

Efficacy and Safety of House Dust Mite Sublingual Immunotherapy Tablet in Allergic Asthma: A Systematic Review of Randomized Controlled Trials



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What is already known about this topic? The Global Initiative for Asthma (GINA) guideline recommends that house dust mite sublingual immunotherapy (HDM SLIT) could be considered in adults and adolescents with suboptimally controlled asthma and HDM allergic rhinitis despite low- to high-dose inhaled corticosteroids.

What does this article add to our knowledge? The HDM SLIT tablets effectively reduced inhaled corticosteroid use in adults and adolescents with well- to partly controlled mild-to-moderate allergic asthma. Adverse events were mainly local, and anaphylaxis rarely occurred. However, the treatment effect in reducing asthma exacerbation in partly controlled moderate-to-severe asthma remains inconsistent and needs further studies.

How does this study impact current management guidelines? The HDM SLIT tablets, in addition to maintenance treatment, could be considered in adults and adolescents with well- to partly controlled mild-to-moderate allergic asthma with a favorable safety profile.

BACKGROUND: House dust mite sublingual immunotherapy (HDM SLIT) effectively treats allergic rhinitis (AR). However, the evidence of HDM SLIT for allergic asthma remained limited. **OBJECTIVE:** To systematically review the efficacy and safety of HDM SLIT tablets in patients with allergic asthma.

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METHODS: We performed a systematic search through PubMed, Scopus, EMBASE, Web of Science, the Cochrane Center of Controlled Trials, and Google Scholar for randomized controlled trials (RCTs) that addressed the efficacy and safety of HDM SLIT tablets compared with placebo or no intervention in allergic asthma from their inception date until September 2021. The primary outcome was the reduction in inhaled corticosteroids (ICS) dose. Additional outcomes were asthma control, exacerbation, lung function, quality-of-life, and adverse events.

RESULTS: There were 7 RCTs, 5 studies in allergic asthma (4 in adults and 1 in children), and 2 in AR with or without asthma. The 6 standardized quality (SQ) HDM effectively reduced ICS dose in well- to partly controlled mild-to-moderate asthma in 1 RCT. Two RCTs evaluated the efficacy of 6 SQ and 12 SQ HDM in reducing asthma exacerbation in partly controlled moderate-to-severe asthma, and their results were inconsistent. One study in children with mild-to-moderate asthma found no benefit of HDM SLIT. Two RCTs in AR with or without mild-to-moderate asthma showed improvement of asthma symptoms. Adverse events were primarily local, and anaphylaxis treated with epinephrine was reported in 3 patients.

CONCLUSIONS: The HDM SLIT tablets tend to effectively reduce ICS use in adults and adolescents with well- to partly controlled mild-to-moderate allergic asthma with a favorable safety profile. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:1342-55)

Key words: Asthma; Adverse events; Efficacy; House dust mite; Safety; Standardized quality; Sublingual; Tablet; Immunotherapy

Abbreviations used

ACQ- Asthma Control Questionnaire
AEs- Adverse events
AQLQ- Asthma Quality of Life Questionnaire
AR- Allergic rhinitis
CT- Computed tomography
FeNO- Fractional exhaled nitric oxide
FEV₁- Forced expiratory volume in 1 second
GINA- Global Initiative for Asthma
HDM- House dust mite
ICS- Inhaled corticosteroids
IgG4- Immunoglobulin G4
IR- Index of reactivity
RCT- Randomized controlled trial
RoB2- Risk-of-Bias 2
SABA- Short-acting beta-2 agonist
sIgG4- Specific immunoglobulin G4
SLIT- Sublingual immunotherapy
SQ- Standardized quality

INTRODUCTION

House dust mite (HDM) is 1 of the most important indoor aeroallergens, especially in hot and humid climates, causing allergic rhinitis (AR) and asthma. Both subcutaneous immunotherapy and sublingual immunotherapy (SLIT) using various aeroallergens have been studied in patients with allergic asthma.¹ The primary concern of subcutaneous immunotherapy is a risk for severe and fatal adverse events (AEs) in asthmatic patients, particularly those with uncontrolled disease.² Therefore, SLIT becomes a modality of interest because its side effects are mainly local, including oral pruritus and lip/tongue swelling.³

The published evidence indicates that SLIT tablets and extract (drops) formulations should not be considered identical because they differ in dosages, schedules, absorption, the strength of evidence for efficacy, and products approval based on phases 1 to 3 trials.⁴ The U.S. Food and Drug Administration approved 4 SLIT tablets, 2 for grasses, 1 for ragweed, and 1 for HDM, but not so far for any SLIT extracts.⁵ Therefore, our systematic review specifically addresses HDM SLIT tablets to be beneficial in applying to clinical practice and minimizing heterogeneity of the results. Currently, HDM SLIT tablets are available in 2 preparations, including standardized quality (SQ) HDM and index of reactivity (IR) HDM.

In patients with partly- controlled moderate-to-severe asthma, 6 SQ and 12 SQ HDM, in addition to maintenance medication, significantly improved time to first moderate-to-severe asthma exacerbation during inhaled corticosteroids (ICS) reduction.⁶ As a result, the addition of HDM SLIT to maintenance therapy in patients with suboptimally controlled asthma, with forced expiratory volume in 1 second (FEV₁) greater than 70% of predicted, has been recommended in the Global Initiative for Asthma (GINA) guideline.⁷ However, the most recent Cochrane Database of Systematic Reviews found that the evidence of SLIT for asthma in reducing exacerbations and improving quality of life remained too limited to draw the conclusion because most studies included subjects with mild asthma, and very few studies measured the number of asthma exacerbation.⁸ These results have raised issues of selecting appropriate asthma outcomes to measure the efficacy of HDM SLIT in clinical trials.

In real-life practice, physicians generally consider HDM SLIT as an add-on controller option only when patients are not well-

controlled in steps 3 or 4 of the GINA guideline.⁷ Because the induction of tolerance by SLIT gradually develops over time, assessing asthma control during ICS reduction instead of exacerbation probably represents a reasonable outcome for SLIT efficacy. Moreover, after achieving 3 to 5 years of treatment, SLIT can be discontinued, and its efficacy remains owing to the disease-modifying effect.⁹ In contrast, biologic agents, which so far have no evidence of disease-modifying effect, usually need continuity, and discontinuation may cause a disease flare-up. Therefore, carefully selecting appropriate asthma patients to receive HDM SLIT would relatively save overall health care costs.

Herein, we first conducted a systematic review to assess the efficacy of HDM SLIT tablets on asthma outcomes, including asthma control during ICS reduction, asthma exacerbation, quality of life, use of short-acting beta-2 agonists (SABA), lung function, fractional exhaled nitric oxide (FeNO) level, IgG4 level, nasal symptom scores in studies evaluating concomitant AR, and AEs.

METHODS

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Intervention¹⁰ and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹¹ The review protocol was registered on PROSPERO (CRD42021271552). The PRISMA checklist is provided in [Figure E1](#) (available in this article's Online Repository at www.jaci-inpractice.org).

Data sources and search strategy

We searched electronic medical and scientific databases, including PubMed/MEDLINE, Scopus, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL), from their inception dates to September 30, 2021, for relevant literature based on our prespecified searching strategy ([Tables E1–E5](#); available in this article's Online Repository at www.jaci-inpractice.org). Controlled vocabulary terms were utilized specifically for each database as applicable, such as the Medical Subject Headings (MeSH) for PubMed. We performed an additional search for gray literature, defined as documents that were not published or controlled by commercial publishers (eg, academic theses, internal reports, working papers),^{12,13} using Google Scholar advanced search.¹⁴ If available, 2 authors (C. W. and T. K.) reviewed reference lists from previous narrative reviews or systematic reviews on the same topic. Deduplication of the included records was done using deduplicate option in citation manager and manual removal by the authors (P. P. and L. L.).

Study selection and outcomes

We included randomized controlled trials (RCTs), regardless of sample size, which fulfilled the following criteria: (1) included patients with asthma in any age groups; and (2) addressed the treatment effects of HDM tablets in comparison with placebo or no intervention. Studies that used HDM extract as a primary intervention, non-English studies, studies without abstract, and studies with unobtainable full text were excluded. We also excluded trials that focused mainly on patients with AR with or without asthma but did not report asthma outcomes.

The primary outcome of interest was the decrease of ICS used after initiating HDM SLIT tablets. The secondary outcomes were

asthma exacerbation, Asthma Control Questionnaire (ACQ) score, Asthma Quality of Life Questionnaire score (AQLQ), the use of SABA during follow-up, lung function test parameters, FeNO level, IgG4 level, and nasal symptom scores. For safety outcomes, we focused on the occurrence of AEs and the acceptability of treatment.

Screening

Deduplicated records from the initial search were imported into ASReview; an open-source machine learning developed for prioritizing all records to be subsequently screened manually by the authors.¹⁵ In this systematic review, we did not perform a manual review to all identified records to be more efficient and avoid human error.^{15,16} We provided ASReview with 3 relevant (all were eligible RCTs identified from prior manual searching) and 3 irrelevant studies (all were not RCTs and studies that were totally irrelevant to our research questions) for the machine to learn and rearrange the imported records for priority screening. Two authors (C. W. and M. S.) screened the rearranged records using ASReview mobile application. The records screening was stopped when each investigator had screened 50% of their records according to the prespecified stopping rule. The justification for screening half of the identified records was based on author consensus and the simulation studies from the developing study of ASReview, which reported that 95% of eligible studies were identified after screening less than 33% of the records.¹⁵ After initial screening with ASReview, 2 authors (C. W. and T. K.) independently evaluated the included records for eligibility based on title, abstract, and full-text article. Any disagreement during this process was resolved by consulting the corresponding author (T. T.).

Data extraction

Two authors (C. W. and T. K.) performed an independent data extraction for studies that fulfilled all inclusion criteria. The following data were extracted: study characteristics (ie, study authorship; year of publication; study period; study location, including environmental and pollution factors; study design; follow-up interval; and inclusion and exclusion criteria), patient characteristics (ie, age groups, gender, number of patients in each treatment arm), potential effect modifiers (ie, asthma severity, ICS dosage at randomization), and outcomes of interest. Any discrepancy during the data extraction was resolved through discussion with the clinical methodologist (P. P.) and clinical expert (T. T.). For studies with incomplete outcome data, we contacted the corresponding authors of those studies via email. If the corresponding authors did not respond within 3 weeks, the data were imputed (if feasible) or reported missing.

For continuous outcomes, we extracted the mean change values and their SDs for each treatment arm. For studies that report only median values, we utilized the methods proposed by Luo et al¹⁷ and Wan et al¹⁸ to estimate the mean and SD. However, if the SDs were not reported, we planned to impute these values according to the methods suggested by the Cochrane Handbook for Systematic Reviews of Interventions.¹⁰ For studies that reported the trend of changes of continuous outcomes using graphs, Digitizeit program (<http://www.digitizeit.de/>) was used for data extraction. The total number of patients and the number of event occurrences within each treatment arm was collected for the categorical end point.

Risk-of-bias assessment

Two authors (L. L. and T. T.) independently evaluated the quality of each included study. The quality of each study was rated

using Risk-of-Bias 2 (RoB2) tool for RCTs by the Cochrane collaboration.¹⁹ The methodological quality was assessed in 5 domains as follows: (1) bias arising from randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Each study was rated as having low risk of bias, high risk of bias, or some concerns according to the RoB2 algorithm. Any discrepancy during this process was resolved through discussion with the clinical methodologist (P. P.) and clinical experts (C. W. and M. S.).

Data synthesis and analysis

For qualitative synthesis, tabulation of extracted data was conducted to present the study characteristics, clinical characteristics, and reported efficacy and safety outcomes of all included studies. Because the data on the outcomes of interest were not sufficiently available for quantitative synthesis and the results of tabulations indicated that the methodological heterogeneity among studies was high, a prespecified pairwise meta-analysis was not conducted from this systematic review.

RESULTS

A total of 4,317 records were identified from all databases. Of these records, 1,295 were duplicates and were removed. The remaining 3,022 records were imported into ASReview for machine learning–assisted priority screening. Altogether, 2 authors (C. W. and M. S.) screened a total of 1,513 records (50.0%) of the inputs. Eighty-four records were identified as relevant from ASReview and were sought for retrieval. Thirty-two records were excluded. The remaining 52 studies were assessed for eligibility. There were 7 studies involving patients with AR with or without asthma, of which 2 studies using SQ HDM^{20,21} and 5 using IR-HDM,^{22–26} were excluded because no asthma outcomes were measured, as summarized in Table E6 (available in this article's Online Repository at www.jaci-inpractice.org). Five studies in patients with asthma and 2 studies in patients with AR with or without asthma were finally included in this systematic review. For gray literature, an additional search through Google Scholar yielded a final 3 potential studies to be included. However, these studies were already identified from database searching and, hence, were excluded. The PRISMA 2020 flow diagram is provided in Figure 1.

Characteristics of the included studies

A total of 7 RCTs were included in this systematic review.^{6,27–32} Five RCTs were conducted in patients with asthma,^{6,27–30} whereas 2 RCTs were conducted in patients with AR with or without asthma.^{31,32} Six studies included adult and adolescent patients, and only 1 study included pediatric patients. Five studies were from the European countries and the United States, and 2 studies were from Japan. Six studies were double-blinded RCTs, and 1 was an open-label RCT. Five studies included patients with mild-to-moderate asthma, and 2 studies included patients with moderate-to-severe asthma. This systematic review included a total of 4,081 patients (2,475 patients with asthma and 1,606 patients with AR with or without asthma). Six studies used SQ HDM tablets, and 1 study used IR HDM tablets. Study duration was 1 year or greater in 6 studies and 6 months in 1 study. The general characteristics and the summary of the main findings for each study are presented in Tables I and II. The measured outcomes of included studies are shown in Table III.

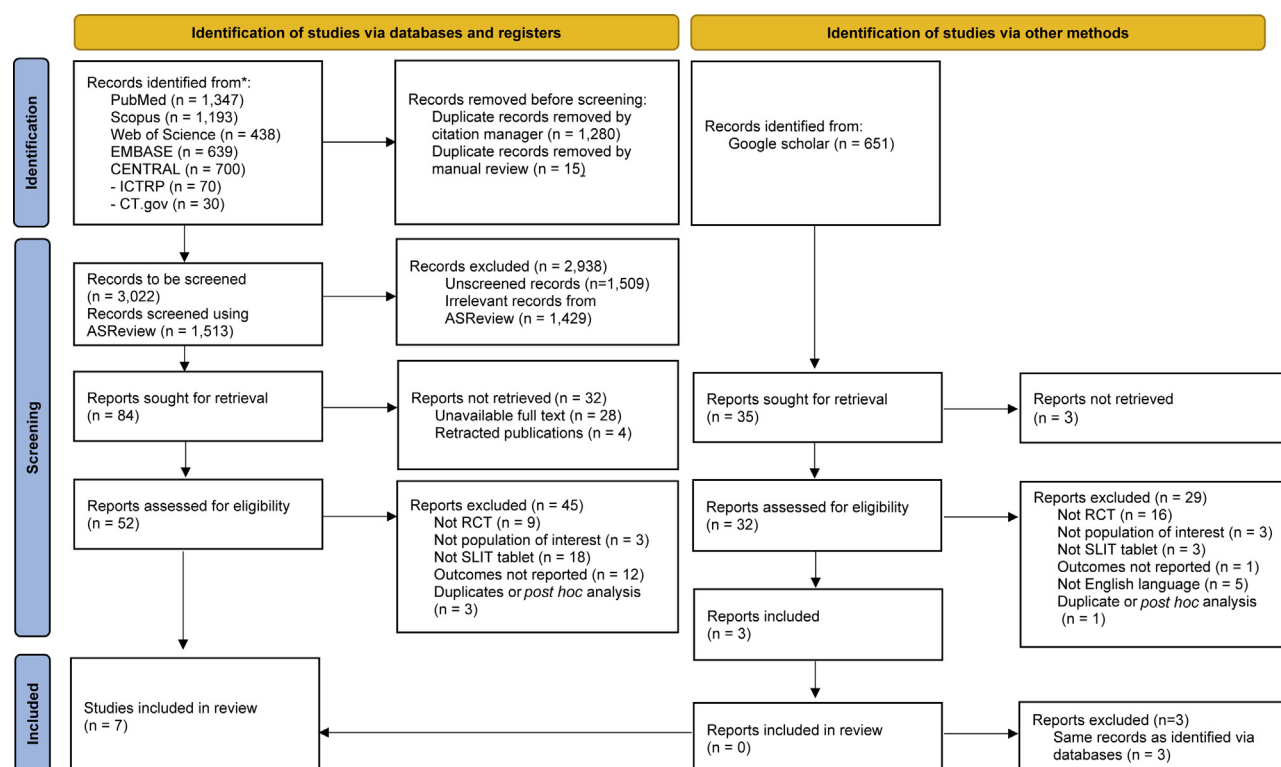


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of included and excluded studies. *RCT*, Randomized controlled trial; *SLIT*, sublingual immunotherapy.

The median and interquartile range of patient age, duration of asthma, baseline ICS used, baseline ACQ score, and baseline FEV₁ from Mosbech et al's study²⁸ were extracted from the graph and converted to mean and SD.

Risk of bias

The risk-of-bias assessment of 7 included studies was conducted according to the guidance of the Cochrane RoB2 tool. Two studies were classified as having low risk of bias (Virchow et al⁶ and Mosbech et al²⁸ studies). Four studies were classified as some concerns of bias (Pham-Thi et al,²⁷ Tanaka et al,³⁰ Nolte et al, 2015,³¹ and Nolte et al, 2016,³² studies). One remaining study was rated as having a high risk of bias (Hoshino et al²⁹), which resulted from our suspicion of selective results reporting. Details on the rating of each RoB2 domain are shown in Figure 2. The summarized proportions for each domain of RoB2 of all included studies are shown in Figure 3. Details of RoB2 evaluation of included studies are shown in Tables E7 to E13 (available in this article's Online Repository at www.jaci-inpractice.org).

Efficacy of HDM SLIT tablets on reducing ICS use

A double-blinded RCT in 604 patients aged 14 years or older with mild-to-moderate asthma concomitant with HDM AR was conducted to evaluate the effect of 6 SQ HDM in decreasing the use of ICS while maintaining asthma control.²⁸ The recruited subjects were treated according to steps 1 to 3 of the GINA guideline. The mean difference in reducing the daily ICS dose between 6 SQ HDM and placebo was 81 µg (95% CI 27–136

mg/d; *P* = .004). Mean and median reductions from baseline in ICS dose were 42% and 50% for 6 SQ HDM and 15% and 25% for placebo, respectively. After 1 year of treatment, 34% of the patients in the 6 SQ HDM group could completely discontinue ICS compared with 21% of those in the placebo group.

The subsequent *post hoc* analysis by de Blay et al³³ on a subgroup of subjects (*n* = 108) with partly controlled asthma (ACQ score of 1–1.5) despite using a daily ICS dose of 400 to 800 µg, revealed a more significant treatment effect toward the 6 SQ HDM group with the difference of ICS reduction of 327 µg compared with the placebo group. Treatment with 6 SQ HDM also significantly improved ACQ and AQLQ in this subgroup. After 1 year of treatment, 59% of patients in the 6 SQ HDM group could reduce ICS use by 75% to 100%, and 45% of those withdrew ICS completely without losing asthma control.

Pham-Thi et al²⁷ conducted an 18-month double-blinded RCT in 111 children aged 5 to 15 years with asthma to evaluate the effect of 300 IR HDM versus placebo. One hundred nine asthmatic children who had received treatment with ICS (budesonide >200 to ≤1,000 µg/d) regularly for at least 6 months were recruited. Seventy-three and 36 patients had mild and moderate asthma, respectively. During a 4-week run-in period before randomization, patients could continue their ICS without changing the dose. At baseline, 50% of the patients had no asthma symptoms, and the use of SABAs was low, indicating that most patients in this study had well-controlled mild asthma. The ICS dose was stepped-down after 5 months, 9 months, and 12 months of treatment by reducing the ICS dose of 20% to 30% at each stage, based on individual asthma status. There was

TABLE I. Characteristics of included studies of HDM SLIT tablets in patients with asthma*

Studies	Site of study	Type/ duration of RCTs	Study size (n)	Intervention (n)	Age (y)	Asthma severity	Baseline ICS used (µg/d)	Duration of asthma (y)	Comorbid AR (%)	Monosensitized (%)	FEV ₁ % predicted	ACQ score	Findings	
													Significantly changed‡	Nonsignificant
Pham-Thi, 2007 ²⁷	France	DBRCT/18 mo	111	HDM 300 IR (12 SQ) (55)	9.6 (5–14)†	Mild to moderate	548 ± 220 BUD	6.1 ± 5	81	NA	91.9 ± 13.4	NA	↑sIgG4, ↑sIgE, ↓SPT, improved severity dimension of QoL	Asthma symptoms scores, asthma-free day, ICS and SABA used, PEFR, FEV ₁ , rhinitis daily score
Mosbech, 2014 ²⁸	Europe	DBRCT multicenter/ 52 wk	604	Placebo (56)	9.5 (5–16)†		534 ± 237 BUD	5.7 ± 4	78	NA	95.1 ± 15.1	NA		
				HDM 6 SQ (156)	31.4 ± 13.92	Mild to moderate	443 ± 416.8 BUD	14.7 ± 11.43	100	17 % of overall subjects	93.3 ± 12.65	0.74 ± 0.50	↓ICS used (6 SQ HDM vs placebo)	ACQ, AQLQ, exacerbation, FEV ₁ , PEF
				HDM 3 SQ (159)	31.2 ± 14.36		391.7 ± 309.7 BUD	14.2 ± 10.59			93.3 ± 11.90	0.74 ± 0.40		
Virchow, 2016 ⁶	Europe	DBRCT multicenter/ 13–18 mo	834	HDM 1 SQ (146)	31.6 ± 14.60		396.7 ± 294.3 BUD	14.4 ± 9.64			92.1 ± 13.10	0.75 ± 0.46		
				Placebo (143)	31.1 ± 14.23		431 ± 377.5 BUD	15.3 ± 11.83			93.3 ± 14.38	0.73 ± 0.46		
				HDM 6 SQ (275)	33.6 ± 11.3	Moderate to severe	582 ± 246 BUD	13 ± 11	100	33	92.32 ± 12.66	1.24 ± 0.17	↓Exacerbation, ↓ICS used, ↑sIgG4 (both 6 SQ and 12 SQ HDM vs placebo)	ACQ, AQLQ
Hoshino, 2019 ²⁹	Japan	Open RCT/48 wk	102	HDM 12 SQ (282)	33.7 ± 11.6		602 ± 246 BUD			32	91.39 ± 12.91	1.23 ± 0.17		
	Japan	Open RCT/48 wk	102	Placebo (277)	33.0 ± 12.2		580 ± 246 BUD			37	94.34 ± 13.79	1.22 ± 0.18		
	Japan	Open RCT/48 wk	102	HDM SLIT 10,000 JAU (6 SQ) (50)	42 ± 11	Mild to moderate	487.5 ± 169.7 BUD	16 ± 15	100	NA	94.0 ± 24.8	NA	↓FeNO, ↓total IgE, improved AQLQ and RQLQ, ↑FEV ₁ , ↑FVC, ↓airway wall thickness	Blood eosinophil
Tanaka, 2020 ³⁰	Japan	DBRCT multicenter/ 13–19 mo	824	No intervention (52)	43 ± 12		530.7 ± 219.2 BUD	14 ± 13	100	NA	95.1 ± 20.3			
	Japan	DBRCT multicenter/ 13–19 mo	824	HDM SLIT 10,000 JAU (6 SQ) (274)	38.4 ± 10.6	Moderate to severe	78.8§	17.3 ± 13.0	79.9	12.0	89.1 ± 13.8	1.20 ± 0.17	↓sIgE, ↑sIgG4	Asthma symptoms, AQLQ, ACQ, ICS used, exacerbation, FEV ₁
	Japan	DBRCT multicenter/ 13–19 mo	824	HDM SLIT 20,000 JAU (12 SQ) (276)	38.3 ± 9.9		75§	17.4 ± 13.3	81.2	11.2	87.4 ± 14.3	1.21 ± 0.17		
				Placebo (274)	37.9 ± 9.4		73.4§	17.5 ± 13.5	78.1	17.2	88.8 ± 14.7	1.19 ± 0.17		

BUD, Budesonide; DBRCT, double-blind, randomized controlled trial; FVC, forced vital capacity; JAU, Japanese allergen unit; NA, not available; PEF, peak expiratory flow; PEFR, peak expiratory flow rate; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; QoL, quality of life; sIgE, specific immunoglobulin E; SPT, skin prick test.

*Numbers are mean ± SD unless stated otherwise.

†Mean (range).

‡Compared active treatment group(s) with placebo.

§Percentage of participants who received fluticasone propionate ≥400 µg/d (equivalent BUD ≥800 µg/d)

TABLE II. Characteristics of included studies of HDM SLIT tablets in patients with AR with or without asthma *

Studies	Site of study	Type and duration of RCTs	Study size (n)	Intervention (n)	Age (y) [†]	Monosensitized (%)	Patients with comorbid asthma (%)	Asthma severity	FEV ₁ % predicted	ACQ score	Significant findings [‡]		
											Rhinitis	Asthma	Asthma
Nolte, 2015 ³¹	Austria	DBRCT single site; 24 wk	124	MK-8237 12 DU (42)	28 (18–58)	12	24	Mild	NA	NA	Improvement [§] in TNSS, TSS, VAS, and RQLQ	Improved asthma symptom score [§]	Asthma
Nolte, 2016 ³²	United States, Canada	DBRCT multicenter; 52 wk	1,482	MK-8237 6 DU (41)	27 (20–48)	10	27		NA	NA			
				Placebo (41)	27 (19–43)	17	22		NA	NA			
				HDM 12 SQ (741)	35 ± 14 (12–77)	25	31	Mild to moderate	98.3 ± 16.7	NA	Improvement in TCERS, conjunctivitis symptom scores, rhinitis DSS, and RQLQ	Improved asthma DSS	Asthma
				Placebo (741)	35 ± 14 (12–85)	23	31		97.2 ± 11.1	NA			

DBRCT, double-blind, randomized controlled trial; DSS, daily symptom score; DU, developmental unit; NA, not available; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TCERS, total combined rhinitis score; TNSS, total nasal symptom score; TSS, total ocular symptom score; TSS, total symptom score; VAS, visual analog scale.

*Numbers are mean ± SD with or without range in parenthesis unless stated otherwise.

[†]Mean (range).

[‡]Compared active treatment group(s) with placebo.

[§]HDM 12 DU was more effective than HDM 6 DU.

no significant difference between HDM SLIT and placebo in improving ICS and SABA used, asthma symptoms scores, lung function, and rhinitis symptom score.

Efficacy of HDM SLIT tablets on asthma exacerbation

Virchow et al⁶ conducted a multicenter European double-blinded RCT comparing the efficacy between SQ HDM and placebo in 834 partly controlled moderate-to-severe asthmatic patients 18 years or older with concomitant HDM AR. After participants received their assigned intervention in addition to budesonide and SABA for 8 to 12 months, the primary outcome, time to first moderate or severe asthma exacerbation, was measured while reducing the ICS dose by 50% for 3 months and then discontinued ICS for 3 more months. The 6 SQ and 12 SQ HDM significantly reduced the risk for a moderate or severe asthma exacerbation compared with placebo while reducing the ICS dose (hazard ratio 0.72 [95% CI 0.52–0.99] for the 6 SQ-HDM group, $P = .045$; and 0.69 [95% CI 0.50–0.96] for the 12 SQ HDM group, $P = .03$). There was no significant treatment effect difference between the 2 doses of SQ HDM, and no significant improvement in ACQ or AQLQ was found for either dose.

Tanaka et al³⁰ conducted another double-blinded RCT similar to Virchow et al's study⁶ in 826 Japanese patients with asthma not well controlled by ICS (equivalent to fluticasone propionate, 200–400 µg), judged by ACQ score of 1.0 to 1.5. All participants continued using their ICS without changing dosage before randomization. Electronic diary recordings of asthma symptoms and medication use of the last 2 weeks before randomization served as individual baseline characteristics. They found no significant difference among the 6 SQ, 12 SQ HDM, and placebo in all asthma outcomes, including exacerbation, ICS use, asthma symptoms, ACQ, AQLQ, and lung function. However, *post hoc* analysis for a subgroup, accounting for 40% of randomized subjects, using SABA during the 14-day baseline period, was performed and found that the 20,000 Japanese allergen unit (equivalent to 6 SQ) HDM could reduce asthma exacerbation with marginal significance ($P = .049$) compared with placebo. This unexpected result may partly be explained by recruiting patients with relatively well-controlled asthma compared with those in Virchow et al's study⁶ at randomization, as shown in Table E14 (available in this article's Online Repository at www.jaci-inpractice.org). Indeed, patients' asthma status at baseline in Virchow et al's study⁶ was more severe than those in Tanaka et al's study³⁰ supported by the difference among total daytime asthma symptom scores, diurnal variability of peak expiratory flow, and 24-hour SABA used. The difference among FEV₁, the amount of ICS used, and the proportion of HDM monosensitized patients could also affect the discrepancy between both studies. Taking the results from those 2 studies into account, the role of HDM SLIT tablets for patients with partly controlled moderate-to-severe asthma remains questionable.

Efficacy of HDM SLIT tablets on ACQ and AQLQ

Post hoc analysis by de Blay et al³³ found that 6 SQ HDM significantly improved ACQ and AQLQ in a subgroup of patients with partly controlled mild-to-moderate asthma. However, the overall analysis in the parent study enrolling mild-to-moderate asthmatic patients with different levels of asthma

TABLE III. Measured outcomes of included studies

Studies	Measured outcomes	Points of measurement	Definition of some measured outcomes
Pham-Thi, 2007 ²⁷	Primary outcome AA symptom score and number of AA symptom-free days Secondary outcomes AA medication score Lung function (FEV₁, PEFr) QoL Rhinitis symptoms scores Skin-prick tests Total and sIgE IgG4	Values at end of study compared with at baseline	AA symptom score consists of nocturnal and diurnal symptoms that were recorded on a 4-point scale 0–3; 0, no symptoms, and 3, severe symptoms Rhinitis symptoms (sneezing, rhinorrhea, nasal blockade, and nasal itching) was rated on a 4-point scale; 0, no symptoms; 1, 1 or several rhinitis symptoms but not disturbing; 2, 1 or several rhinitis symptoms and disturbing; and 3, 1 or several rhinitis symptoms and severe QoL was assessed using 2 forms of the CAQ including CAQ-B for children 6–11 y and CAQ-C for children 12–16 y
Mosbech, 2014 ²⁸	Primary outcome Reduction in ICS dose from baseline Secondary outcomes Lowest ICS dose providing symptom control ACQ score FEV₁ PEFR AQLQ Number of AA exacerbations Safety	Values at end of study compared with at baseline	AA exacerbation was defined as 1 of the following criteria: (1) Need for OCS (2) Unscheduled visits to the trial site (3) Hospitalization The lowest optimal ICS dose providing controlled AA for each subject was the dose to gain control with ACQ score < 1.5
Virchow, 2016 ⁶	Primary outcome Time from randomization to first moderate or severe AA exacerbation during the period of ICS reduction. Secondary outcomes Time from start of the ICS reduction period to first AA exacerbation AA exacerbation AA symptoms Lung function (FEV₁ and PEFr) Asthma symptomatic medication ACQ score AQLQ AEs Immunology profiles (sIgE, IgG4) Safety	Outcomes assessed 11–15 mo and 14–18 mo after receiving intervention (period of ICS reduction by 50% and 100%, respectively)	Criteria for moderate AA exacerbation included (1) Nocturnal awakening due to AA requiring SABA used for at least 2 consecutive nights or an increase of at least 0.75 points in DSS on at least 2 consecutive days (2) Increase in SABA use on at least 2 consecutive d (a minimum increase of 4 puffs/d) (3) 20% or more decrease in PEF or FEV₁ on at least 2 consecutive mornings or evenings (4) ER visit or an unscheduled visit to trial site for AA treatment not requiring systemic corticosteroids Criteria for severe AA exacerbation included (1) Requirement for systemic corticosteroids for asthma symptoms for at least 3 d (2) ER visit due to AA requiring systemic corticosteroids or hospitalization for > 12 h

(continued)

TABLE III. (Continued)

Studies	Measured outcomes	Points of measurement	Definition of some measured outcomes
Hoshino, 2019 ²⁹	Primary outcome Airway inflammation and dimensions assessed by FeNO, Lung CT scan and blood eosinophil count Secondary outcomes Lung function Asthma and rhinitis score AQLQ RQLQ Total IgE and sIgE	Values at end of study compared with at baseline	FeNO was measured using a portable nitric oxide analyzer Lung CT scan was performed by using a 64-multislice scanner Blood eosinophil count was measured using hemocytometry Lung function was measured by computed spirometry Total and sIgE levels were measured using radioallergosorbent fluoroenzyme immunoassay test AQLQ contains 32 items covering 4 domains (symptoms, activities, emotions, and environment) using a 7-point scale RQLQ consists of 28 items in 7 domains (activities, sleep, non-nose and noneye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional), with each score on a 7-point scale
Tanaka, 2020 ³⁰	Primary outcome Time from randomization to first moderate or severe AA exacerbation during the period of ICS reduction. Secondary outcomes Time from the start of ICS reduction period to the first AA exacerbation Moderate or severe AA exacerbation Each asthma symptom score Lung function QoL HDM sIgE HDM sIgG4 Safety	Outcomes assessed 10–16 mo and 13–19 mo after receiving intervention (period of ICS reduction by 50% and 100%, respectively)	Criteria for moderate AA exacerbation included (1) Nocturnal awakening due to AA requiring SABA used for at least 2 consecutive nights or an increase of at least 0.75 points in DSS on at least 2 consecutive d (2) Increase in SABA use on at least 2 consecutive d (a minimum increase of 4 puffs/d) (3) 20% or more decrease in PEF or FEV₁ on at least 2 consecutive mornings or evenings (4) ER visit or an unscheduled visit to trial site for AA treatment not requiring systemic corticosteroids Criteria for severe AA exacerbation included (1) Requirement for systemic corticosteroids for asthma symptoms for at least 3 d (2) ER visit due to AA requiring systemic corticosteroids or hospitalization for > 12 h

(continued)

TABLE III. (Continued)

Studies	Measured outcomes	Points of measurement	Definition of some measured outcomes
Nolte, 2015 ³¹	Primary outcome	Values at the wk 8, 16, 24 compared with at baseline	TNSS was the sum of the 4 nasal symptoms, with a maximum score of 12
	Average TNSS at wk 24		
Nolte, 2015 ³¹	Secondary outcomes		TOSS was the sum of the 2 ocular symptoms, with a maximum score of 6
	Average TNSS at wk 8 and 16		
	Average TSS at wk 8, 16, and 24		
	Average TOSS at wk 8, 16, and 24		
	HDM serum sIgE and IgG4 levels at wk 8		
	Onset of action of HDM SLIT		
	Asthma symptom score		
	RQLQ[S] 12+		
	Rhinoconjunctivitis VAS		
	Safety		
	Active anterior rhinometry		
Nolte, 2016 ³²	Primary outcome	Last 8 wk of treatment compared with at baseline	The TCRS was the sum of rhinitis DSS and rhinitis DMS
	Average TCRS		
Nolte, 2016 ³²	Secondary outcomes	Blood HDM sIgE and IgG4 values at wk 4, 20, and final week of treatment	TCS was the sum of rhinoconjunctivitis DSS and rhinoconjunctivitis DMS
	Average rhinitis DSS		
	Average rhinitis DMS		
	Average TCS		
	AR/C symptoms assessed by VAS		
	Asthma DSS		
	Average RQLQ[S] 12+		
	Serum HDM sIgE and IgG4 levels		
	AEs		

AA, Asthma; AR/C, allergic rhinitis with or without conjunctivitis; CAQ, Childhood Asthma Questionnaire; DMS, daily medication score; DSS, daily symptom score; ER, emergency room; IgE, immunoglobulin E; OCS, oral corticosteroids; PEF, peak expiratory flow; PEFr, peak expiratory flow rate; QoL, quality of life; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RQLQ[S] 12+, Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities for Subjects ≥ 12 years old; sIgE, specific immunoglobulin E; TCRS, total combined rhinitis score; TCS, total combined score; TNSS, total nasal symptom score; TOSS, total ocular symptom score; TSS, total symptom score; VAS, visual analog scale.

control did not demonstrate the same treatment effect.²⁸ Another open RCT in mild-to-moderate asthmatic patients also found that 6 SQ HDM significantly improved AQLQ in emotion domains with the mean difference of 0.42 (95% CI 0.15–0.69; $P = .019$).²⁹

Efficacy of HDM SLIT tablets on lung function

Hoshino et al²⁹ found that 6 SQ HDM significantly improved FEV₁ and forced vital capacity with the mean difference of 103.02 mL (95% CI 29.16–176.88; $P < .001$) and 117.27 mL (95% CI 110.85–123.68; $P = .002$) compared with placebo. In contrast, Mosbech et al's,²⁸ Tanaka et al's,³⁰ and Pham-Thi et al's studies²⁷ revealed no significant change in lung function.

Efficacy of HDM SLIT tablets in AR patients with or without asthma

There were 2 studies reporting asthma outcomes of using SQ HDM in patients with AR with or without asthma. The asthma

outcomes were assessed using asthma symptom score (sum of cough, wheeze, and dyspnea; each symptom rated using a 4-point scale from 0, no symptoms, to 3, severe). First, Nolte et al³¹ conducted a 24-week double-blinded RCT in an environmental exposure chamber in 124 patients aged 18 to 58 years with AR to evaluate the efficacy of 6 SQ and 12 SQ HDM versus placebo. Twenty-four percent of those patients had concomitant mild asthma. *Post hoc* analysis showed that asthma symptom scores were improved by 65% and 53% greater than placebo with 12 SQ and 6 SQ HDM, respectively, at week 24.³⁴ Total nasal symptom score was also improved by 48.6% and 26.6% greater than placebo with 12 SQ and 6 SQ HDM, respectively. The onset of action of 12 SQ HDM was observed as early as 8 weeks of treatment. Second, the 12 SQ HDM was used for a 52-week double-blinded RCT in 1,482 subjects aged 12 years or older with AR.³² In the 12 SQ HDM group ($n = 741$), 31% of those patients ($n = 228$) had concomitant mild-to-moderate asthma, of whom 28% ($n = 66$) used ICS at baseline. The difference of least-square mean asthma symptom score was

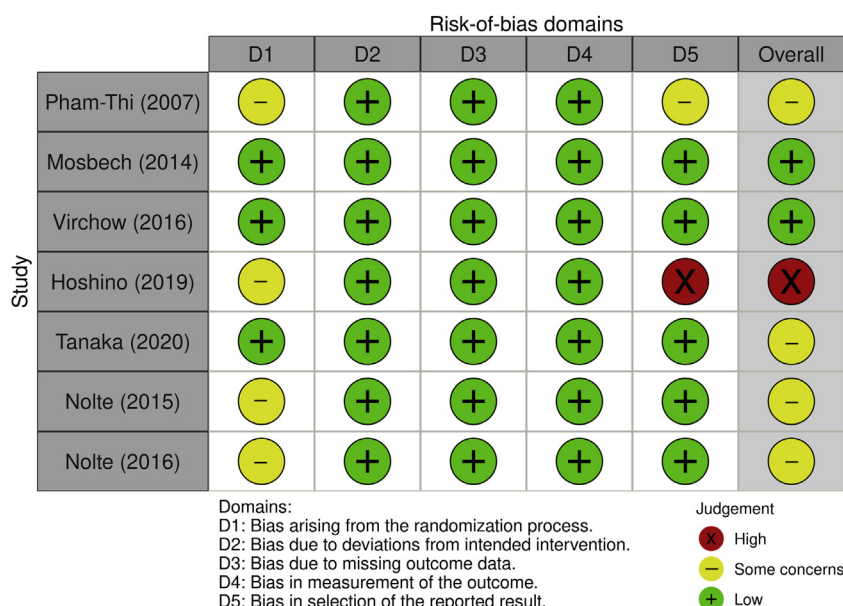


FIGURE 2. Risk-of-bias assessment of the included studies.

−0.46 (95% CI −0.83 to −0.10), corresponding to a 25% improvement between 12 SQ HDM and placebo.³²

Efficacy of HDM SLIT tablets on airway inflammation and immunological parameters

Hoshino et al²⁹ conducted an open RCT in 102 mild-to-moderate asthmatic patients to evaluate the effect of 6 SQ HDM in addition to pharmacotherapy versus pharmacotherapy alone. The primary objective was to assess airway inflammation by measuring FeNO and quantitative computed tomography (CT) of the lung in addition to clinical symptoms and lung function. The 6 SQ HDM effectively improved airflow limitation correlated with CT parameters and FeNO level. The reduced FeNO independently associated with increased FEV₁ ($r^2 = 0.623$; $P = .037$).

The SQ HDM SLIT was reported to induce specific IgG4 (sIgG4) production in most included studies.^{6,27,30–32} The significant increase of sIgG4 could occur as early as 8 weeks after initiating treatment.³¹ Specific immunoglobulin E to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* initially increases after treatment and gradually decreases over time.^{27,30,32} Improved rhinitis symptoms in AR patients almost always

correlate with increased sIgG4,^{31,32} whereas asthma symptoms and other asthma outcomes may not necessarily do so.^{6,27,30}

Adverse events

The percentage of participants reporting at least 1 AE ranged from 39% to 96.4% in the intervention group. Among all AEs, local AEs were the most common. The symptoms include local swelling of the mouth, lips, tongue, or ear along with pruritus and some degree of gastrointestinal discomfort. Some AEs reported are considered nonspecific and are unlikely to be hypersensitivity reactions (eg, dizziness and migraine). The AEs reported from the included studies are summarized in Table IV.

Of the 7 included studies, only Nolte et al's study³² reported 7 subjects treated with epinephrine due to AEs. Three subjects used epinephrine for 12 SQ HDM-related AEs. The other 4 epinephrine administrations were considered unrelated to 12 SQ HDM, 3 related to food/environmental allergies, and 1 (in the placebo group) related to complex allergy symptoms. The details of 3 subjects who received epinephrine for 12 SQ HDM-related AEs are shown in Table E15 (available in this article's Online Repository at www.jaci-inpractice.org). The AEs of asthma with mild-to-moderate severity were reported from 1.3% and 2.4% of

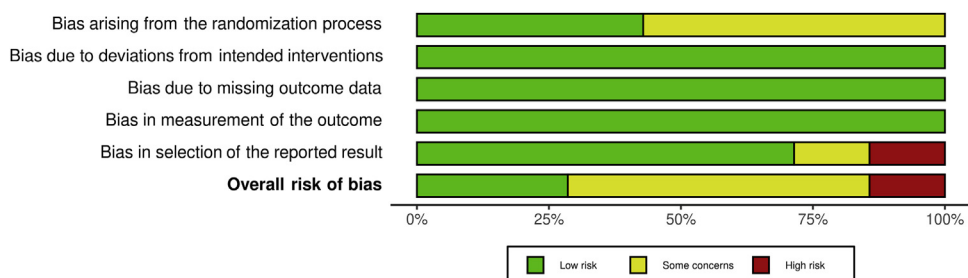


FIGURE 3. Summarized proportions for each domain of version 2 of the Cochrane Risk-of-Bias tool for randomized trials.

subjects in the 12 SQ HDM and placebo groups, respectively. Of note, only Nolte et al's 2016 study³² conducted in the United States prescribed self-injectable epinephrine along with 12 SQ HDM, whereas Nolte et al's 2015 study³¹ in Europe did not, and the other 5 included studies did not mention the epinephrine prescription.^{6,27-30}

DISCUSSION

This systematic review included 7 RCTs, 5 RCTs conducted in patients with asthma^{6,27-30} and 2 RCTs in patients with AR with or without asthma.^{31,32} Only 1 RCT was conducted in children²⁷; the rest were conducted in adolescents and adults. The HDM SLIT tablets effectively improved ICS use in adults and adolescents but had no treatment effect in a very mild group of pediatric asthmatics. The efficacy of HDM SLIT tablets on asthma exacerbation remained inconsistent, and again, the negative results were in a relatively mild group of asthmatics. The AEs were mainly local, and their severity was mild. Several factors may contribute to the variable results from the included RCTs.

The severity of asthma and asthma control of patients enrolled in the studies are critical and need to correlate with the measured outcomes. For instance, the measured outcome should be the reduced dose or discontinuation of ICS in well-controlled mild-to-moderate asthmatic patients with few exacerbations. Mosbech et al²⁸ conducted a large RCT targeting mild-to-moderate asthmatic patients and found that SQ HDM effectively reduced ICS dose and finally discontinued ICS in a significant number of patients. The treatment effect was even more significant when analyzing a subgroup of patients with partly controlled asthma.³³ The efficacy of SQ HDM on ICS dose reduction may be associated with the decrease of airway inflammation concordant with the change of FeNO level.²⁹ In addition, studies mainly focusing on AR patients with coexisting well-controlled mild-to-moderate asthma also confirmed the efficacy of SQ HDM in improving asthma symptoms alongside rhinitis symptoms.^{31,32} Nevertheless, Pham-Thi et al's study²⁷ results failed to show the benefit of HDM SLIT compared with placebo. This study enrolled relatively mild asthma patients whose ICS doses could be safely reduced, regardless of assigned interventions. Therefore, the decrease of ICS dose as the primary outcome may not be suitable for well-controlled, very mild asthmatic patients.

For studies enrolling partly controlled, moderate-to-severe asthmatic patients, the decreased exacerbation rate would be the reasonable outcome to be measured, whereas reducing the ICS dose would not be appropriate and unethical. Virchow et al⁶ used this approach to conduct a large RCT to evaluate the efficacy of SQ HDM in patients with partly controlled, moderate-to-severe asthma. After 8 to 12 months of SQ HDM treatment, the ICS dose was carefully stepped down by 50% for 3 months and completely discontinued consecutively for the next 3 months. The treatment effect of SQ HDM in reducing exacerbation was sustained even during the period of ICS reduction. As a result, their study design and methodology were feasible for ethical concern and applicable for clinical use. Nevertheless, the efficacy on decreased exacerbation was not reproducible in another similar study in Japanese patients,³⁰ probably owing to recruiting relatively well-controlled asthmatic subjects compared with those in Virchow et al's study. This resulting discrepancy leads to questions of whether recruiting patients with partly controlled moderate-to-severe asthma and measuring asthma

exacerbation may not be proper, at least, in subgroups of asthma, of which their phenotypes are rather heterogeneous. In real-life practice, clinicians generally step up treatment to high-dose ICS with long-acting beta-2 agonists plus long-acting muscarinic antagonist when handling this asthma subgroup. Then, if asthma remains suboptimally controlled, low-dose oral corticosteroid or biologic agents would be the reasonable options. Therefore, our systematic review is tempted to propose that HDM SLIT would be suitable for partly or well-controlled mild-to-moderate asthma to reduce ICS dose while maintaining asthma control.

It should be noted that recruiting truly HDM-allergic asthmatic patients is crucial for evaluating the efficacy of HDM SLIT. A survey of HDM allergens in U.S. mattresses found that 46.2% had HDM allergen level of 2 µg/g of dust, sufficient to elicit sensitization.^{35,36} Therefore, asymptomatic HDM sensitization in healthy subjects and asthmatic patients is widespread.³⁷ House dust mite-sensitized asthmatic patients are likely to be truly allergic if they have concomitant rhinitis symptoms. This might partly explain why Pham-Thi et al's²⁷ and Tanaka et al's³⁰ studies enrolling asthmatic subjects without AR in approximately 20% of overall patients yielded negative results. In contrast, other studies that enrolled patients with asthma concomitant with AR demonstrated the treatment efficacy.^{6,28,29,31,32} This concept supports the GINA guideline,⁷ stating that HDM SLIT is indicated in asthmatic patients coexisting with AR. However, HDM allergen level of 10 µg/g of dust was reported to induce asthma symptoms directly.³⁶ As a result, patients with asthma without AR who have positive specific immunoglobulin E to HDM could be truly HDM-allergic irrespective of rhinitis symptoms. Therefore, variation of HDM exposure and fluctuation of HDM allergen levels in the environment among studies may affect the evaluation of treatment efficacy. This issue was not addressed in most included RCTs.

The AEs of HDM SLIT tablets reported from the included studies were primarily local, and anaphylaxis treated with epinephrine was reported in only 3 patients. Epinephrine administrations for treating SLIT tablet-related reactions in clinical trials are uncommon, and no fatalities have been reported.³⁸ Nevertheless, the EudraVigilance (European database of suspected adverse drug reactions) has recently reported a progressive increase in the number of reported suspected cases of anaphylaxis related to HDM SLIT tablets.³⁹ The U.S. Food and Drug Administration currently recommends a prescription of auto-injectable epinephrine in patients receiving SLIT, whereas it is not a standard practice outside the United States.^{4,39} Therefore, prescribing self-injectable epinephrine along with SLIT is still an issue of debate and urgently needs further studies on cost-effectiveness analysis.⁴⁰

This systematic review carries several limitations. First, the number of high-quality RCTs addressing our clinical questions was small. In addition, each RCT also focused on different primary end points or different aspects of asthma control. Second, most studies were conducted in the European countries and the United States, limiting the generalizability of the conclusions to other populations. Third, machine learning-assisted prioritized screening to screen half the records may miss some relevant studies. However, owing to the proven effectiveness of ASReview¹⁵ and our additional review through manual search, the likelihood of missing important studies was probably low. Fourth, Hoshino et al's study²⁹ was subjected to a high risk of

TABLE IV. Summary of AEs reported from included studies

	Pham-Thi, 2007 ²⁷		Mosbech, 2014 ²⁸		Nolte, 2015 ³¹			Nolte, 2016 ³²		Virchow, 2016 ⁶			Hoshino, 2019 ²⁹		Tanaka, 2020 ³⁰		
	HDM SLIT (n = 55)	PL (n = 56)	HDM SLIT (n = 461)*	PL (n = 143)	6 SQ HDM (n = 41)	12 SQ HDM (n = 42)	PL (n = 41)	12 SQ HDM (n = 743)	PL (n = 738)	6 SQ HDM (n = 275)	12 SQ HDM (n = 282)	PL (n = 277)	6 SQ HDM (n = 50)	PL (n = 52)	10,000 JAU HDM (n = 274)	20,000 JAU HDM (n = 276)	PL (n = 274)
AEs																	
Participants with at least 1 event, n (%)	39 (71)	37 (66)	290 (63)	77 (54)	25 (61)	32 (76)	2 (5)	NA	NA	222 (79)	203 (74)	174 (63)	NA	NA	257 (93.8)	266 (96.4)	243 (88.7)
Number of overall AEs (events)	93	77	915	198	NA	NA	NA	91%†	73%†	747 74%†	829 79%†	508 63%†	NA	NA	1,385	1,495	1,091
Number of treatment-related AEs (events)	NA	NA	334‡	32‡	NA	NA	NA	84%†	41%†	247 39%†	351 46%†	69 17%†	NA	NA	371 62.8%†	413 67.0%†	138 26.6%†
Participants discontinuation due to AE, n (%)	1 (1.81)	2 (3.57)	14 (3)	1 (<1)	0	3 (7.14)	6 (14.63)	73 (9.9)	18 (2.4)	12 (4)	25 (9)	8 (3)	6 (12)	0	9 (3.3)	16 (5.8)	8 (2.9)
Local AEs (events [% of overall AEs])																	
Oromucosal reaction (mouth, lip, tongue, throat, or ear swelling or pruritus or paresthesia)	10 (10.75)	5 (6.49)	19%†	5%†	34%†	52%†	0%†	67%†	22%†	145 (19.41) 13%†	223 (26.90) 20%†	15 (2.95) 3%†	NA	NA	253 (18.27) 19%†	306 (20.47) 20.7%†	45 (4.12) 4%†
Systemic AEs (events [% of overall AEs])																	
Gastrointestinal complaints (abdominal discomfort, nausea, vomiting)	19 (20.43)	2 (2.59)	NA	NA	2%†	10%†	0%†	13%†	5%†	0	8 (0.97) 3%†	0	NA	NA	8 (0.57) 2.2%†	5 (0.33) 1.8%†	0
Respiratory complaints (rhinitis or asthma)	64 (68.81)	67 (87.01)	NA	NA	NA	NA	NA	1.3%†	2.4%†	NA	NA	1 (0.19) 0.35%†	NA	NA	92 (6.64) 16.8%†	109 (7.29) 21.7%†	77 (7.06) 18.2%†
Systemic reaction causing epinephrine administration	0	0	0	0	0	0	0	3 events	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

JAU, Japanese allergen unit; NA, not available; PL, placebo.

*Overall active arm (1 SQ, 3 SQ, and 6 SQ HDM).

‡Includes only events that are considered probable or possible causality.

†Number of participants with experienced AEs/all participants (per participants).

bias, and the control arm (no intervention) was different from the other 6 studies. However, this study was still consistent with our inclusion criteria. Although it was an open controlled study, the primary outcomes, including airway inflammation and dimensions assessed by FeNO, lung CT scan, and blood eosinophil count, were objective measures and should reasonably compensate for its drawbacks. Moreover, our predefined primary outcome was the decrease of ICS used, which was not assessed in Hoshino et al's study.²⁹ As a result, excluding this study would not change the overall perspective of the systematic review. Finally, although the contrast groups were similar and seemingly comparable across studies, the reported outcomes varied substantially. Only 2 studies^{27,28} reported our intended primary outcome of interest. Moreover, the measurements of asthma outcomes, asthma severity, and level of asthma control of the recruited population differed among studies, leading to a limitation in conducting quantitative synthesis and concluding clinical benefit. Further studies with predefined asthma outcome measurement according to asthma status at randomization are warranted to evaluate the efficacy of the HDM SLIT tablets. The clinical efficacy of HDM SLIT tablets in asthmatic children also remains to be clarified.

In conclusion, our systematic review revealed that HDM SLIT tablets tend to be effective in improving asthma outcomes in partly or well-controlled mild-to-moderate asthma patients with HDM AR. However, the asthma outcomes to be measured and the asthma severity levels to start treatment remain issues to perform further studies. Adverse events were mild and transient. Few serious AEs occurred, and no fatalities have been reported.

Acknowledgments

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Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	9–10
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	10
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	11
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	11, Tables E1–E5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	11–12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	12–13
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	11–12
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	11–12
Study risk-of-bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	13–14
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA as meta-analysis was not feasible
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	14
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	13
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	14
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA as meta-analysis was not feasible
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA as meta-analysis was not feasible

FIGURE E1. 2020 PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA as meta-analysis was not feasible
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA as meta-analysis was not feasible
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	14-15 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	14 Table E6
Study characteristics	17	Cite each included study and present its characteristics.	15 Tables I–III
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	15-16 Figures 2–3 Tables E7–E13
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables I–II
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA as meta-analysis was not feasible
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA as meta-analysis was not feasible
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA as meta-analysis was not feasible
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA as meta-analysis was not feasible
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA as meta-analysis was not feasible
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA as meta-analysis was not feasible
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	21
	23b	Discuss any limitations of the evidence included in the review.	24-25
	23c	Discuss any limitations of the review processes used.	24-25
	23d	Discuss implications of the results for practice, policy, and future research.	22-23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	10
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	10
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	2
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

NA, Not available.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

For more information, visit: <http://www.prisma-statement.org/>

FIGURE E1. (continued).

TABLE E1. Searching strategies from PubMed

Database	Step	Search algorithm	Items found
MeSH	1	Asthma	133,194
	2	Asthma/immunology	20,252
	3	Asthma/therapy*	60,183
	4	Sublingual immunotherapy/methods*	245
	5	Treatment outcome	1,137,061
	6	1 OR 2 OR 3	133,194
	7	6 AND 4 AND 5	26
Domain/population	8	Asthma	200,509
	9	Allergic asthma	41,333
	10	Bronchial asthma	200,501
	11	8 OR 9 OR 10	200,509
Intervention	12	AIT	34,343
	13	AIT	4,647
	14	Asthma controller medication	20,668
	15	<i>Dermatophagoides</i>	7,726
	16	<i>Dermatophagoides pteronyssinus</i>	5,455
	17	<i>Dermatophagoides farinae</i>	4,983
	18	HDM	7,513
	19	HDM	2,672
	20	HDM SLIT	428
	21	HDM SLIT	75
	22	SLIT	2,221
	23	SLIT	20,567
	24	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23	85,941
Comparators/control	25	Placebo	245,642
Outcomes	26	Asthma attack	6,089
	27	Asthma control	47,782
	28	Asthma control questionnaire score	2,441
	29	Asthma control test score	2,406
	30	Asthma exacerbation	15,230
	31	Asthma quality of life questionnaire score	2,068
	32	Asthma symptoms	99,995
	33	Rescue asthma medication	1,313
	34	Short acting beta 2 agonist	1,452
	35	SABA	8,152
	36	Inhaled corticosteroid	17,740
	37	ICS dose	1,963
	38	ICS reduction	955
	39	26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38	144,556
Design	40	RCT	720,149
	41	RCT	27,764
	42	40 OR 41	729,501
	43	11 AND 24 AND 25 AND 39 AND 42	1,326
	44	7 OR 43	1,347

AIT, Allergy immunotherapy.

TABLE E2. Searching strategies from Scopus

Database	Step	Search algorithm	Items found
Domain	1	(allergic AND asthma)	210,809
Intervention	2	(house AND dust AND mite AND sublingual AND immunotherapy) OR (HDM AND SLIT) OR (sublingual AND immunotherapy)	9,112
Outcomes	3	(asthma AND quality AND of AND life) OR (asthma AND exacerbate) OR (asthma AND control)	314,692
Design	4	(randomized AND controlled AND trial)	2,964,187
	5	1 AND 2 AND 3 AND 4	2,836
	6	Article only	1,317
	7	English only	1,193

TABLE E3. Searching strategies from Web of Science

Database	Step	Search algorithm	Items found
Domain/population	1	ALL = (Asthma)	188,498
	2	ALL = (Allergic asthma)	40,969
	3	ALL = (Bronchial asthma)	19,175
	4	1 OR 2 OR 3	188,492
Intervention	5	ALL = (Allergy immunotherapy)	17,193
	6	ALL = (AIT)	13,903
	7	ALL = (Asthma controller medication)	1,097
	8	ALL = (<i>Dermatophagoides</i>)	3,133
	9	ALL = (<i>Dermatophagoides pteronyssinus</i>)	2,209
	10	ALL = (<i>Dermatophagoides farinae</i>)	1,437
	11	ALL = (House dust mite)	7,677
	12	ALL = (HDM)	3,673
	13	ALL = (House dust mite sublingual immunotherapy)	882
	14	ALL = (HDM-SLIT)	114
	15	ALL = (Sublingual immunotherapy)	3,477
	16	ALL = (SLIT)	30,875
	17	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	70,720
Comparators/control	18	ALL = (Placebo)	209,455
Outcomes	19	ALL = (Asthma attack)	3,356
	20	ALL = (Asthma control)	46,446
	21	ALL = (Asthma control questionnaire score)	2,126
	22	ALL = (Asthma control test score)	2,342
	23	ALL = (Asthma exacerbation)	15,025
	24	ALL = (Asthma quality of life questionnaire score)	2,080
	25	ALL = (Asthma symptoms)	32,110
	26	ALL = (Rescue asthma medication)	882
	27	ALL = (Short acting beta-2 agonist)	1,384
	28	ALL = (SABA)	13,026
	29	ALL = (Inhaled corticosteroid)	12,981
	30	ALL = (ICS dose)	2,164
	31	ALL = (ICS reduction)	1,597
	32	19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31	96,067
Design	33	ALL = (Randomized controlled trial)	423,115
	34	ALL = (RCT)	28,542
	35	33 OR 34	431,945
	36	4 AND 17 AND 18 AND 32 AND 35	438

AIT, Asthma immunotherapy.

TABLE E4. Searching strategies from EMBASE

Database	Step	Search algorithm	Items found
Domain/population	1	Asthma	346,359
	2	Allergic asthma	87,476
	3	Bronchial asthma	48,719
	4	#1 OR #2 OR #3	346,359
Intervention	5	Allergy immunotherapy	24,221
	6	AIT	11,544
	7	Asthma controller medication	1,389
	8	<i>Dermatophagoides</i>	13,955
	9	<i>Dermatophagoides pteronyssinus</i>	6,895
	10	<i>Dermatophagoides farinae</i>	3,913
	11	House dust mite	11,599
	12	HDM	5,319
	13	House dust mite sublingual immunotherapy	762
	14	HDM-SLIT	210
	15	Sublingual immunotherapy	4,639
	16	SLIT	37,743
Comparators/control	17	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	88,370
	18	Placebo	487,661
Outcomes	19	Asthma attack	5,091
	20	Asthma control	61,469
	21	Asthma control questionnaire score	2,397
	22	Asthma control test score	2,794
	23	Asthma exacerbation	25,123
	24	Asthma quality of life questionnaire score	2,243
	25	Asthma symptoms	54,908
	26	Rescue asthma medication	1,688
	27	Short acting beta-2 agonist	1,791
	28	SABA	17,212
	29	Inhaled corticosteroid	19,683
	30	ICS dose	5,485
	31	ICS reduction	2,904
	32	19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31	151,647
Design	33	Randomized controlled trial	960,922
	34	RCT	48,744
	35	33 OR 34	978,317
	36	4 AND 17 AND 18 AND 32 AND 35	639

AIT, Asthma immunotherapy.

TABLE E5. Searching strategies from CENTRAL

Database	Step	Search algorithm	Items found
Cochrane library			
Domain/population	1	Asthma	35,411
	2	Allergic asthma	6,064
	3	Bronchial asthma	6,213
	4	1 OR 2 OR 3	35,411
Intervention	5	Allergy immunotherapy	2,795
	6	AIT	733
	7	Asthma controller medication	403
	8	<i>Dermatophagoides</i>	1,024
	9	<i>Dermatophagoides pteronyssinus</i>	532
	10	<i>Dermatophagoides farinae</i>	233
	11	House dust mite	1,222
	12	HDM	682
	13	House dust mite sublingual immunotherapy	303
	14	HDM-SLIT	125
	15	Sublingual immunotherapy	1,176
	16	SLIT	2,565
	17	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	7,165
Comparators/control	18	Placebo	337,987
Outcomes	19	Asthma attack	781
	20	Asthma control	11,235
	21	Asthma control questionnaire score	1,312
	22	Asthma control test score	1,402
	23	Asthma exacerbation	3,451
	24	Asthma quality of life questionnaire score	1,109
	25	Asthma symptoms	8,115
	26	Rescue asthma medication	1,159
	27	Short-acting beta-2 agonist	485
	28	SABA	832
	29	Inhaled corticosteroid	3,530
	30	ICS dose	1,978
	31	ICS reduction	864
	32	19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31	20,322
Design	33	Randomized controlled trial	1,087,023
	34	RCT	37,432
	35	33 OR 34	1,092,328
	36	4 AND 17 AND 18 AND 32 AND 35	700

AIT, Asthma immunotherapy.

TABLE E6. Summary of HDM SLIT tablets studies excluded from the review

Studies	Subjects	Age (y)	Intervention	Measured outcomes	Reasons for exclusion
Studies involving SQ HDM tablets					
Masuyama, 2018 ²¹	AR ± AA (AA 3.5%)	5–17	6 SQ HDM or placebo	TCRS, rhinitis symptoms, medication scores, QoL, global evaluation by adolescents or legal representatives and physicians	No asthma outcomes were assessed
Demoly, 2016 ²⁰	AR ± AA (AA* 46%)	18–65	6 SQ, 12 SQ HDM or placebo	TCRS, rhinitis symptoms, medication scores, QoL, combined rhinoconjunctivitis score	No asthma outcomes were assessed
Studies involving IR HDM tablets					
Demoly, 2021 ²²	AR ± AA (AA* 37.6%)	12–65	300 IR HDM or placebo	TCS, RTSS, RMS, combined symptom and medication score, individual rhinoconjunctivitis symptom scores, the proportion of symptom-controlled days, QoL	No asthma outcomes were assessed
Okamoto, 2019 ²³	AR ± AA (AA 14%)	5–16	300 IR HDM or placebo	AASS, RTSS, RMS, individual rhinoconjunctivitis symptom scores, overall assessments by patients or their guardians, and investigators	No asthma outcomes were assessed
Okamoto, 2017 ²⁴	AR ± AA (AA no. not reported)	12–64	300 IR, 500 IR HDM, or placebo	AASS, RTSS, individual rhinoconjunctivitis symptom scores, rescue medication use, QoL	No asthma outcomes were assessed
Roux, 2016 ²⁵	AR ± AA (AA 12.7%)	18–55	100 IR, 300 IR, 500 IR HDM, or placebo	Change from baseline of AUC of RTSS, individual rhinitis symptom scores, VAS	No asthma outcomes were assessed
Bergmann, 2014 ²⁶	AR ± AA (AA 29.8%)	18–50	300 IR, 500 IR HDM, or placebo	AASS, RTSS, RMS, individual rhinitis symptom scores, and patient's global evaluation	No asthma outcomes were assessed

AA, Asthma; AASS, average adjusted symptom score; AUC, area under the curve; QoL, quality of life; RMS, rescue/relief medication score; RTSS, rhinitis total symptom score; TCRS, total combined rhinitis score; TCS, total combined score (sum of RTSS and RMS); VAS, visual analog scale.

*Subjects with asthma receiving treatment according to the GINA guideline steps 1–2.

TABLE E7. Quality assessment using Cochrane RoB2 for the study by Pham-Thi, 2007²⁷

Unique ID	1	Study ID	Pham-Thi, 2007		
Reference or label	Pham-Thi	Aim	Assignment to intervention (the intention-to-treat effect)		
Experimental	HDM SLIT	Comparator	Placebo	Source	Journal article(s)
Outcome	Asthma Symptom Score				
Domain	Signalling question		Response		Comments
Bias arising from the randomization process	1.1	Was the allocation sequence random?	PY		Stratified randomization based on ICS intake with no information of randomization methods and concealment.
	1.2	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI		
	1.3	Did baseline differences between intervention groups suggest a problem with the randomization process?	N		No apparent imbalance among 2 groups.
	Risk-of-bias judgment		Some concerns		
Bias due to deviations from intended interventions	2.1.	Were participants aware of their assigned intervention during the trial?	N		Study was double-blind. Placebo and active products were identical in appearance, presentation, taste, and color. Study was double-blind; no information of randomization concealment.
	2.2.	Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN		
	2.3.	If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA		
	2.4.	If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA		
	2.5.	If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA		The study used modified ITT analysis plan that excluded participants with missing data.
	2.6.	Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY		
	2.7.	If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	NA		
	Risk-of-bias judgment		Low		
Bias due to missing outcome data	3.1	Were data for this outcome available for all, or nearly all, participants randomized?	Y		Data from 1 of 55 patients of SLIT group, and 1 of 56 patients in placebo were missing.
	3.2	If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA		

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk-of-bias judgment	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Patients were asked to keep daily record on diary card.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The study was double-blind, assumed no awareness of type of intervention.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk-of-bias judgment	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No prespecified analysis plan available.
	5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	NI	
	5.3 ... multiple eligible analyses of the data?	NI	
	Risk-of-bias judgment	Some concerns	
Overall bias	Risk-of-bias judgment	Some concerns	

ICH, International Conference on Harmonisation - Good Clinical Practice guideline; ID, Identification number; ITT, ; N, no; NA, not available; NI, no information; PN, probably no; PY, probably yes; Y, yes.

TABLE E8. Quality assessment using Cochrane RoB2 for the study by Mosbech, 2014²⁸

Unique ID	2	Study ID	Mosbech, 2014	
Reference or label	Mosbech	Aim	Assignment to intervention (the intention-to-treat effect)	
Experimental	HDM SLIT	Comparator	Placebo	Source
Outcome	Reduction in ICS dose			
Domain	Signalling question		Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?		Y	Randomization was performed in block of 8, by SAS software according to the sponsor-generated allocation schedule at trial-independent statistician. The randomization code copy was held in sealed envelope, concealed until the time of unblind.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N	All parameters were generally similar among groups.
	Risk-of-bias judgment		Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		N	The study was double-blind. Placebo and active product were similar in appearance, smell, and taste.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		PY	The analysis followed the ICH intent-to-treat principle.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?		NA	
	Risk-of-bias judgment		Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?		PN	Withdrawn participants were more than 10% in each group.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?		Y	The study performed imputation using last-observed-carried-forward method and sensitivity analysis.

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk-of-bias judgment	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	The reduction of ICS dose was collected based on the individual's baseline dose. No statistically difference between active and placebo groups. The study was double-blind, assumed no awareness to the type of intervention.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk-of-bias judgment	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Analysis and ACQ score was indicated as secondary outcome in the protocol registered in Clinicaltrials.gov . Means of ACQ scores reported at each visit.
	5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk-of-bias judgment	Low	
Overall bias	Risk-of-bias judgment	Low	

ID, Identification number; intention-to-treat N, no; NA, not available; NI, no information; PN, probably no; PY, probably yes; Y, yes.

TABLE E9. Quality assessment using Cochrane RoB2 for the study by Virchow, 2016⁶

Unique ID	3	Study ID	Virchow, 2016	
Reference or label	Virchow	Aim	Assignment to intervention (the intention-to-treat effect)	
Experimental	HDM SLIT	Comparator	Placebo	Source
Outcome	Time to first asthma exacerbation			
Domain	Signalling question		Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?		Y	Randomization was performed in block of 6 using SAS software. The list was generated by trial-independent statisticians. The randomized codes were kept strictly and held in sealed envelope at a trial-independent department.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N	No appearance imbalance among 3 groups.
	Risk-of-bias judgment		Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		N	The study was double-blinded. Placebo and active products were similar in appearance, smell, and taste. The randomization codes were concealed until end of trial.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA	Analysis was in accordance with intent-to-treat principle.
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?		NA	
	Risk-of-bias judgment		Low	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN	ITT in full analysis set with dropout participants accounted for more than 5% in all groups (20 of 277 in placebo, 38 of 275 in 6 SQ SLIT, 34 of 282 in 12 SQ SLIT). The outcome was analyzed using FAS with and without multiple imputation. Data from both methods were consistent.
	3.2 If N/PN/Ni to 3.1: Is there evidence that result was not biased by missing outcome data?	N	No further analysis for missing outcome.
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	Discontinuation due to lack of efficacy, loss of follow-up, and different proportion of adverse events between groups suggested the missingness depended on its true value.
	3.4 If Y/PY/Ni to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk-of-bias judgment	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Time to first moderate or severe asthma exacerbation was measured from the start of period 3 of trial until the time of first exacerbation which defined according to ATS/ERS recommendation.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The study was double-blind, assumed no awareness of types of intervention.
	4.4 If Y/PY/Ni to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/Ni to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk-of-bias judgment	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	The outcomes intended to measure were mentioned in the registered protocol.
	5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk-of-bias judgment	Low	
Overall bias	Risk-of-bias judgment	Low	

ATS, American Thoracic Society; ERS, European Respiratory Society; ID, identification number; ITT, intention-to-treat; N, no; NA, not available; Ni, no information; PN, probably no; PY, probably yes; Y, yes.

TABLE E10. Quality assessment using Cochrane RoB2 for the study by Hoshino, 2019²⁹

Unique ID	4	Study ID	Hoshino, 2019	
Reference or label	Hoshino	Aim	Assignment to intervention (the intention-to-treat effect)	
Experimental	HDM SLIT + drug	Comparator	Drug alone	Source
Outcome	FeNO level			
Domain	Signalling question			Response Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?		PY	Computer generated randomization. Open, parallel-group controlled study.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		PN	No significant difference observed in baseline characteristics between groups
	Risk-of-bias judgment		Some concerns	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		Y	Open, parallel-group controlled study. It was suggested in clinical trial protocol that assessors were blinded.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PN	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		PY	Intent-to-treat analysis principle that performed as full analysis set with multiple imputation. No sensitivity analysis was mentioned.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?		NA	
Bias due to missing outcome data	Risk-of-bias judgment		Low	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?		N	More than 10% of missing data in both groups (only 42 of 50 in treatment, 46 of 52 in control groups completed the trial).
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?		PY	Multiple imputation was performed in FAS analysis without sensitivity analysis. Dropouts in both groups were not significantly different.

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/Ni to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk-of-bias judgment	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Airway inflammation and dimension were measured by spirometry, FeNO level and CT scan.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Both groups received similar measurements.
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	The study was unblinded, but FeNO measurement was probably objective.
	4.4 If Y/PY/Ni to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	FeNO and lung function probable not influence the outcome assessment.
	4.5 If Y/PY/Ni to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk-of-bias judgment	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	Serum periostin was specified as the primary outcome in registered protocol, but no data of the serum periostin reported.
	5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk-of-bias judgment	High	
Overall bias	Risk-of-bias judgment	High	

ID, Identification number; N, no; NA, not available; Ni, no information; PN, probably no; PY, probably yes; Y, yes.

TABLE E11. Quality assessment using Cochrane RoB2 for the study by Tanaka, 2020³⁰

Unique ID	5	Study ID	Tanaka, 2020	
Reference or label	Tanaka	Aim	Assignment to intervention (the intention-to-treat effect)	
Experimental	HDM SLIT	Comparator	Placebo	Source
Outcome	Time to asthma exacerbation			
Domain	Signalling question		Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?		Y	Computer-generated randomization was performed in blocks of 3. No specific information of randomized code concealment reported, but all the investigators, sponsors, subjects, and trial personnel were blinded until database lock.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N	No significant difference observed in demographic and asthma characteristics among groups.
	Risk-of-bias judgment		Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		PN	Double-blind study, placebo, and active products were similar in appearance, smell, and taste.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PN	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA	Full analysis set included all randomized subjects with multiple imputation of missing data.
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?		NA	
Bias due to missing outcome data	Risk-of-bias judgment		Low	More than 10% of dropouts observed in 3 groups: 237 of 274 in placebo, 229 of 274 in 10,000 JAU, and 227 of 276 in 20,000 JAU completed the trials.
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?		PN	

	3.2 If N/PN/Ni to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	No sensitivity analysis reported, but multiple imputation was performed for missing data. Multiplicity was controlled by a closed testing procedure.
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/Ni to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk-of-bias judgment	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Time from randomization to the first moderate or severe asthma exacerbation which defined according to the ATS/ERS.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	No significant difference observed between groups
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	The study was double-blinded, with all investigators, trial personnel were blinded and assumed no awareness of the type of intervention.
	4.4 If Y/PY/Ni to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/Ni to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk-of-bias judgment	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	Only efficacy, dose dependency, and safety specified in registered protocol.
	5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk-of-bias judgment	Low	
Overall bias	Risk-of-bias judgment	Some concerns	

ATS, American Thoracic Society; ERS, European Respiratory Society; ID, identification number; JAU, Japanese allergen unit; N, no; NA, not available; Ni, no information; PN, probably no; PY, probably yes; Y, yes.

TABLE E12. Quality assessment using Cochrane RoB2 for the study by Nolte, 2015³¹

Unique ID	6	Study ID	Nolte, 2015	
Reference or label	Nolte, 2015	Aim	Assignment to intervention (the intention-to-treat effect)	
Experimental	HDM SLIT	Comparator	Placebo	Source
Outcome	Total nasal symptom score			
Domain	Signalling question		Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?		PN	The randomization numbers were assigned by providing next available number and kit (ordered sequentially). No information of concealment provided.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		PN	Clinical demographics were balanced among treatment and placebo groups.
	Risk-of-bias judgment		Some concerns	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		N	Placebo and active products were identical in appearance, smell, taste, and packaging. Study was double-blind.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA	The full analysis set of efficacy analysis loss 2% –5% of participants in each group. No imputation and sensitivity analysis mentioned in the context.
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?		NA	
	Risk-of-bias judgment		Low	Full analysis set of primary outcomes lost less than 5% of all participants in each group.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?		PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?		NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk-of-bias judgment	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Symptom scores before and after the treatments were measured.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	The study was double-blind.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk-of-bias judgment	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	All reported outcomes were consistent with prespecified protocol.
	5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk-of-bias judgment	Low	
Overall bias	Risk-of-bias judgment	Some concerns	

ID, Identification number; N, no; NA, not available; NI, ; PN, ; PY, ; Y, yes.

TABLE E13. Quality assessment using Cochrane RoB2 for the study by Nolte, 2016³²

Unique ID	7	Study ID	Nolte, 2016	
Reference or label		Aim	Assignment to intervention (the intention-to-treat effect)	
Experimental	HDM SLIT	Comparator	Placebo	Source
Outcome	Total combined rhinitis score			
Domain	Signalling question	Response	Comments	
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Randomization was done by investigators using web response system. No information of randomization concealment.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Demographic and baseline characteristics were similar between groups.	
	Risk-of-bias judgment	Some concerns		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	The study was double-blind. Placebo and active drug were identical in appearance, smell, taste, and packaging.	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN		
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	Full analysis set consists of nearly all of participants. Only 1 participant (of 741) in treatment group lost. No imputation and sensitivity analysis method specified in article.	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY		
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	NA		
Bias due to missing outcome data	Risk-of-bias judgment	Low	Only 1 participant(of 741) lost in full analysis set of efficacy outcome.	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y		
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA		
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA		

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk-of-bias judgment	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	The symptom scores were assessed by nasal symptom score and daily medication score.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	The study was double blind, assumed no awareness on type of intervention.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk-of-bias judgment	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	The reported outcomes were consistent with prespecified protocol registered at clinicaltrials.gov .
	5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk-of-bias judgment	Low	
Overall bias	Risk-of-bias judgment	Some concerns	

ID, Identification number; N, no; NA, not available; NI, no information; PN, probably no; PY, probably yes; Y, yes.

TABLE E14. Comparison of baseline characteristics between Virchow and Tanaka studies

Baseline characteristics	Virchow, 2016 ⁶	Tanaka, 2020 ³⁰
Patients, n	834	824
Age, y*	33.4 ± 11.7	38.2 ± 10.0
Gender, male/female, n (%)	52/48	51/49
Duration of asthma, y*	13 ± 11	17.4 ± 13.3
Comorbid AR, %	100	80
Sensitization status, n (%)		
Only HDM	283 (34)	111 (13.5)
1 other than HDM	140 (17)	125 (15.2)
2 others than HDM	126 (15)	137 (16.6)
≥3 others than HDM	285 (34)	451 (54.7)
Total asthma daytime symptom score*†	2.64 ± 1.98	1.70 ± 1.50
ACQ*	1.23 ± 0.17	1.20 ± 0.17
Morning PEF, L/min*	444 ± 127	415 ± 102
Diurnal variability in PEF, %*	8.61 ± 5.30	3.70 ± 7.70
FEV ₁		
Liter*	3.39 ± 0.84	2.89 ± 0.75
% of predicted*	92.67 ± 13.17	88.5 ± 14.2
ICS used	BUD 588 ± 252 µg/d*	FP 200 µg/d (23.9%) FP 300 µg/d (0.4%) FP 400 µg/d (75.7%)
24-h SABA intake, n of puffs*	1.32 ± 1.63	0.42 ± 0.86

BUD, Budesonide; PEF, peak expiratory flow.

*The value is mean ± SD.

†Total asthma daytime symptom score ranges 0 to 12 (sum of each asthma symptom score including wheezing, coughing, shortness of breath, and chest tightness on a 0–3 scale; 0 = no symptoms, 3 = severe symptoms).

TABLE E15. Summary of 3 subjects who received epinephrine for 12 SQ HDM–related adverse events

Subject	Event details	Day of SLIT	Epinephrine treatment	Outcomes
1	Moderate AEs (systemic reaction, facial flushing, itchy palms, and swollen throat) occurred within minutes of SLIT administration on the first day of treatment under medical supervision	1	Treated with epinephrine by the investigator	Discontinue intervention
2	Severe AEs (local swelling, throat tightness) occurred on d 7 of treatment within 30 min of SLIT administration	7	Self-administered epinephrine and subsequently treated in the emergency department	Discontinue intervention
3	Moderate throat and chest discomfort within 30 min of SLIT administration on d 128	128	Self-administered epinephrine	Continued the trial and tolerated subsequent treatments