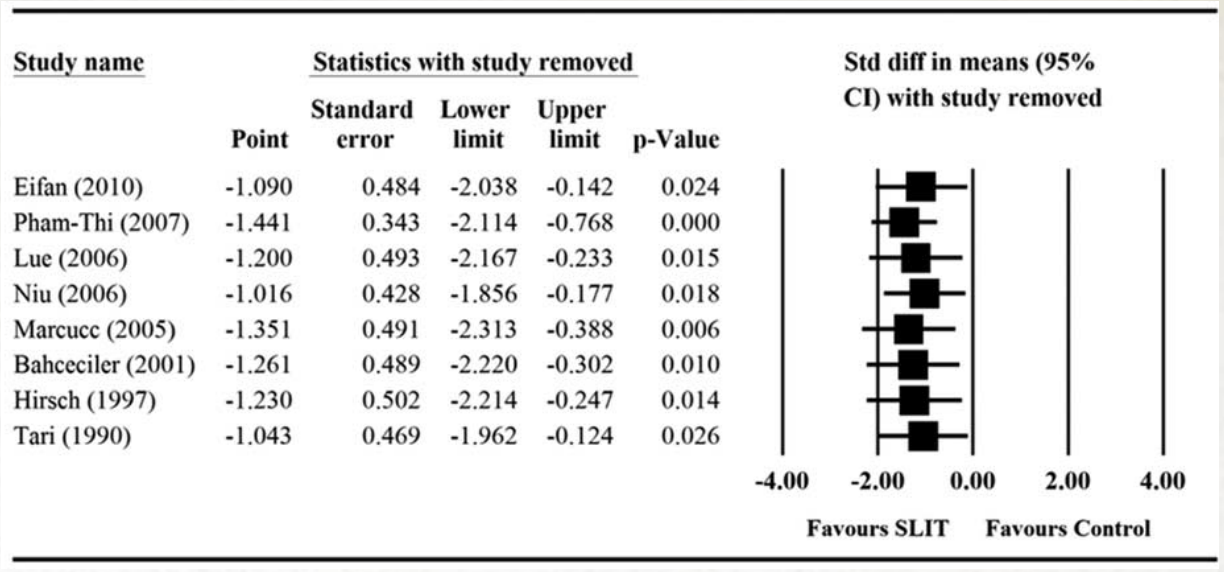
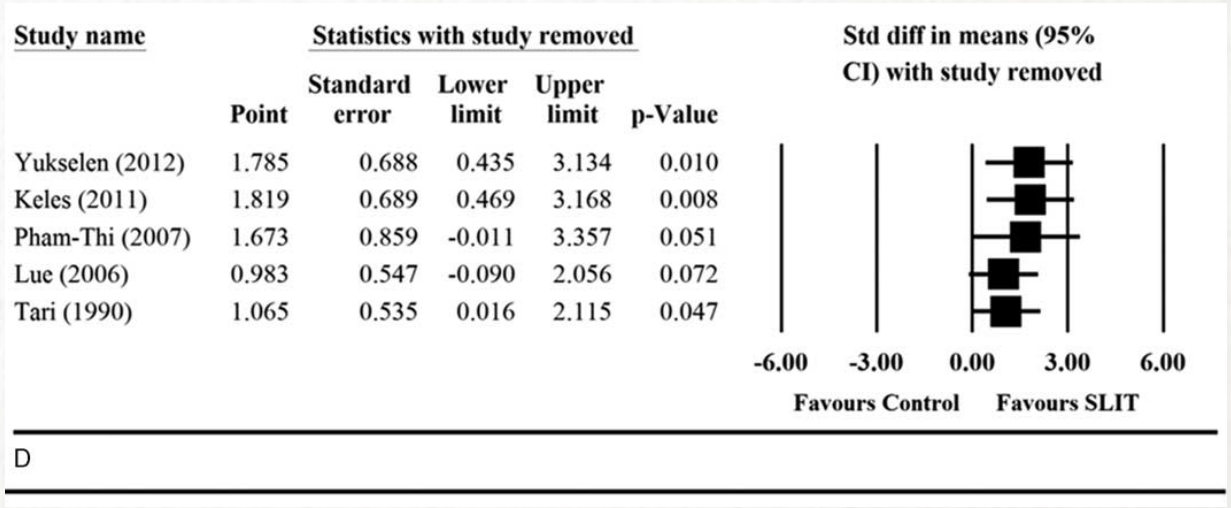
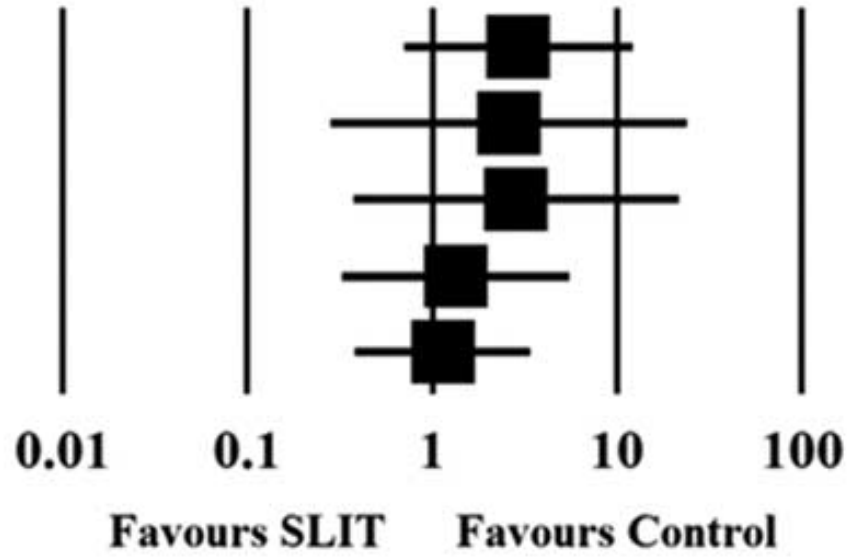




D

FIGURE 5. Sensitivity analyses of the comparisons of (A) asthma symptom score, (B) medication score, (C) specific *Dermatophagoides pteronyssinus* IgE levels, (D) sIgG4 levels, and (E) adverse event between two treatment groups. CI = confidence interval, IgE = immunoglobulin E, sIgG4 = serum immunoglobulin G4.

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Yukselen (2012)	2.938	0.717	12.039	1.497	0.134
Pham-Thi (2007)	2.597	0.287	23.502	0.849	0.396
Niu (2006)	2.858	0.384	21.271	1.026	0.305
Pajno (2000)	1.343	0.330	5.476	0.412	0.681
Tari (1990)	1.141	0.388	3.355	0.240	0.811



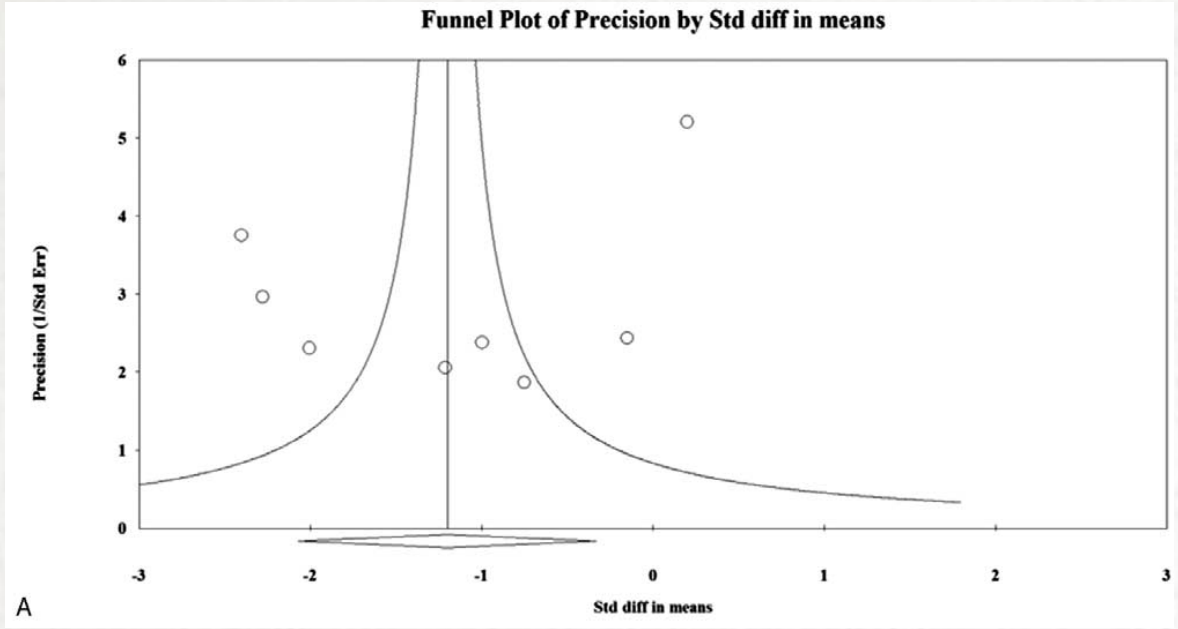
E

FIGURE 5. (Continued)

TABLE 4. Quality Assessment of Included Studies

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Did the Analysis Include an Intention-to-Treat Analysis?
Yukselen (2012)	Y	Y	Y	Y	Y	Y	NA
Keles (2011)	Y	Y	NA	Y	Y	Y	NA
Eifan (2010)	Y	Y	N	N	Y	Y	NA
Pham-Thi (2007)	Y	Y	Y	Y	Y	Y	Y
Lue (2006)	Y	Y	Y	Y	Y	Y	NA
Niu (2006)	Y	Y	Y	Y	Y	Y	Y
Marcucci (2005)	Y	Y	Y	Y	Y	Y	NA
Bahçeciler (2001)	Y	Y	Y	Y	Y	Y	NA
Pajno (2000)	Y	Y	Y	Y	Y	Y	NA
Hirsch (1997)	Y	Y	Y	Y	Y	Y	NA
Tari (1990)	Y	NA	Y	Y	Y	Y	NA

N = high risk of bias, NA = not available, Y = low risk of bias.



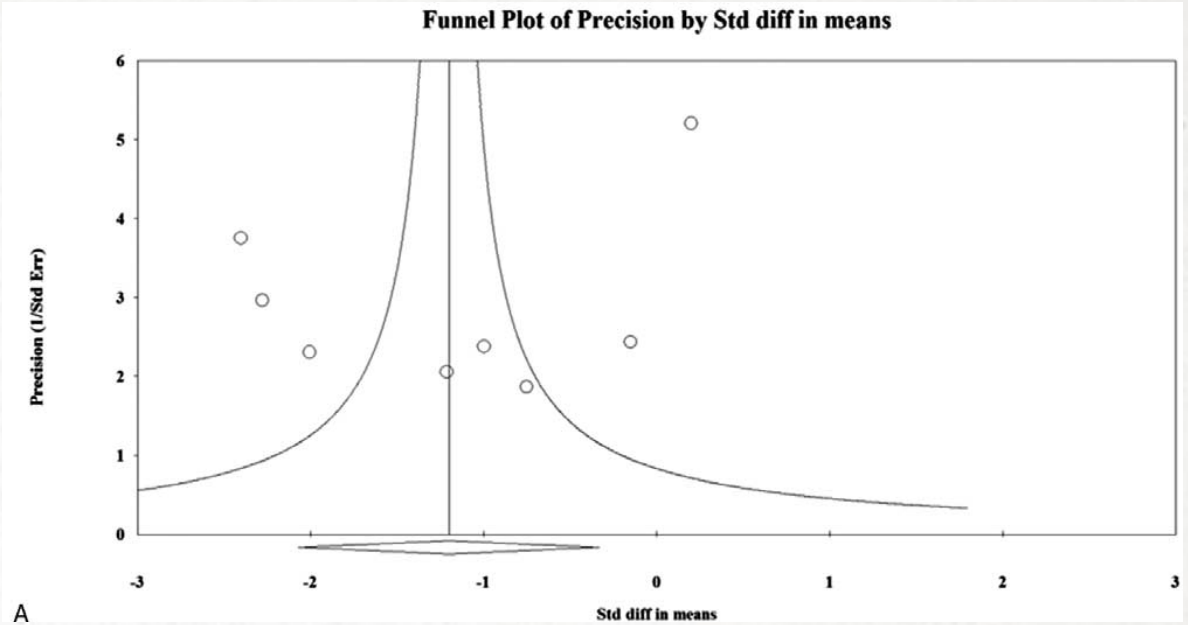


FIGURE 6. Funnel plots of evaluation of publication bias. (A) asthma symptom score and (B) specific *Dermatophagoides pteronyssinus* IgE levels. IgE = immunoglobulin E.

DISCUSSION

- This study found that the reduction in asthma symptom score and the increase in sIgG4 levels were significantly greater in children treated with dust mite SLIT than in children treated with control.
- Dust mite SLIT did not significantly decrease medication score or specific Dp IgE compared with control.
- Dust mite SLIT was well tolerated by children, and in most studies the frequency of adverse events also did not differ between dust mite SLIT and control.
- Sensitivity analysis indicated that generally the finding for the primary analysis of asthma symptom score was not dependent on any one study, and there was no publication bias.

DISCUSSION

- Several prior meta-analyses have assessed the use of SLIT in treating children with asthma or allergic rhinitis.
- Penagos et al evaluated the efficacy of SLIT in children with asthma (3-18 years of age). They found, similar to the present study, SLIT with standardized extracts was associated with an overall reduction in symptom score (P=0.02) and use of rescue medication (P=0.007).
- Only the study by Olaguibel and Alvarez Puebla evaluated medication score, and they did find a significant benefit to SLIT for this outcome. The lack of significance in our analysis may reflect the fact that the methods for evaluating medication score differed across the included studies, possibly confounding the findings.

DISCUSSION

- In conclusion, our study indicates that dust mite SLIT therapy was effective in reducing asthma symptom score and increasing sIgG4, but did not significantly reduce medicine scores and specific Dp IgE.
- Our findings are not enough to support the use of dust mite SLIT in children with asthma.
- However, the data in our meta-analysis, as well as others, suffers from the small number of clinical studies included and the small sample size of these studies. Larger well-designed studies that use similar scoring systems and monitor dust mite SLIT are necessary to further explore this question.

Cochrane Database Syst Rev. 2015 Aug 28;8:CD011293. doi: 10.1002/14651858.CD011293.pub2.

Sublingual immunotherapy for asthma.

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Author information

Abstract

BACKGROUND: Asthma is a common long-term respiratory disease affecting approximately 300 million people worldwide. Approximately half of people with asthma have an important allergic component to their disease, which may provide an opportunity for targeted treatment. Sublingual immunotherapy (SLIT) aims to reduce asthma symptoms by delivering increasing doses of an allergen (e.g. house dust mite, pollen extract) under the tongue to induce immune tolerance. However, it is not clear whether the sublingual delivery route is safe and effective in asthma.

OBJECTIVES: To assess the efficacy and safety of sublingual immunotherapy compared with placebo or standard care for adults and children with asthma.

SEARCH METHODS: We identified trials from the Cochrane Airways Group Specialised Register (CAGR), ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) and reference lists of all primary studies and review articles. The search is up to date as of 25 March 2015.

SELECTION CRITERIA: We included parallel randomised controlled trials (RCTs), irrespective of blinding or duration, that evaluated sublingual immunotherapy versus placebo or as an add-on to standard asthma management. We included both adults and children with asthma of any severity and with any allergen-sensitisation pattern. We included studies that recruited participants with asthma, rhinitis, or both, providing at least 80% of trial participants had a diagnosis of asthma.

DATA COLLECTION AND ANALYSIS: Two review authors independently screened the search results for included trials, extracted numerical data and assessed risk of bias, all of which were cross-checked for accuracy. We resolved disagreements by discussion.We analysed dichotomous data as odds ratios (ORs) or risk differences (RDs) using study participants as the unit of analysis; we analysed continuous data as mean differences (MDs) or standardised mean differences (SMDs) using random-effects models. We rated all outcomes using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) and presented results in the 'Summary of findings' table.

MAIN RESULTS: Fifty-two studies met our inclusion criteria, randomly assigning 5077 participants to comparisons of interest. Most studies were double-blind and placebo-controlled, but studies varied in duration from one day to three years. Most participants had mild or intermittent asthma, often with co-morbid allergic rhinitis. Eighteen studies recruited only adults, 25 recruited only children and several recruited both or did not specify (n = 9).With the exception of adverse events, reporting of outcomes of interest to this review was infrequent, and selective reporting may have had a serious effect on the completeness of the evidence. Allocation procedures generally were not well described, about a quarter of the studies were at high risk of bias for performance or detection bias or both and participant attrition was high or unknown in around half of the studies.One short study reported exacerbations requiring a hospital visit and observed no adverse events. Five studies reported quality of life, but the data were not suitable for meta-analysis. Serious adverse events were infrequent, and analysis using risk differences suggests that no more than 1 in 100 are likely to suffer a serious adverse event as a result of treatment with SLIT (RD 0.0012, 95% confidence interval (CI) -0.0077 to 0.0102; participants = 2560; studies = 22; moderate-quality evidence).Within secondary outcomes, wide but varied reporting of largely unvalidated asthma symptom and medication scores precluded meaningful meta-analysis; a general trend suggested SLIT benefit over placebo, but variation in scales meant that results were difficult to interpret.Changes in inhaled corticosteroid use in micrograms per day (MD 35.10 mcg/d, 95% CI -50.21 to 120.42; low-quality evidence), exacerbations requiring oral steroids (studies = 2; no events) and bronchial provocation (SMD 0.69, 95% CI -0.04 to 1.43; very low-quality evidence) were not often reported. This led to many imprecise estimates with wide confidence intervals that included the possibility of both benefit and harm from SLIT.More people taking SLIT had adverse events of any kind compared with control (OR 1.70, 95% CI 1.21 to 2.38; low-quality evidence; participants = 1755; studies = 19), but events were usually reported to be transient and mild.Lack of data prevented most of the planned subgroup and sensitivity analyses.

AUTHORS' CONCLUSIONS: Lack of data for important outcomes such as exacerbations and quality of life and use of different unvalidated symptom and medication scores have limited our ability to draw a clinically useful conclusion. Further research using validated scales and important outcomes for patients and decision makers is needed so that SLIT can be properly assessed as clinical treatment for asthma. Very few serious adverse events have been reported, but most studies have included patients with intermittent or mild asthma, so we cannot comment on the safety of SLIT for those with moderate or severe asthma. SLIT is associated with increased risk of all adverse events.

J Allergy Clin Immunol. 2015 Aug 17. pii: S0091-6749(15)00935-5. doi: 10.1016/j.jaci.2015.06.036. [Epub ahead of print]

Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized double-blind, placebo-controlled phase III trial.

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Author information

Abstract

BACKGROUND: The SQ HDM SLIT-tablet (ALK) has been developed for treatment of house dust mite (HDM)-induced respiratory allergic disease.

OBJECTIVE: This trial investigated the efficacy and safety of the SQ HDM SLIT-tablet in adults with moderate-to-severe HDM-induced allergic rhinitis (AR).

METHODS: The trial was a randomized, double-blind, placebo-controlled phase III trial conducted in 12 European countries including 992 adults with moderate-to-severe HDM-induced AR despite treatment with pharmacotherapy. Subjects were randomized 1:1:1 to 1 year of daily treatment with placebo, 6 SQ-HDM, or 12 SQ-HDM. The primary end point was the total combined rhinitis score (ie, the sum of rhinitis symptom and medication scores) during the efficacy assessment period (approximately the last 8 weeks of the treatment period). Key secondary end points were rhinitis symptoms, medication scores, quality of life, and the combined rhinoconjunctivitis score.

RESULTS: Analysis of the primary end point (observed data) demonstrated absolute reductions in total combined rhinitis score of 1.18 ($P = .002$) and 1.22 ($P = .001$) compared with placebo for 6 SQ-HDM and 12 SQ-HDM, respectively. The statistically significant treatment effect was evident from 14 weeks of treatment onward. For all key secondary end points, efficacy was confirmed for 12 SQ-HDM, with statistically significant reductions of rhinitis symptoms and medication scores, improved quality of life, and a reduced combined rhinoconjunctivitis score in the efficacy assessment period compared with placebo. The treatment was well tolerated.

CONCLUSION: The trial confirmed the efficacy and favorable safety profile of both 6 SQ-HDM and 12 SQ-HDM in adults with HDM-induced AR. The treatment effect was present from 14 weeks of treatment onward.

? FOR THE AUDIENCE

- Any burning questions or comments?
- Any opinions or criticisms on these papers in particular?
- How many of your opinions changed based on results of these papers?
- If the FDA becomes convinced that the HDM SLIT tablets are efficacious (albeit less than SCIT) with minimal side effects (no anaphylaxis compared to SCIT), would the HDM SLIT tablets be applicable to your practice?

OTHER THOUGHTS?