Comparative Effectiveness Review
Number 196

The Role of Immunotherapy in the Treatment of Asthma

AHRQ
Agency for Healthcare Research and Quality

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The Role of Immunotherapy in the Treatment of Asthma

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2015-00006-I

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AHRQ Publication No. 17(18)-EHC029-EF
March 2018

Key Messages

Purpose of review

To assess the efficacy and safety of immunotherapy for treating allergic asthma.

Key messages

- Subcutaneous immunotherapy reduces use of long-term control medications. It may also improve quality of life and $FEV_{1,}$ (a measure of the ability to exhale) and reduce the use of quick-relief medications (short-acting bronchodilators) and systemic corticosteroids.
- Sublingual immunotherapy improves asthma symptoms, quality of life and FEV_1, and reduces the use of long-term control medications. It may also reduce the use of quick-relief medications.
- Local and systemic reactions to subcutaneous immunotherapy and sublingual immunotherapy are common but infrequently required changes in treatment. Life-threatening events (such as anaphylaxis) are reported rarely.

This report is based on research conducted by the Johns Hopkins University EPC under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00006-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Suggested citation: Lin SY, Azar A, Suarez-Cuervo C, Diette GB, Brigham E, Rice J, Ramanathan M, Gayleard J, Robinson KA. The Role of Immunotherapy in the Treatment of Asthma. Comparative Effectiveness Review No. 196 (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No.290-2015-00006-I). AHRQ Publication No. 17(18)-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2018. Posted final reports are located on the Effective Health Care Program search page.
DOI: https://doi.org/10.23970/AHRQEPCCER196.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge Jeanette Edelstein, M.A., for copy editing the final report.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Task Order Officer (TOO) and the Evidence-based Practice Center (EPC) work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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The Role of Immunotherapy in the Treatment of Asthma

Structured Abstract

Objectives. To evaluate the efficacy and safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in the treatment of allergic asthma.

Data Sources. We searched PubMed, Embase, and CENTRAL through May 8, 2017.

Methods. Two reviewers independently selected randomized controlled trials (RCTs) of the efficacy of SCIT and SLIT and RCTs, observational studies, and case series or case reports on safety. Two reviewers independently assessed the risk of bias for each study and together graded the strength of the evidence.

Results. We identified 54 RCTs on efficacy: 31 assessed SCIT and 18 assessed SLIT and 5 on SCIT versus SLIT. We included 80 studies on safety: 26 RCTs and 18 non-RCTs for SCIT, 20 RCTs and 10 non-RCTs for SLIT and one non-RCT on SCIT versus SLIT.

SCIT reduces the use of long-term control medications [moderate strength of evidence (SOE)]. SCIT may improve quality of life, reduce the use of quick-relief medications (short-acting bronchodilators), reduce the need for systemic corticosteroids, and improve FEV_1 (low SOE). There was insufficient evidence regarding the effect of SCIT on asthma symptoms and health care utilization. Local and systemic allergic reactions were frequent but infrequently required a change in treatment. We are unable to draw conclusions about whether SCIT increased risk of anaphylaxis, primarily because anaphylaxis was not directly measured (insufficient SOE). There was one case report of a death determined possibly to be caused by SCIT.

SLIT improves asthma symptoms (high SOE); decreases use of long-term control medication and improves FEV_1 (moderate SOE). SLIT may decrease quick-relief medication use, and may improve quality of life (low SOE). There was insufficient evidence about the effect of SLIT on systemic corticosteroid use and health care utilization. Local and systemic allergic reactions were common but infrequently required changes in treatment. Life-threatening reactions were not commonly reported, with three case reports of anaphylaxis (insufficient SOE) and no deaths (moderate SOE) reported.

There was insufficient evidence to draw conclusions about the comparative effects of SCIT versus SLIT or for differential effects of immunotherapy based on patient age, setting of administration, or type of allergen.

Conclusions. Overall, SLIT and SCIT were beneficial for the majority of asthma-related outcomes assessed in this report. Local and systemic allergic reactions were common but infrequently required changes in treatment. Life-threatening events (such as anaphylaxis) were reported rarely.

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Evidence Summary

Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Approximately 56 percent of individuals with asthma also have environmental allergies.[1] Allergic asthma and non-allergic asthma generally have the same symptoms; however, allergic asthma is triggered by inhaling airborne allergens (aeroallergens).

There are currently three treatment options for patients with allergic asthma: allergen avoidance, pharmacotherapy including biologics, and allergen immunotherapy (AIT). AIT consists of the repeated administration of one or multiple allergens to which the patient is sensitized. In subcutaneous immunotherapy (SCIT) a solution containing an allergen(s) is injected under the skin. Sublingual immunotherapy (SLIT), which may be dosed at home, consists of exposure to the allergen via an aqueous solution or tablet formulation placed under the tongue.

In 2007, the Expert Panel Report (EPR-3) from The National Heart, Lung, and Blood Institute (NHBLI)[2] included SCIT as a therapy to be considered in cases of mild to moderate persistent asthma. A working group was convened in 2015 to select the most relevant topics for systematic review to update the EPR-3. This systematic review focuses on one of those high priority topics: expanding the scope of a prior evidence report to assess the efficacy and safety of SCIT and SLIT, in aqueous and tablet forms, in people with allergic asthma.

Key Questions

Key Question 1. What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Question 2. What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Question 3. What is the evidence for the efficacy of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

Key Question 4. What is the evidence for the safety of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

Methods

The protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42016047749, and posted on the AHRQ Web site (http://www.effectivehealthcare.ahrq.gov/).

We rescreened all of the included studies from our prior 2013 evidence report.[3] We searched PubMed, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2005 through May 8, 2017.

As for all evidence reports, our draft report was peer reviewed and posted for public comment.

Results

We identified 31 randomized controlled trials (RCTs) (35 articles) that addressed the efficacy of SCIT (Key Question [KQ] 1), 26 RCTs (31 articles) and 18 non-RCTs that addressed the safety of SCIT (KQ2), 18 RCTs (20 articles) that addressed the efficacy of SLIT (KQ3), and 20 RCTs (23 articles) and 10 non-RCTs that addressed the safety of SLIT (KQ4). We provide details of studies identified per age group in Table A.

Table A. Number of studies included per Key Question, study design, age group, and setting

		KQ1 SCIT Efficacy	KQ2 SCIT Safety (RCT/Non-RCT)	KQ3 SLIT Efficacy	KQ4 SLIT Safety (RCT/Non RCT)	SCIT vs. SLIT	TOTAL
Study Design	RCTs	31	26	18	20	5	61
	Non-RCTs	0	18	0	10	1	29
Age Group	Adult	13	19 (12/7)	11	14 (9/5)	3	43
	Mixed Age	15	23(10/13)	4	9 (7/2)	1	34
	Children	3	6 (3/3)	3	7 (4/3)	2	12
Setting	Clinic	28	36 (24/12)	2	6 (4/2)	5	48
	Home	0	0	4	6 (4/2)	0	8
	Not Specified	3	8 (2/6)	12	13 (10/4)	0	23
	Both	0	0	0	5 (2/3)	1	5
	TOTAL	**31**	**44**	**18**	**30**	**6**	**90**

KQ = Key Question; RCT = randomized controlled trial; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Key Question 1. What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Points

- SCIT reduces the need for long-term control medication (moderate strength of evidence [SOE]).
- SCIT may improve asthma-specific quality of life, decrease use of quick-relief medications, decrease use of systemic corticosteroids, and improve FEV_1 (forced expiratory volume) (low SOE).
- There was insufficient evidence regarding the effect of SCIT on asthma symptom control and health care utilization.
- There was insufficient evidence about any differential effect of SCIT in pediatric patients.

Table B. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Asthma Symptoms: ACT	No RCTs	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Quality of Life: AQLQ	4 RCTs.[4-7] N=194	Medium	Consistent	Direct	Imprecise	Undetected	SCIT may improve asthma-quality of life	Low
Medication Use: Quick-relief medication	1 RCT [8] N=31	Low	Unknown	Direct	Imprecise	Undetected	SCIT may reduce the use of quick-relief medications	Low

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Medication Use: Long-term medication	6 RCTs [5, 6, 8-11] N=404	Medium	Consistent	Direct	Precise	Undetected	SCIT reduces the use of long-term control medications	Moderate
Medication Use: Systemic corticosteroids use	2 RCTs[11, 12] N=150	Low	Unknown	Direct	Imprecise	Undetected	SCIT may reduce the use of systemic corticosteroids	Low
Health care Utilization	2 RCTs [11, 13] N=161	Medium	Consistent	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology: FEV_1	6 RCTs[4, 5, 14-16] N=548	High	Consistent	Direct	Precise	Undetected	SCIT may improve pulmonary function when measured with FEV_1	Low

ACT = asthma control test; AQLQ = asthma quality of life questionnaire; FEV_1= forced expiratory volume; NA = not applicable; RCT = randomized controlled trial; SCIT = subcutaneous immunotherapy

Key Question 2. What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Points

- Local reactions to SCIT were frequent; however, reactions also commonly occurred with placebo injections (risk differences ranged from -0.317 to 0.4), and local reactions infrequently required a change in the SCIT dosing.
- Systemic allergic reactions to SCIT were reported frequently (risk differences ranged from 0 to 0.319). The majority of systemic allergic reactions were mild, and only a small number was consistent with anaphylaxis and required treatment with injectable epinephrine.
- There was insufficient evidence to draw conclusions regarding the effect of SCIT on anaphylaxis or death.
- Serious adverse events such as anaphylaxis and death were not reported in the included studies in the pediatric population (total of 462 patients in 4 RCTs).
- None of the studies reported providing patients SCIT in the home setting.

Table C. Summary of the strength of evidence for the safety of subcutaneous immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Anaphylaxis	5 RCTs[9, 15, 17-19] N=245 6 cases	Medium	Inconsistent	Indirect	Imprecise	Undetected	Unable to draw conclusions	Insufficient
	1 non-RCT[20] 1 case series[21] 1 case report[22] N=792 55 cases	Likely (Likelihood of causality)						
Death	No RCTs or non-RCTs						Unable to draw conclusions	Insufficient
	1 case report[23] 1 case series[24] N=145 1 case	Possible (Likelihood of causality)						

RCT = randomized controlled trial; SOE = strength of evidence

Key Question 3. What is the evidence for the efficacy of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

Key Points

- SLIT improves asthma symptoms, as measured by validated instruments (high SOE).
- SLIT improves disease-specific quality of life and decreases use of long-term control medications (specifically, ICS), and improves FEV_1 (moderate SOE).
- SLIT may decrease quick-relief medication use (short-acting bronchodilators) and may improve disease-specific quality of life (low SOE).
- There is insufficient evidence on the effect of SLIT on systemic corticosteroid use or health care utilization.
- There is insufficient evidence about the efficacy of SLIT in children.

Table D. Summary of the strength of evidence for the efficacy of sublingual immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Asthma Symptoms: ACT	4 RCTs [25-28] N=1193	Low	Consistent	Direct	Precise	Undetected	SLIT improves asthma symptoms	High
QOL: AQLQ	3 RCTs[25-27] N=1120	Low	Consistent	Direct	Precise	Undetected	SLIT may improve asthma QOL	Low

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Medication Use: Quick-relief medication	5 RCTs [28-32] N=298	Medium	Consistent	Direct	Imprecise	Undetected	SLIT may reduce the need of quick-relief medication	Low
Medication Use: Long-term control medication	4 RCTs[26, 27, 31, 33] N=1409	Medium	Consistent	Direct	Precise	Undetected	SLIT reduces the need for long-term control medication	Moderate
Medication Use: Systemic Corticosteroids use	1 RCT[31] N=110	Medium	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Health care Utilization	No RCTs	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology: FEV_1	10 RCTs[26-28, 30-37] N=1694	Medium	Consistent	Direct	Precise	Undetected	SLIT improves pulmonary function (FEV_1)	Moderate

FEV_1 = forced expiratory volume; QOL = quality of life; RCT = randomized controlled trial; SLIT = sublingual immunotherapy; SOE = strength of evidence

Key Question 4. What is the evidence for the safety of sublingual immunotherapy (SLIT) in the treatment of asthma?

Key Points

- Local reactions to SLIT were frequent (some reactions occurring in up to 80% of patients in RCTs); however, reactions also commonly occurred with placebo (risk differences ranged from -0.03 to 0.765).
- Systemic allergic reactions to SLIT were frequent (some reactions occurring in up to 22% of patients in RCTs), with only a few reports of anaphylaxis and no reports of deaths (risk differences ranged from -0.03 to 0.06).
- Although rates of anaphylaxis with SLIT compared to no treatment could not be determined (no cases reported in RCTs, insufficient evidence), three case reports suggest that rare cases may occur with SLIT treatment. Two of the three reports of anaphylaxis secondary to SLIT were in patients who received multiple-allergen therapy.
- No deaths secondary to SLIT therapy were reported (moderate SOE).

Table E. Summary of the strength of evidence for the safety of sublingual Immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusions	SOE
Anaphylaxis	6 RCTs[25, 26, 33, 38-40] N=1772 No cases No Non-RCTs	Medium	Inconsistent	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
	3 case reports[41-43]	2 Certain 1 Likely (Likelihood of causality)					Unable to draw conclusions	
Death	3 RCTs specifically reported no deaths[25, 27, 44] N=4231 Events 0	Medium (1 low, 1 medium, 1 high)	Consistent	Direct	Precise	Undetected	SLIT does not increase the risk of death	Moderate

RCT = randomized controlled trial; SLIT = sublingual immunotherapy; SOE = strength of evidence

Discussion

Our findings are consistent with our prior JHU EPC evidence report and other prior systematic reviews and support the efficacy of SCIT and SCIT for asthma in the allergic patient. The Cochrane review of SCIT concluded that it resulted in significant reduction in asthma symptoms and the need for asthma medications, as well as improvement in allergen-specific bronchial hyper-reactivity.[45] Our prior evidence report similarly concluded that there was high strength of evidence that SCIT reduces asthma symptoms and medication use.[3] Both of these reviews noted the significant heterogeneity between the studies, as we found. In contrast, we could not draw conclusions about the effect of SCIT on asthma symptoms, as we limited our review to studies that used validated tools to measure asthma symptoms and identified none. A 2015 Cochrane review found there was low-quality evidence supporting the use of SLIT in changing ICS use and very low quality evidence regarding bronchial provocation.[46] This Cochrane review further noted that the largely non-validated asthma symptom scores, medications scores, and available data for quality of life precluded meaningful synthesis of these outcomes. Our prior evidence report examined SLIT in aqueous form only, and concluded that SLIT reduced asthma symptoms.[3] This review expanded our scope to consider SLIT in tablet form and came to similar conclusions.

Future Research Needs

We were limited in our ability to synthesize results owing to lack of studies for specific populations, interventions, and outcomes; substantial heterogeneity; and limited reporting. We detail below specific areas for future research.

Population

- The overwhelming majority of studies that met inclusion criteria for this review included patients with mild to moderate asthma; there is a need to investigate the safety and efficacy of immunotherapy in patients with severe asthma.
- Not all studies provided information about asthma severity or control of study patients. Because severity and control are potentially important modifiers of treatment effect, studies are needed that clearly report the severity and control of enrolled patients.
- There were few studies conducted in children only, and few studies of all ages that reported outcomes for children separately. To inform asthma treatment guidelines, investigators should consider including only children 5 to 11 years of age in studies, or, if a broader age is studied, reporting separately findings on children 5 to 11 years of age and older.

Intervention and Comparison

- There is a specific need for studies investigating the efficacy and safety of multiple-allergen regimens for SCIT or SLIT. Multiple-allergen treatment is frequently used in the United States, but most of the studies include single-allergen regimens. There is increasing discussion in the scientific community about the clinical use and efficacy of single-allergen versus multiple-allergen therapy, and there is a lack of studies which compare these head-to-head.
- For both SCIT and SLIT, additional studies are needed to assess compliance/adherence, and the effect compliance may have on management.
- Immunotherapy dosing quantity, frequency, and formulation varied substantially and details were often lacking. Standardized methods and reporting of therapy would be helpful.
- Most studies we identified were of house dust mite allergen; additional studies of the efficacy of SCIT or SLIT treatment with other allergens would be useful.

Outcomes

- For both SCIT and SLIT, studies are needed that address health care utilization.
- Many studies used nonvalidated scoring of outcomes. For instance, we found no trials of SCIT that assessed asthma symptoms using a validated tool. Future studies would benefit from standardized methods and validated instruments to report outcomes such as asthma symptoms and adverse events.

Conclusion

SCIT reduces the need for long-term control medication and may improve asthma-specific quality of life, use of quick-relief medications, systemic corticosteroids use, and FEV_1. SLIT improves asthma symptoms, reduces long-term control medication use, improves disease-specific quality of life, and may reduce the need for quick-relief medication and improve FEV_1. Local and systemic allergic reactions to SCIT and SLIT are common but infrequently required changes in treatment. Life-threatening events (such as anaphylaxis) are reported rarely. There is insufficient evidence on the comparative effectiveness of SCIT versus SLIT or for differential effects by patient age, type of allergen, or setting.

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Introduction

Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.[1] In the United States, the current prevalence of asthma has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24.0 million Americans in 2014.[2, 3] Asthma can significantly impact patients' and families' quality of life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th based on the burden of disease, as measured by disability adjusted life years.[4]

Asthma affects people of all ages, but it most often starts during childhood. Approximately 56 percent of individuals with asthma also have environmental allergies.[5] Allergic asthma and non-allergic asthma generally have the same symptoms; however, allergic asthma is triggered by inhaling airborne allergens (aeroallergens). An allergen is a typically harmless substance such as house dust mite (HDM), pet dander, pollen, or mold. Allergens trigger an IgE-mediated hypersensitivity reaction that eventually results in airway inflammation and swelling. In the United States, 78 percent of asthmatic children and 75 percent of middle-aged adult asthmatics are allergic to one or more inhalant allergens, as evidenced by allergy skin testing.[5]

There are currently three treatment options for patients with allergic asthma: allergen avoidance, pharmacotherapy including biologics, and allergen immunotherapy (AIT). AIT consists of the repeated administration of one or multiple allergens to which the patient is sensitized. It offers the advantage of modulating the immune system, reducing IgE-mediated hypersensitivity, and therefore could have long-lasting effects on the control of allergic asthma.

In subcutaneous immunotherapy (SCIT) a solution containing an allergen(s) is injected under the skin. At the beginning of a course of SCIT, the allergen solution is very dilute; during the course of treatment, the allergen solution is more concentrated, increasing the dose of allergen over time. This "build-up phase" generally takes about 3 to 6 months to complete. When the individual reaches a predetermined therapeutic effective dose or "maintenance dose," the frequency of injections is reduced to every 2 to 4 weeks; the dose generally remains the same with each injection during this "maintenance phase." The duration of the build-up phase of SCIT is sometimes shortened by providing injections more frequently in order to reach maintenance more rapidly; this is referred to as "accelerated schedule." With cluster immunotherapy, two or more injections are provided at every visit, usually one to two times per week, allowing maintenance doses to be reached in as little as 4 weeks. Rush and ultra-rush schedules are more rapid than cluster immunotherapy, and maintenance can be reached in a few days. Accelerated schedules may carry a higher risk of systemic allergic reactions. Although the optimal duration of SCIT is not well defined, most patients are treated for a duration of 3 to 5 years.[6] Expert recommendations indicate that patients should receive SCIT injections under the supervision of their provider in a facility with the appropriate equipment, medications, and personnel to treat anaphylaxis, and be monitored for systemic reactions for 30 minutes.[7]

Other routes of administration for AIT have been assessed, including sublingual immunotherapy (SLIT), which may be dosed at home and consists of exposure to the allergen via an aqueous solution or tablet formulation placed under the tongue. The rationale for this route of therapy is based on its perceived improved safety margin (reduced risk of anaphylaxis), simple and convenient oral dosing regimen (avoiding the discomfort of injections and the inconvenience of office visits required for allergy shots). Currently, in the United States, there are two forms of SLIT: tablet and "off-label" aqueous

solution (which involves the use of those allergens approved for SLIT in an "off-label" form of administration, as there are no aqueous products specifically approved by the FDA for sublingual use). Typical regimens for SLIT include daily home administration, with dosing regimens such as year-round or pre/co-seasonal for several years. The tablets approved for use in the United States do not involve escalation; for aqueous formulations, there have been papers describing both the use of escalation and no escalation. However, owing to the at-home dosing of SLIT, it can be difficult for providers to determine compliance with the treatment.

The 2011 Practice Parameters by the Joint Task Force (comprised of members from the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council on Allergy, Asthma and Immunology) concluded that certain patients with allergic asthma might benefit from SCIT after failure of standard of care.[7] A 2010 Cochrane review concluded, based on moderate quality evidence, that SCIT produced a significant reduction in asthma symptoms and medication in patients with allergic asthma and an improvement in nonspecific bronchial hyperreactivity, as measured by response to methacholine or acetylcholine challenge tests.[8] A 2015 Cochrane review found there was low quality evidence that SLIT reduces inhaled corticosteroid use and very low quality evidence regarding bronchial provocation in patients that included those with asthma with rhinitis and other associated conditions.[9] In 2013, the Johns Hopkins University Evidence-based Practice Center (JHU EPC) completed a review of AIT for the treatment of allergic rhinoconjunctivitis and/or asthma.[10] The evidence report found high strength of evidence (SOE) that SCIT reduces asthma symptoms and medication use and that SLIT in the aqueous form reduces asthma symptoms.

Current asthma guidelines recommend assessment of asthma control and severity, in order to guide treatment. These assessments include factors such as symptom frequency, use of medications, acute care visits, and other indicators of asthma health. In 2007, the Expert Panel Report (EPR-3) from The National Heart, Lung, and Blood Institute (NHBLI)[1] included SCIT as a therapy to be considered in cases of mild to moderate persistent asthma. In 2015, a working group was convened to select the most relevant topics for systematic review to update the EPR-3. This systematic review focuses on one of those high priority topics: expanding the scope of the prior evidence report to assess the efficacy and safety of SCIT and SLIT, in aqueous and tablet forms, in people with allergic asthma.

Key Questions

Key Question 1. What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

a. Does this vary among subpopulations of interest?
b. Does this vary by setting?
    i. Clinic
    ii. Home

Key Question 2. What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

a. Does this vary among subpopulations of interest?
b. Does this vary by setting?
    i. Clinic
    ii. Home

Key Question 3. What is the evidence for the efficacy of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

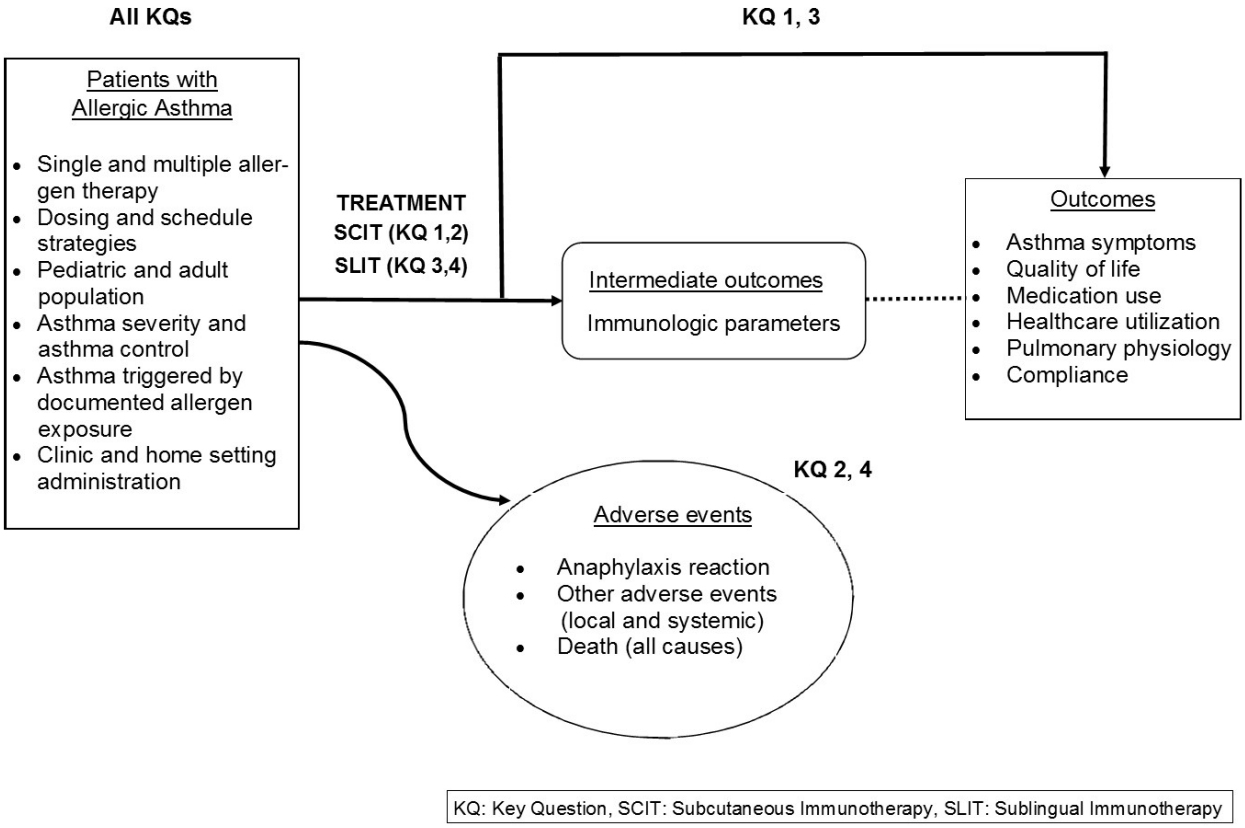
a. Does this vary among subpopulations of interest?
b. Does this vary by setting?
    i. Clinic
    ii. Home

Key Question 4. What is the evidence for the safety of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

a. Does this vary among subpopulations of interest?
b. Does this vary by setting?
    i. Clinic
    ii. Home

Figure 1 depicts the Key Questions (KQs). It illustrates how immunotherapy administered to patients with allergic asthma may affect intermediate outcomes, such as changes in immunologic parameters and/or outcomes such as symptoms, quality of life, and medication use. In addition, adverse events may occur at any point after treatment is received.

Figure 1. Analytic framework



Methods

Protocol

We recruited a Technical Expert Panel that provided input during the development of the protocol. Protocol development was conducted with guidance from our Task Order Officer (TOO) and from representatives from both the Agency for Health Care Research and Quality (AHRQ) and the National Heart, Lung, and Blood Institute (NHLBI).

The protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42016047749, and posted on the AHRQ Web site (http://www.effectivehealthcare.ahrq.gov/).

Search Strategy

We searched PubMed, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2005 through May 8, 2017 (see Appendix B for detailed search strategy). We requested Scientific Information Packages (SIPs) from industry representatives, but no information was provided. We also hand searched prior reviews and guidelines,[7, 8, 11, 12] searched ClinicalTrials.gov, and reviewed the FDA Adverse Event Reporting System (FAERS).

We uploaded the search results into DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based service for systematic review and data management. We used this database to track the search results at the levels of abstract and full-text screening and for data abstraction.

Study Selection

We followed the PICOTS (Table 1) framework in developing the criteria for inclusion of studies. We included studies of patients of any age with diagnosis of allergic asthma. We included studies of patients with asthma and studies of asthma and other allergic conditions (when outcomes were reported separately for the subgroup with asthma). Studies had to report on the outcomes pre-specified on our PICOTS and had to have an intervention arm receiving either SCIT or SLIT (tablet or aqueous). We excluded studies on food allergies or aeroallergens not related to asthma or if the type of allergen was not specified. Study inclusion was not restricted by language of publication or treatment duration. We included only randomized controlled trials (RCTs) for the Key Questions on efficacy (KQs 1 and 3). We included RCTs, observational studies, case series, and case reports for the Key Questions on safety (KQs 2 and 4), to be as inclusive as possible of any safety concerns. We also re-evaluated all of the included studies in the 2013 systematic review[10] to confirm eligibility for this review.

Abstracts and full-text articles were screened independently by two reviewers. Any disagreements regarding inclusion were resolved through discussion, and unresolved conflicts were adjudicated during team meetings.

For studies published in a foreign language with an English abstract, we assessed the abstract against all inclusion/exclusion criteria. If the study fit inclusion criteria, we translated the publication when possible.

Table 1. PICOTS (Populations, Interventions, Comparisons, Outcomes, Timing, and Setting) criteria for including studies in the review

PICOTS	Criteria

Populations	• Patients of any age with allergic asthma
	• Patients with diagnosis of asthma and positive allergy testing based on allergen specific Immunoglobulin E (IgE) sensitization diagnosis: Serologic multi-allergen screen IgE tests (skin prick tests, serum tests, or both)
	• Patients with all severity grades and control status of asthma (based on the EPR-3 classification)
	• Subgroups
	  o Single-allergen vs. multiple-allergen
	  o Pediatric (younger than 12 years of age) and adult population (12 years of age and older)

Interventions	• Subcutaneous Immunotherapy • Sublingual Immunotherapy (tablet or aqueous)
Comparators	Immunotherapy vs. • Placebo • Pharmacotherapy (usual care) • Immunotherapy

Outcomes	**Outcomes for Key Questions 1 and 3**
	• Asthma symptoms/outcomes
	  o Asthma control composite scores
	  ▪ Asthma Control Test (ACT)
	  ▪ Asthma Control Questionnaire (ACQ)
	  ▪ Pediatric Asthma Control Test (P-ACT)
	• Quality of life
	  o Asthma-specific quality of life: Asthma Quality of Life Questionnaire (AQLQ)
	  o Pediatric Asthma-specific quality of life: Asthma Quality of Life Questionnaire (PAQLQ)
	  o School/Work absences
	• Medication use
	  o Asthma-specific medication use (name, dose, duration)
	  o Long-term control medication use
	  o Quick-relief medication use (short-acting bronchodilators)
	  o Systemic corticosteroids for asthma
	• Asthma exacerbations / Health care utilization
	  o Asthma-specific hospitalizations
	  o Asthma-specific Emergency Department (ED) visits (separate urgent care visits when they can be differentiated)
	  o Asthma-specific ICU admission/intubations
	  o Asthma-specific outpatient visits
	  o Resource use related to the intervention (personnel time and equipment)
	• Pulmonary physiology:
	  o Spirometry: peak expiratory flow (PEF), forced expiratory volume in one second(FEV_1), forced vital capacity (FVC), forced expiratory flow (FEF) as absolute, percent predicted, and important ratios (FEV_1/FVC) that reflect airway flow.
	• Airway hyperresponsiveness (AHR) (methacholine challenge, allergen challenge, and exercise challenge)
	• Compliance with immunotherapy
	<u>Intermediate outcomes (KQ1 and KQ3)</u>
	• Immunologic parameters
	  o Allergy skin testing
	  o Allergen-specific IgE
	  o Allergen-specific Immunoglobulin G4 (IgG4)
	Outcomes for Key Questions 2 and 4
	• Anaphylaxis reaction
	• Hypersensitivity reaction*
	• Other adverse effects of immunotherapy (local and systemic effects)
	• Death (all-cause, asthma related)

Timing	Studies with all lengths of followup duration considered

PICOTS	Criteria
Setting	Home or clinic

*Hypersensitivity refers to a mechanism, rather than a clinical description of a reaction or specific outcome. The majority of systemic (and some local) reactions fall under the umbrella of hypersensitivity reactions to the allergens. Hypersensitivity is thus not discussed as a separate outcome.

Risk of Bias Assessment

Two reviewers independently assessed each study's risk of bias using a tool specific to the study design. We resolved disagreements through discussion or adjudication by a third reviewer, as needed.

Randomized Controlled Trials

We assessed the risk of bias of RCTs using the Cochrane Collaboration's tool, according to the guidelines in Chapter 8 of the C*ochrane Handbook for Systematic Reviews of Interventions*.[13] The following domains were assessed for each RCT:

- Allocation sequence generation
- Allocation concealment
- Blinding of participants and investigators
- Blinding of outcome assessors
- Incomplete outcome data adequately addressed
- Selective outcome reporting
- Other potential threats to validity

Each criterion was reported as "Yes" (low risk of bias), "No" (high risk of bias), or "Unclear" (information is insufficient to assess). Overall risk of bias was graded as Low, Moderate, or High.

We did not re-assess each risk of bias domain for the RCTs from our prior review. However, we re-assessed the overall risk of bias for each study, to be consistent with the methodology of this review.

Observational Studies

We used the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool to assess the methodological quality of non-randomized studies included.[14] (See Appendix C for abstraction and instruction forms.) We evaluated:

- Selection bias: sequence generation and allocation concealment
- Detection bias: masking of participants, study investigators, outcome assessors
- Attrition bias: incomplete outcome data
- Reporting bias: selective outcome reporting
- Other sources of bias

Each criterion was reported as Low, Moderate, Serious, Critical, or No-info. Overall risk of bias was graded as Low, Medium, or High, following the guidance in ROBINS-I.

Case Reports and Case Series

We used the World Health Organization (WHO) criteria to judge the likelihood that the intervention was causally related (dose- and time-related) to the observed serious adverse event.[15] Following this guidance, we reported causality as Certain/Probable, Likely/Possible, Unlikely/Conditional, Unclassified/Unassessable, or Unclassifiable.

Data Synthesis

We completed a qualitative synthesis for all questions. We considered meta-analyses but determined that the studies were not sufficiently homogenous to analyze together, with variability in patient characteristics, allergen and dose used, study duration and outcome definitions.

To select studies for our preplanned subgroup analysis based on age, we classified studies as pediatric (under 12 years of age) or adult (12 years of age or older). Studies that did not provide separate results for each population were classified as mixed-age population. (In some of these studies, the population age clearly included both categories and ages crossed the 12-year-old cutoff. In other studies, authors did not provide enough data, or authors provided only means or medians without standard deviations.)

To select studies for our preplanned subgroup analysis based on allergen, we classified studies as single- and multiple-allergen and, within the single-allergen group, we grouped studies based on specific allergens (e.g., HDM, grasses, weeds, molds, animals).

We did not prepare any funnel plots to assess reporting bias, owing to our inability, as a result of high heterogeneity, to pool more than 10 studies for any outcome analyzed.

Strength of the Body of Evidence

We graded the strength of evidence on the most critical outcomes, as specified in the protocol: asthma control composite scores, health care utilization (asthma-specific hospitalizations, asthma-specific emergency department (ED) visits, asthma-specific intensive care unit (ICU) admissions/intubations and asthma-specific outpatient visits), asthma-specific detailed medication use (quick-relief medications, long-term control medications, systemic corticosteroids), spirometry (FEV_1 percent predicted), quality of life, anaphylaxis, and death. We used the grading scheme recommended in the EPC Methods Guide.[16,17] We considered all domains when grading the strength of evidence for an outcome: study limitations (called risk of bias in this review), directness, consistency, precision, and reporting bias.[16] We classified the SOE for each critical outcome into four category grades: high, moderate, low, and insufficient. We graded RCT and non-RCT evidence; we did not grade case reports/case series.

Applicability

We considered elements of the PICOTS framework when evaluating the applicability of evidence to answer our Key Questions, as recommended in the Methods Guide.[16] We considered important patient characteristics, differences in severity of asthma and types of allergens, and intervention characteristics that may cause heterogeneity of treatment effects and limit applicability of the findings. We also considered the use of validated tools and heterogeneity of outcomes definitions.

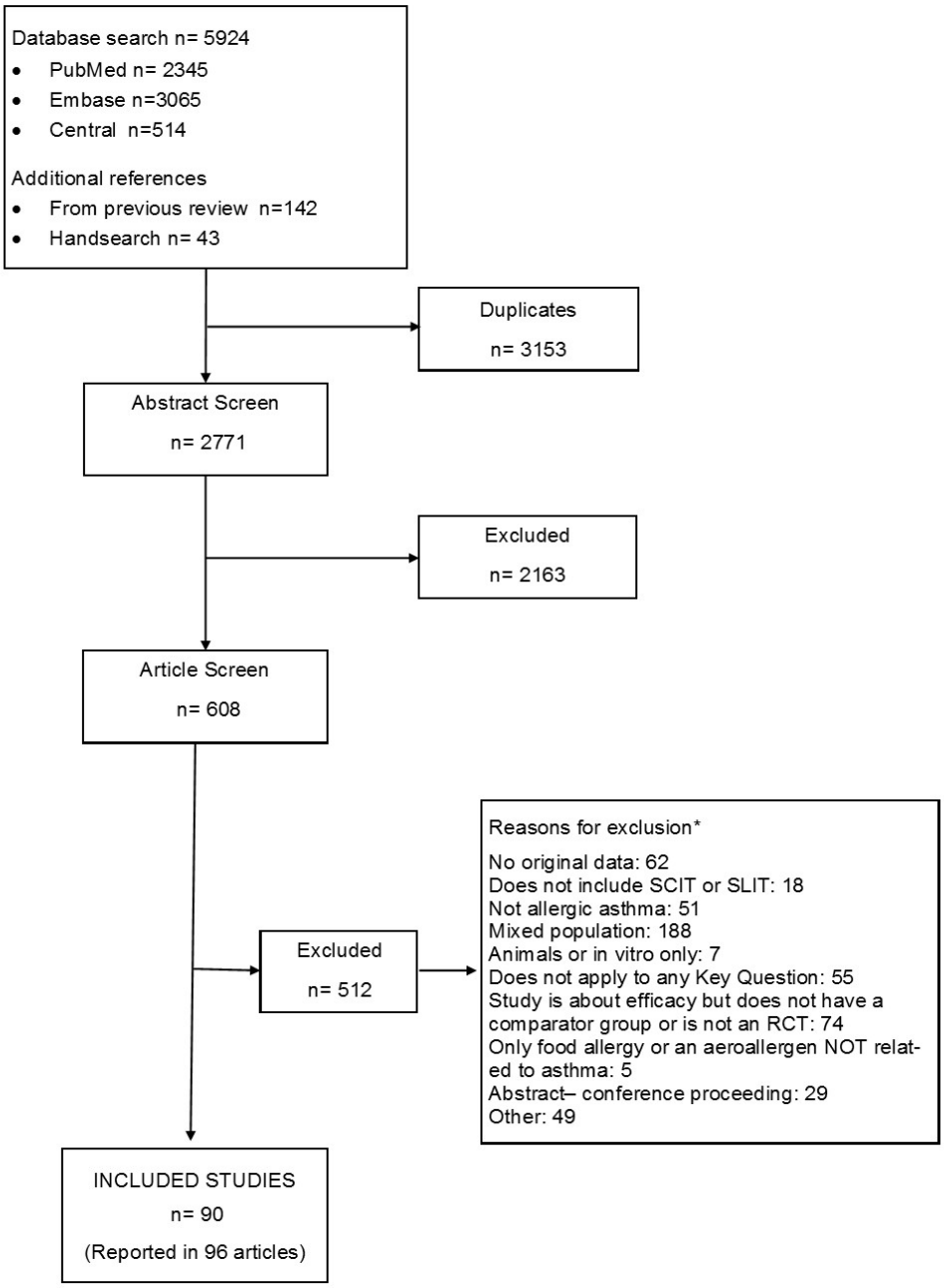
Results

Results of the Literature Search

The search identified 2,771 citations, and we included 142 articles from the previous review. We excluded 2,163 articles during abstract screening. During article screening, we excluded an additional 512 articles (see Appendix C, List of excluded articles) that did not meet one or more of the inclusion criteria. We included 61 RCTs (reported in 68 articles) and 29 non-RCTs. (See Figure 2 for a diagram of our results.)

Appendix C lists the studies we excluded at the full-text review stage. We excluded all studies we identified from ClinicalTrials.gov (n=105), of which 12 were ongoing, because none of them were specific to asthma.

Figure 2. Search flow diagram



*Total may exceed number in corresponding box, as articles could be excluded for more than one reason. Not in English
Other reasons for exclusion: No outcomes of interest, Type of allergen or immunotherapy not specified, pooled data, data not abstractable.

Overall Study Characteristics

We identified 31 RCTs (35 articles) that addressed the efficacy of SCIT (KQ1), 26 RCTs (31 articles) and 18 non-RCTs that addressed the safety of SCIT (KQ2), 18 RCTs (20 articles) that addressed the efficacy of SLIT (KQ3), and 20 RCTs (23 articles) and 10 non-RCTs that addressed the safety of SLIT (KQ4). We included 43 studies of adults (12 years of age and older) only, 34 studies with mixed-age population (studies that included adults and children and studies that did not provide separate results for each population), and 12 studies that included only children (younger than 12 years of age). We provide details of studies identified per age group on Table 2.

Thirty-six studies compared immunotherapy versus placebo, 12 studies compared immunotherapy versus pharmacotherapy, 11 studies compared immunotherapy versus immunotherapy (one compared 3 vs. 5 years of treatment[18] and one compared children vs. adults[19]), one study compared SCIT versus a desensitization vaccine (the control group received standardized glucocorticoid management and a desensitization vaccine, details not provided), 24 studies did not have a comparator and 6 studies compared SCIT versus SLIT.

Table 2. Number of studies included per Key Question, study design, age group, and setting

		KQ1 SCIT Efficacy	KQ2 SCIT Safety (RCT/Non-RCT)	KQ3 SLIT Efficacy	KQ4 SLIT Safety (RCT/Non RCT)	SCIT vs. SLIT	TOTAL
Study Design	RCTs	31	26	18	20	5	61
	Non-RCTs	0	18	0	10	1	29
Age Group	Adult	13	19 (12/7)	11	14 (9/5)	3	43
	Mixed	15	23(10/13)	4	9 (7/2)	1	34
	Children	3	6 (3/3)	3	7 (4/3)	2	12
Setting	Clinic	28	36 (24/12)	2	6 (4/2)	5	48
	Home	0	0	4	6 (4/2)	0	8
	Not Specified	3	8 (2/6)	12	13 (10/4)	0	23
	Both	0	0	0	5 (2/3)	1	5
	TOTAL	**31**	**44**	**18**	**30**	**6**	**90**

All RCTs required patients to have positive allergy skin testing (via SPT) and/or in vitro specific IgE testing; however, criteria varied widely within studies (wheal diameter within 3 and 7 mm and IgE values varied in values and units) and some studies did not describe criteria for what was considered a positive test. Allergy diagnosis criteria was not reported in eight of the non-RCTs included for safety on SCIT.[20-26]

No consistent criteria were applied among the studies we included to establish asthma diagnosis (the criteria were not described in 37 studies; the Global Initiative for Asthma (GINA) criteria were used in 30 studies; and the remaining studies used clinical criteria, pulmonary function testing, or other definitions). We found no consistency in how asthma severity or level of asthma control was defined among studies. Asthma severity at baseline was not specified in 37 studies; 24 studies included patients with mild to moderate asthma (defined as mild and moderate or mild to moderate); and the remainder of studies included patients with mild asthma, moderate, or moderate to severe asthma. One study included all severities,[27] and one study specifically excluded patients with severe asthma.[28] Asthma control status was not specified in 56 studies, control status in the remainder of studies varied from grade of control (poorly controlled or controlled) to type of control (need and type of medications).

Patients were monosensitized in 44 studies (23 on SCIT, 17 on SLIT, and 4 on SLIT vs. SCIT) and polysensitized in 14 studies (8 on SCIT, 5 on SLIT and 1 on SLIT vs. SCIT). Eleven studies (5 on SCIT

and 6 on SLIT) included both monosensitized and polysensitized patients, eight studies (7 on SCIT and 1 on SLIT) did not report the results of the allergy diagnosis and/or allergen identified, and 13 studies (9 on SCIT, 3 on SLIT, and 1 on SLIT vs. SCIT) did not clearly report sensitization status (patients were specifically sensitive to one allergen but authors did not specify sensitization status to other allergens). (See definitions in Appendix B.)

Patients received single-allergen immunotherapy in 69 studies (55 RCTs and 14 non-RCTS) and multiple-allergen immunotherapy in 14 studies (3 RCTs and 11 non-RCTs).

House dust mite (HDM) was the most common allergen used, with 49 HDM studies (D Pter, D far, D Pter-D far combined, or unspecified HDM). All the other allergens were used much less frequently; 14 studies used multiple allergens, 11 used grass, five used trees (4 birch and 1 cypress), two used mold (*Alternaria* and *Cladosporium*), three used animal allergens (2 cat and 1 dog) and one used ragweed.

Details of study and patient characteristics are provided in Tables 1 and 2 and Appendices E, F, G, and H.

Key Question 1. What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Points

- SCIT reduces the need for long-term control medication (moderate SOE).
- SCIT may improve asthma-specific quality of life, decrease use of quick-relief medications, decrease use of systemic corticosteroids, and improve FEV_1 (low SOE).
- There was insufficient evidence regarding the effect of SCIT on asthma symptom control and health care utilization.
- There was insufficient evidence about any differential effect of SCIT in pediatric patients.

Overall Study Characteristics

We identified 31 RCTs (35 articles) that addressed the efficacy of SCIT. Thirteen RCTs (15 articles) included only adults, 15 RCTs (17 articles) included a mixed-age population, and 3 studies included only children. Eighteen studies compared SCIT versus placebo, nine studies compared SCIT versus pharmacotherapy, three studies compared SCIT versus SCIT (one compared 3 versus 5 years of treatment), and one study compared SCIT versus a desensitization vaccine (standardized glucocorticoid management and a desensitization vaccine, details not provided).

Patients were monosensitized in 17 studies and polysensitized in five studies.[28-32] Two studies included both polysensitized and monosensitized patients,[18, 33] and seven studies did not clearly report sensitization status.[27, 34-39] Patients received single-allergen immunotherapy in 28 studies and multiple-allergen immunotherapy in two studies.[29, 32] One study used both single- and multiple-allergen immunotherapy.[28]

HDM was the most common allergen used (20 studies). All the other allergens were used much less frequently: three studies used multiple allergens, two used cat, two grass, two mold (*Alternaria* and *Cladosporium*), one ragweed, and one dog.

We provided details about the studies, patient characteristics, and interventions in Appendix D and components in the assessment of risk of bias in Appendix I.

Asthma Symptoms

No studies reported on asthma symptom control using Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), or Pediatric-Asthma Control Test (P-ACT) scores.

Quality of Life

Four studies, three with HDM allergen and one with *Alternaria* allergen, with a total of 194 patients, examined the impact of SCIT on disease-specific quality of life using the Asthma Quality of Life Questionnaire (AQLQ).[40-43] Two studies included only adults, and two studies included mixed ages. We assessed three studies as having moderate risk of bias and one study as high risk of bias (based on lack of allocation concealment and blinding).

Two studies showed statistically significant differences in quality of life compared to control [42, 43] while two showed differences that were not significant.[40, 41] The two studies with significant improvement in quality of life included only adults with mild and moderate persistent asthma, treated with HDM allergen for 54 and 55 weeks.[42, 43] The differences in overall AQLQ from these two studies were approximately 4 points (P=0.043) and 6 points (P=0.0025), respectively. The studies that did not show statistically significant improvements in AQLQ were in mixed-age populations with mild or moderate persistent asthma, treated with either *Alternaria* allergen for 12 months or HDM allergen for 8 months.[40, 41]

Overall, SCIT may improve quality of life as measured by the AQLQ (low SOE, with consistent but imprecise results and medium risk of bias). See Table 3. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy for details.

No studies reported asthma-specific quality of life using the Pediatric Asthma-Specific Quality of Life Questionnaire (PAQLQ) or school or work absences.

Medication Use

We identified seven studies that reported on medication use.[32, 39, 41, 42, 44-47]

Quick-relief medications. One study of adults receiving HDM SCIT reported a decrease in the use of quick-relief medication [short-acting beta agonists (SABAs)]. The study reported a statistically significant reduction in medication use among those receiving SCIT (decrease from 27 to 14 puffs/week, P<0.05), and a non-significant reduction in the control group (decrease from 52 to 46 puffs/week, P NS).[44] There was a substantial change, but the duration of treatment was not clear from the study report. Overall, SOE was low for the effect of SCIT on quick-relief medication use, based on one small study (n=31) with low risk of bias. See Table 3. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy for details.

Long-term control medications. We identified six studies that reported changes in the use of long-term control medications, including two in adult populations,[42, 44] three in mixed-age populations,[39, 41, 45] and one in children.[32] All of these studies reported use of inhaled corticosteroids (ICS), though the metrics varied (e.g., dose in micrograms, rates of discontinuation, or number of weeks free of use). The approach to adjustment of ICS varied across studies and did not appear to follow strict protocols for dosage adjustment. One of these studies also compared a variety of regimens including leukotriene receptor antagonists (LTRA) and long-acting beta agonists (LABA), in addition to the use of ICS.[41] Overall risk of bias was low in two studies, moderate in two, and high in one, the latter with issues of allocation concealment and blinding. The six studies included 404 patients. Five of the studies used HDM allergen, and the sixth (the pediatric study) used multiple allergens.[32] Treatment ranged from 8 months to 54 weeks.

One study of adults with mild to moderate persistent asthma showed a statistically significant increase in weeks free from inhaled corticosteroids use in the SCIT group when compared to placebo (P<0.001).[42] Similarly, in another study that compared SCIT alone and SCIT with co-administration of

Vitamin D, the SCIT groups (analyzed together) had a higher rate of ICS discontinuation compared to the control group (28 versus 0 %, *P*=0.002).[39] One study reported a significant reduction in ICS dose in the SCIT group during the study (38%, *P* <0.05) and a non-significant change in the control group,[44] while another showed a significantly greater reduction in ICS dose in SCIT versus control after 3 years of treatment (*P*=0.027).[45] In the latter study, the control group received treatment with a desensitization vaccine (standardized glucocorticoid management and a desensitization vaccine, details not provided). Finally, in the study that assessed use of multiple long-term control regimens (including ICS, LTRA, and LABA) there was a significant reduction in need for any long-term control medication in the SCIT group (decrease from 17 to 8 of 21) [*P*<0.046), but not in the control group (increase from 11 to 13 of 20] (*P*=0.158).[41] The study that used multiple allergens in children found a statistically significant decrease in the number of days of ICS use in the SCIT arm but not in the placebo arm. However, there was no significant difference in the use of ICS between arms.[32]

Overall there was moderate strength of evidence that SCIT reduces use of long-term control medications, based on consistent and precise evidence, with medium risk of bias. See Table 3. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy for details.

Systemic corticosteroids. Two studies of SCIT, including 150 patients, reported change in systemic corticosteroid use.[32, 46] The studies included a mixed-age population treated with HDM allergen for 3 years and a pediatrics study of treatment with multiple allergens for 27 months. Asthma severity was not reported in either study. In the mixed-age study, there was a significantly greater reduction in annual days of systemic corticosteroid use in the SCIT group (decrease from 22 to 1 day per year) compared to the controls (decrease from 25 to 12 days per year), (SCIT versus control, *P*<0.01).[46] In the pediatric study, there was no significant difference in systemic corticosteroid use in SCIT versus control (-1.9 vs. -1.7 days in past 60 days, *P*=0.49)[32] Overall there was low SOE that SCIT reduces use of systemic corticosteroids given the inconsistent results in the two studies. See Table 3. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy for details.

Asthma Exacerbations

Two studies of SCIT reported asthma exacerbations.[31, 46] The studies, enrolling 95 patients, treated mixed-age populations with HDM allergen for either 2 or 3 years. One study included patients with well-controlled asthma[31] and, in the other study, asthma severity and control status were not reported.[46] In the study that treated for 3 years there was a statistically significantly greater reduction in risk of asthma exacerbations in the SCIT group (decrease from 8+/-1.8 to 1+/-0.5 per year) compared with controls (decrease from 8.5 +/- 1.7 to 4.25 +/- 0.25 per year) (SCIT vs. control, *P* <0.01).[46] In the other study, exacerbation rates were low for each group (two in the SCIT group and one in the control), but there were no reported comparisons between groups.[31]

Health Care Utilization

Two RCTs in children reported on health care utilization.[32, 48] One RCT evaluated HDM SCIT compared with pharmacotherapy alone for 6 months in 40 children and found that patients in the SCIT arm had a significantly higher number of clinic visits in 6 months compared with controls, but the number of emergency room visits and hospitalizations were not significantly different between arms.[48] The authors do not provide an explanation for the significant increase in clinic visits in the SCIT arm. The second RCT enrolled 121 children and compared multiple-allergen SCIT versus placebo for 30 months.[32] This RCT reported no difference in the number of office visits, ED visits, or hospitalizations between baseline and final followup for either arm, and there were no differences between groups for any outcome. Two small RCTs with medium risk of bias found the following: inconsistent and

imprecise results for clinic visits, and consistent but imprecise findings that there was no significant change in hospitalizations or ED visits. Overall, the strength of evidence was insufficient. See Table 3. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy for details.

Pulmonary Physiology

PEF. Ten studies of SCIT, including 704 patients, reported peak expiratory flow rate (PEF) as an outcome.[31, 32, 34, 40, 45, 48-52] Most of these studies enrolled mixed-age populations, two enrolled adults only,[34, 52] and two enrolled children only.[32, 48] Most of these studies (6 of 10) employed HDM allergen. Two studies were of mold allergens (*Cladosporium* and *Alternaria*), one was of ragweed allergen, and one was of mixed allergens. Peak flow values were reported in the studies as a mean daily, morning, and/or evening value. Treatment ranged from 6 months to 2 years. Overall risk of bias was low in four studies, moderate in four, and high in one, the latter with issues of allocation concealment and blinding.

Seven of nine studies reported statistically significantly improved PEF with SCIT compared with controls.[31, 32, 34, 40, 45, 49, 52] In one study of HDM allergen,[50] there was a significant increase in PEF in the SCIT group during the study, but the change was not significantly different when compared with the change in the control group. This study enrolled patients with mild to moderate persistent asthma and treated for 1 year. In the study of *Cladosporium* allergen, there was not a significant difference in PEF between the SCIT and control groups.[51] This study enrolled patients with mild and moderate persistent asthma and treated for 10 months.

Both studies in adults showed significant improvement in PEF. In one study of HDM allergen in only adults,[34] morning PEF improved significantly in the SCIT group but not the controls. In this study, treatment was for 6 months and the asthma patients were controlled at baseline. In the other study of adults, ragweed allergen was used and there was a statistically significant difference in PEF between SCIT and control, when measured in the morning during the peak allergen season.[52]

Both studies in children showed increase in PEF. In the HDM study, PEF increased in the SCIT arm and decreased in the control arm, but the difference between arms was not statistically significant.[48] The other RCT used multiple-allergen SCIT versus placebo and noted a clinically small increase in PEF in the SCIT arm compared with placebo (95% CI -7.8 to 0.1, P= 0.05).[32]

FEV_1. There were six studies of SCIT, including 548 patients, that reported FEV_1 as an outcome,[28, 40, 41, 50, 53, 54] including one of the studies that also reported PEF as an outcome.[50] Four studies were of HDM allergen, one of *Alternaria*, and one of multiple allergens. In one study, there was a significantly greater increase in FEV_1 percent predicted in SCIT versus control (change from 82 to 99 percent predicted vs. 86 to 83 percent predicted, P <0.001).[54] In this study, patients were treated with 7 weeks of therapy with HDM allergen. Asthma severity and control at baseline were not reported. In another study, FEV_1 improved in the SCIT group (73 to 96 percent predicted, P=0.008), but the change was not compared with the change in the control group.[40] This study used *Alternaria* allergen in patients with mild and moderate persistent asthma for 12 months. In one of the pediatric studies, the authors reported the number of patients with improvement in the study groups, with a significantly greater number improved in SCIT compared with control (P=0.0001).[28]

In the study that also reported significantly improved PEF,[50] there was not a corresponding increase in FEV_1. Another study reported significant changes in FEV_1within the SCIT arm (P<0.001) but not for the placebo arm (P>0.05), without providing direct comparison between the groups.[53] Another simply reported that at 8 months all patients had FEV_1 > 80 percent predicted, but did not report changes from baseline.[41]

Overall, there was low SOE that SCIT improves FEV_1. The findings were consistent and precise, but risk of bias was high. See Table 3. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy for details.

FEV_1/FVC. No study of SCIT reported FEV_1/FVC as an outcome.

FVC. One study reported change in FVC.[50] This study randomized 132 patients with mild to moderate asthma and treated with HDM allergen for 1 year. There was no statistically significant increase in FVC in either the SCIT or placebo groups.

Airway Hyperresponsiveness (AHR)

Methacholine challenge. Seven studies reported methacholine challenges results, with two HDM studies in adults,[46, 49] two HDM studies in mixed-age populations,[31, 55] one *Alternaria* study in mixed-age populations,[40] one of cat allergen in adults,[35] and one of multiple allergens in children.[32] The studies included 388 patients. Overall, two studies showed improvement in AHR, while five did not.

The study of *Alternaria* did show significant improvement in AHR when compared to pharmacotherapy (P=0.03).[40] In this study, monosensitized patients with mild and moderate persistent asthma were treated for 12 months.

Of the four studies of HDM allergen, one showed significant improvement in AHR, while three did not show an improvement. In the study showing improvement in AHR, patients in the SCIT group had a significant increase in PD20 (dose of allergen required to cause a fall of 20% in FEV1) compared to control group, after 3 years of treatment. Disease severity was not reported.[46] In the three studies that did not show improvement, asthma status of enrollees was mild to moderate severity, well-controlled, and not specified, with treatment durations of 3 years and 2 years and 7 months, respectively.[31, 49, 55] Neither the study of cat allergen[35] or multiple allergens[32] showed improvement in AHR. (See Appendix D, Table D10 for details.)

Allergen challenge. There were 13 studies that reported results of allergen challenges, including eight with HDM; two with cat; and one each with dog, *Cladosporium*, and ragweed. Nine studies were done in adults (n=369),[34-36, 42-44, 52, 54, 55] and four included mixed-age populations (n=110).[27, 30, 37, 51]

Overall, most studies(9 of 13) showed statistically significant improvement in AHR with SCIT compared with the control group, and one study showed significant improvement in the SCIT group but not in the control group.[34] In three studies, there was not significant improvement in SCIT versus control.[27, 30, 35]

The eight studies of HDM allergen included six in adults and two in mixed-age populations.[27, 34, 37, 42-44, 54, 55] In three studies, asthma severity was not reported; two studies included patients with mild and moderate asthma; one study included all severities; one study included patients whose asthma was controlled, and one study included patients whose asthma was poorly controlled. In six of the studies, there was significant improvement in AHR compared with control; in one study the improvement was demonstrated in the SCIT group but not in the control group; and in one study there was no significant difference in AHR with control. Treatment durations ranged from 7 weeks to 2 years. The study that did not show improvement in AHR was of 7 months duration.

Of the two studies of cat allergen, one study showed improvement in AHR.[36] This study enrolled adults and asthma severity was not reported. Patients were monosensitized to cat allergen and were treated for at least 1 year. In the other study of cat allergen, there was not improvement in AHR.[35] In this study of adults with controlled asthma, patients who were monosensitized to cat allergen were treated for 16 weeks.

For the study of dog allergen challenge, there was not improvement in AHR.[30] This study enrolled mixed-age patients with monosensitization to dog allergen. Asthma severity was not reported and treatment was for 1 year.

The study of *Cladosporium* allergen showed significant improvement in AHR with allergen challenge after a duration of 10 months treatment.[51] This study enrolled mixed-age patients with mild to moderate asthma that was controlled.

In the study of ragweed allergen, adults with moderate to severe, uncontrolled asthma were enrolled.[52] Patients had to have had exacerbations of asthma during the fall season. Significant improvement in AHR was shown after 2 years of treatment. (See Appendix D, Table D10 for details.)

Exercise challenge. No SCIT studies reported exercise challenge outcomes.

Compliance

One study comparing multiple-allergen SCIT to placebo in 121 children reported that both arms had high levels of compliance (measured at each visit on the basis of prescribed doses and doses recorded in diaries) (92.6% vs. 93.6%) and there was no difference between arms.[32]

Immunological Outcomes

Allergen testing. Six RCTs reported allergen skin testing results before and after SCIT.[28, 29, 45, 47, 56, 57] Five studies exclusively looked at skin test reactivity to HDM,[29, 45, 47, 56, 57] and one study examined mixed reactivity to multiple allergens including HDM, mold, trees, animals, and grass.[28]

Only one study did not find any differences in SPT for HDM between SCIT and placebo over a 3 year period.[45] Five studies reported significant improvement in allergen skin reactivity after SCIT using different skin testing parameters,[28, 29, 47, 56, 57] one that used a cutaneous tolerance index reported improvement over a period of 15 weeks for HDM (95% CI 0.27; 0.11-0.56, $P<0.05$).[47] One study on HDM found statistically significant improvement in multiple intradermal skin testing parameters over 3 years, including immediate phase ($P=0.04$) and late phase skin reactions ($P=0.002$), and skin prick titration tests to determine the estimated allergen concentration that caused histamine equivalent skin reactions (HEP)($P=0.0001$).[29] Another study demonstrated improved histamine equivalent skin test reactions for HDM over 54 weeks ($P=0.029$).[56] The only study comparing SCIT with pharmacotherapy demonstrated significant improvement in HEP over 4 months.[57] Lastly, the study using multiple allergens reported general improvement in skin testing parameters for mixed allergens for 1 year in SCIT patients compared with placebo ($P=0.0001$).[28]

Overall risk of bias was low in one study and moderate in five. The six studies included 525 patients and five used HDM allergen. Treatment ranged from 1 to 3 years. The administration of SCIT was associated with improvement in allergen skin reactivity, mainly with HDM.

Immunoglobulin E. Eleven RCT studies reported IgE levels: eight examined HDM,[18, 29, 31, 39, 45, 47, 56, 58] one examined *Alternaria*,[40] and two looked at mixed allergens for HDM, mold, trees, animals, and grass.[28, 32] Six studies demonstrated significant reductions in IgE levels after SCIT.[28, 29, 31, 40, 45, 58] Four studies demonstrated statistically significant decreases in serum specific IgE levels for HDM from 1 to 3 years in the SCIT group compared to either placebo, desensitization vaccine (not specific desensitization method), ICS, or untreated patients.[29, 31, 45, 58] Three studies demonstrated significant reductions in specific IgE for *Alternaria* and mixed allergens, respectively, when SCIT was compared to pharmacotherapy.[28, 32, 40] Four studies showed no change in total IgE after treatment.[18, 39, 47, 56]

Immunoglobulin G4. Five SCIT RCTs reported serum IgG4 levels specific for HDM,[31, 37, 39, 47, 56] all of which demonstrated statistically significant reduction of IgG4 levels. All studies compared SCIT versus placebo: one study lasted 15 weeks, two studies for 1 year, and two studies for 2 years. One study compared SCIT to standard pharmacotherapy,[39] while another examined SCIT and ICS versus ICS alone.[31] One study reported a significant decrease in the HDM-specific IgE/IgG4 ratio in patients undergoing SCIT compared with placebo.[56]

Variation per Setting

Three studies did not specify setting.[40, 45, 53] All other studies (n=28) were done in the clinical setting and no study was conducted in the home setting. There are no data to draw conclusions on any variation per setting.

Variation per Population

Adults

Asthma Symptoms. No studies in adults reported on asthma symptom outcomes using ACT, ACQ, or P-ACT scores.

Quality of Life. Two studies in adults assessed quality of life with AQLQ. Both studies showed statistically significant improvement in quality of life with SCIT compared with control.[42, 43] These studies included adults with mild and moderate persistent asthma who were treated with HDM allergen for 54 and 55 weeks.[42, 43] The differences in overall AQLQ were approximately 4 points (P=0.043) and 6 points (P=0.0025), respectively. Both of these studies of adults were positive, and SOE was moderate with consistent and precise results and medium risk of bias.

Medication Use.

Quick-relief medications. One study of adults receiving HDM SCIT for 12 months reported decrease in quick-relief medication use (SABA).[44] This study included 31 patients with unspecified asthma severity or control at baseline. The study reported a statistical significant reduction in medication use among those receiving SCIT (decrease from 27 to 14 puffs/week, P<0.05) and a non-significant reduction in the control group (decrease from 52 to 46 puffs/week, P NS). There was a substantial change in the use of medications. Overall, SOE was low for the effect of SCIT on quick-relief medication use, based on one small study (n=31) (imprecise, unknown consistency) with low risk of bias.

Long-term control medications. Two studies in adults evaluated the effect of SCIT on the use of long-term control medications. One study of adults with mild asthma showed statistically significant reduction in long-term control medication use in the SCIT group when compared with placebo.[42] This study reported a greater number of weeks free from ICS use in SCIT compared with placebo (P<0.001). This was a study of 64 patients with mild or moderate persistent asthma, treated with HDM allergen. Another study of adults[44] reported a significant reduction in ICS dose in the SCIT group during the study (38%, P <0.05) and a non-significant change in the control group. This study enrolled 31 patients with unspecified baseline asthma severity and control. For the subgroup of adults, SCIT may reduce long-term medication use, based on consistent results from two small studies (imprecise) (low SOE).

Systemic corticosteroids. There were no studies of the effect of SCIT on systemic corticosteroids in adults.

Asthma Exacerbations. There were no studies of the effect of SCIT on asthma exacerbations in adults.

Health Care Utilization. There were no studies of the effect of SCIT on health care utilization in adults.

Pulmonary Physiology

PEF. Two studies in adults showed significant improvement in PEF. In one study of HDM allergen in 16 adults,[34] morning PEF improved significantly in the SCIT group but not the controls. In this study, treatment was for 6 months and the asthma patients were controlled at baseline. In the other study of adults, 90 patients were studied who had uncontrolled asthma at baseline. Ragweed allergen was used and there was a significant difference in PEF between SCIT and control, when measured in the morning during the peak allergen season.[52]

FEV_1. Only one study in adults assessed FEV_1 and it reported significant changes within the SCIT arm but not for placebo ($P<0.001$ vs $P>0.05$); it did not directly compare the groups.[53]

FEV_1/FVC. There were no studies of the effect of SCIT on FEV_1/FVC in adults.

FVC. There were no studies of the effect of SCIT on FVC in adults.

Airway Hyperresponsiveness. There were nine studies performed in adults that assessed the effect of SCIT on allergen challenge. Of these, six used HDM allergen, two cat, and one ragweed.[34, 35, 44, 52, 54, 55] Of these studies in adults, all showed improvement in AHR compared with control, except one that only showed improvement in the SCIT group but not in the control and one that showed no significant difference. Studies of SCIT in adults that examined AHR by specific allergen challenges had consistent and precise results supportive of improvement.

Compliance. There were no studies of the effect of SCIT on compliance in adults.

Children

Three studies, including 403 children, reported on the efficacy of SCIT for clinical outcomes in children 5 to 12 years of age with asthma. One study was completed in the United States,[32] and two were completed in Asia.[28, 48] Asthma diagnosis was per GINA criteria in two of the studies,[28, 48] and physician diagnosis in the third.[32] Two studies included children with moderate to severe persistent asthma,[32, 48] and one study excluded patients with severe uncontrolled asthma.[28] Allergy diagnosis was made by SPT and specific IgE elevation in all studies.[28, 32, 48] One study enrolled patients monosensitized to HDM and used HDM SCIT;[48] two studies included polysensitized patients, one of which used multi-allergen SCIT[32] and the other of which used both single and multiple allergens.[28] One study compared SCIT to placebo,[32] and the other two studies compared SCIT to pharmacotherapy.[28, 48]

Asthma Symptoms. There were no studies of the effect of SCIT on asthma symptom outcomes using ACT, ACQ, or P-ACT scores in children.

Quality of Life. There were no studies of the effect of SCIT on asthma quality of life using the AQLQ, PAQLQ, or school or work absences in children.

Medication Use. One RCT that compared multiple-allergen SCIT to placebo in 121 children reported the number of days of medication use in the previous 60 days, at baseline, and at final followup.[32] This study found a statistically significant decrease in the number of days of ICS use in the SCIT arm but not in the placebo arm. However, there was no significant difference in the use of ICS between arms. This study also reported that there was no significant difference within or between arms for the use of systemic steroids. There is insufficient evidence on the effect of SCIT on asthma-specific medication use in children.

Asthma Exacerbations. There were no studies of the effect of SCIT on asthma exacerbations in children.

Health Care Utilization. As noted above, two RCTs reported on health care utilization in children with allergic asthma.[32, 48] Overall, the strength of evidence is insufficient.

Pulmonary Physiology

***PEF*.** Two RCTs reported PEF in a total of 161 children.[32, 48] One RCT used HDM SCIT versus pharmacotherapy alone (asthma medications per GINA guidelines) and found that the PEF increased in the SCIT arm and decreased in the control arm; however, the change both within and between arms was not statistically significant.[48] The other RCT used multiple-allergen SCIT versus placebo and noted a clinically small increase in PEF in the SCIT arm compared with placebo (95% CI -7.8 to 0.1, P= 0.05).[32]

FEV_1. One RCT that used both single- and multiple-allergen SCIT versus pharmacotherapy alone (beclomethasone inhaler 200-300 µg daily and aminophylline 100mg tablet twice daily) reported FEV_1 in 242 children treated for 12 months and found that patients in the SCIT arm had significant improvement in their FEV_1 compared with the pharmacotherapy arm (P= 0.0001).[28] However, we were unable to draw conclusions due to insufficient evidence (unknown consistency, imprecise, medium risk of bias).

FEV_1/FVC. There were no studies of the effect of SCIT on FEV_1/FVC in children.

FVC. There were no studies of the effect of SCIT on FVC in children.

Airway Responsiveness. One study comparing multiple-allergen SCIT to placebo in 121 children reported methacholine challenge results.[32] Both arms had a significant decrease in bronchial sensitivity to methacholine but there was no difference between arms (mean difference -0.02 (95% CI -0.66 to 0.61) P >0.99).[32]

Compliance. One study comparing multiple-allergen SCIT to placebo in 121 children reported that both arms had high levels of compliance (92.6 versus 93.6 percent), but the difference between arms was not reported. Compliance was measured by pill counts and the weight of metered-dose-inhaler canisters at each visit.[32]

Table 3. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy

Outcome	n of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Asthma Symptoms: ACT	No RCTs	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Quality of Life: AQLQ	4 RCTs.[40-43] N=194	Medium	Consistent	Direct	Imprecise	Undetected	SCIT may improve asthma-quality of life	Low
Medication Use: Quick-relief medication	1 RCT [44] N=31	Low	Unknown	Direct	Imprecise	Undetected	SCIT may reduce the use of quick-relief medications	Low
Medication Use: Long-term medication	6 RCTs [32, 39, 41, 42, 44, 45] N=404	Medium	Consistent	Direct	Precise	Undetected	SCIT reduces the use of long-term control medications	Moderate
Medication Use: Systemic corticosteroids use	2 RCTs[32, 46] N=150	Low	Unknown	Direct	Imprecise	Undetected	SCIT may reduce the use of systemic corticosteroids	Low
Health care Utilization	2 RCTs [32, 48] N=161	Medium	Consistent	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology: FEV_1	6 RCTs[28, 40, 41, 50, 54] N=548	High	Consistent	Direct	Precise	Undetected	SCIT may improve pulmonary function when measured with FEV1	Low

FEV_1= Forced Expiratory Volume

Key Question 2. What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Points

- Local reactions to SCIT were frequent; however, reactions also commonly occurred with placebo injections (risk differences ranged from -0.317 to 0.4), and local reactions infrequently required a change in the SCIT dosing.
- Systemic allergic reactions to SCIT were reported frequently (risk differences ranged from 0 to 0.319). The majority of systemic allergic reactions were mild, and only a small number was consistent with anaphylaxis and required treatment with injectable epinephrine.
- There was insufficient evidence to draw conclusions regarding the effect of SCIT on anaphylaxis or death.
- Serious adverse events such as anaphylaxis and death were not reported in the included studies in the pediatric population (total of 462 patients in 4 RCTs).
- None of the studies reported providing patients SCIT in the home setting.

Overall Study Characteristics

Our search identified a total of 44 articles on 42 unique studies/populations reporting safety data on SCIT. Of the included studies, 26 were RCTs (28 articles), and 18 were either cohort, case-control, or case reports. Of all studies included (RCTs and non-RCTs), 19 included only adults, 21 included a mixed-age population, and 4 included children. The articles were published between 1984 and 2017, with 52 percent of studies originating from Europe, 21 percent from Asia, and 21 percent from the United States.

We provided details about the studies, patient characteristics, and interventions in Appendix E and components in the assessment of risk of bias in Appendix I.

Summary and Description of Characteristics in RCTs

Of the 26 RCTs (28 articles) (N=1,512), 12 studies enrolled only adults (defined as 12 years of age and older),[29, 34-36, 42, 43, 47, 52-56, 59, 60] 10 enrolled mixed-age populations,[30, 31, 37, 39, 41, 45, 51, 57, 61, 62] and four enrolled children only.[18, 28, 30, 32, 45, 48] SCIT was compared to placebo in 15 studies,[29, 30, 32, 34-37, 42, 43, 47, 51-54, 56, 57, 62] to pharmacotherapy in six studies,[28, 31, 39, 41, 48, 55] and to SCIT in a modified dose or duration in five studies.[18, 45, 59-61]

GINA criteria were used for asthma diagnosis in 10 studies (11 articles),[18, 28, 29, 31, 39, 43, 48, 51, 59-61] a positive bronchial response to methacholine was used in two studies,[52, 54] to histamine in one study,[34] to cat allergen in one study,[35] and to HDM allergen in one study.[55] The diagnosis was clinical or not specified in the remaining 11 studies.(12 articles)[30, 36, 37, 41, 42, 45, 47, 53, 56, 57, 62, 63]

Asthma was classified as mild or moderate persistent in 14 studies(16 articles),[18, 28, 29, 37, 39, 41-43, 45, 47, 51, 56, 57, 59-61] three studies included patients with severe persistent asthma,[48, 52, 62] and in nine studies the severity was not classified.[30-32, 34-36, 53-55] Asthma control status prior to initiation of SCIT was described in six studies: asthma was reported as controlled in four studies,[34, 35, 51, 61] and uncontrolled or poorly controlled in two studies.[37, 52]

Documentation of allergic sensitization was made through SPT and/or serum IgE in all studies.

Patients were monosensitized in 14 studies and polysensitized in five studies.[28-32] One study included both polysensitized and monosensitized patients,[18] and six studies did not clearly report sensitization status.[34-37, 39, 61] Patients received single-allergen immunotherapy in 23 studies and multiple-allergen immunotherapy in two studies,[28, 29, 32, 59] and both multiple- or single-allergen immunotherapy in one study.[28] The allergen provided included HDM in the majority (60%) of studies. Other allergens were grass, ragweed, cat, *Cladosporium* mold, and dog. In the three studies where multiple allergens were provided, the type of allergen was not specified. In 24 studies, SCIT was provided in the clinic setting; the location was not specified in two studies.[45, 53]

Adults

Of the 26 RCTs, 12 studies enrolled only adults.[29, 34-36, 42, 43, 47, 52-56, 59, 60] SCIT was compared to placebo in all studies except for two studies where it was compared to pharmacotherapy,[29,55] and one study where it was compared to a modified SCIT (a depigmented-glutaraldehyde polymerized extract).[60]

GINA criteria were used for asthma diagnosis in three studies,[29, 43, 59, 60] a positive bronchial response to methacholine was used in two studies,[52, 54] to histamine in one study,[34] to cat allergen in one study [35] and HDM allergen in one study.[55] The diagnosis was clinical or not specified in four studies.[36, 42, 47, 53, 56]

Asthma was classified as mild or moderate persistent in five studies,[29, 42, 43, 47, 56, 59, 60] one study included patients with severe asthma,[52] and in six studies the severity was not classified.[34-36, 53-55]Asthma control status prior to initiation of SCIT was described in three studies: asthma was reported as controlled in two studies[34, 35] and uncontrolled or poorly controlled in one study.[52]

Documentation of allergic sensitization was made through SPT and/or serum IgE in all studies. Patients were monosensitized to a single allergen in all except for one study where patients were polysensitized.[29, 59] In all studies except for one,[29, 59] a single allergen was provided in SCIT. The allergen provided included HDM in 50 percent of studies. Other allergens were grass, ragweed, and cat. In the studies where multiple allergens were provided, the type of allergen was not specified.

Children

Four RCTs reported on the safety of SCIT in 466 children with asthma. Studies included children with moderate and severe persistent asthma,[32, 48] mild and moderate persistent asthma,[18] and one specifically excluded those with uncontrolled asthma.[28] In two studies, patients had at least an allergy to HDM and HDM SCIT was used in the trial.[18, 48] Two studies included polysensitized patients and used multiple-allergen SCIT.[28, 32] Two studies compared SCIT to pharmacotherapy alone,[28, 48] one compared SCIT to placebo,[32] and one study compared 3 year to 5 year SCIT.[18]

Summary and Description of Characteristics in Non-RCTs

Of the 18 non-RCTs, seven studies included adults only (defined as 12 years of age and older)[20, 21, 23, 64-67] and 11 studies included mixed-age populations.[19, 22, 24-26, 68-71]

SCIT was provided in a cluster, rush, or ultra-rush protocol in 6 of the 18 studies (33%).[20, 21, 24, 25, 66, 70] Documentation of allergic sensitization was made through SPT and/or serum IgE in 10 articles,[19, 64-68, 70, 71] otherwise it was not specified. Allergen identified was not reported in seven studies,[20, 21, 23, 24, 26, 65, 69] four studies had monosensitized patients,[25, 67, 68, 71] three polysensitized patients,[22, 70, 72] three had both monosensitized and polysensitized patients,[19, 64, 73] and one did not clearly report sensitization status.[66] Nine studies treated with single allergen and nine with multiple allergens.

Adults

SCIT was provided in a cluster, rush, or ultra-rush protocol in three (43%) of seven studies.[20, 21, 66] Documentation of allergic sensitization was made through SPT and/or serum IgE in four articles,[64-67] otherwise it was not specified. Two studies included polysensitized patients, one monosensitized patients, one both polysensitized and monosensitized patients, and four did not specify sensitization status. In four studies patients were treated with multiple allergens. Four of the studies were case reports.[21, 23, 65, 67] (See Appendix F for further details.)

Children

There were no non-RCTs assessing safety of SCIT in the pediatric population.

Local Reactions

Summary and Description of Events in RCTs

Local reactions consisting of itching, pain, paresthesia, heat, erythema, and induration at the site of injections were reported in 6.25 percent[42] to 33.3 percent[31] of patients. Notably, local reactions occurred with the placebo injections in zero up to 12.5 percent of patients.[35, 42, 47] Calculated risk differences ranged from -0.317 to 0.4 (a range of 32 additional cases of local reactions in the placebo group to 40 additional cases per 100 people treated with SCIT). In one study, patients who received SCIT to dog allergens had 20 episodes of local swelling per patient, as compared to 21 episodes per patient in those receiving placebo injections (calculated risk difference -0.317),[30, 63] compared with one study with HDM, in which eight patients who received HDM SCIT presented local swelling at injection site and

none of the patients receiving placebo presented local swelling at injection (calculated risk difference 0.4).[48]

Adults. Local reactions, described as local erythema or induration at the site of injections, were reported in 6.25 percent[42] to 22 percent[35] of patients. In the latter report,[35] two of nine patients (22%) had three large local reactions severe enough to require modifications of the immunotherapy schedule, while none of the placebo patients has similar reactions. Local reactions were described with placebo injections in zero to 12.5 percent of patients.[35, 42, 47]

Children. One study reported local, red swelling at the site of HDM SCIT injection in eight children (calculated risk difference 0.4).[48]

Summary and Description of Events in Non-RCTs

Local reactions, described as swelling or urticarial plaques at the site of injections, were reported in four studies and ranged from 5.6 to 27.3 percent of patients treated,[20, 22, 66] and in 6.5 to 10.7 percent of SCIT doses given.[20] In the study in which the size of the local swelling was reported, 10.1 percent had a small reaction (<5 cm in diameter) and 13.2 percent had a large reaction (≥ 5 cm in diameter).[22]

Adults. Local reactions consisting of swelling or urticarial plaques at the site of injections were reported in 5.6 to 27.3 percent of patients,[20, 66] and in 6.5 to 10.7 percent of SCIT doses given.[20] One patient developed multiple subcutaneous itchy nodules on the lateral aspects of both arms, at the site of previous immunotherapy injections to timothy grass pollen.[23]

Children. There were no non-RCTs assessing local adverse events of SCIT in the pediatric population.

Systemic Allergic Reactions

Summary and Description of Events in RCTs

Systemic allergic reactions were described in 16 studies, including 540 patients treated with SCIT compared with 182 patients treated with placebo injections and 265 patients treated with pharmacotherapy. In four studies there were specifically no systemic allergic reactions reported. The rate of systemic allergic reactions ranged from zero to 44 percent of patients (4 out of 9 patients receiving SCIT for cat);[35] when reported as number of injections, the highest rate of systemic allergic reactions was 11.7 percent of total injections given (203 reactions out of 1735 total injections).[45] Types of reactions included pruritus, urticaria, eczema, skin rash, rhinitis, conjunctivitis, nasal congestion, nasal obstruction, cough, asthma, bronchospasm, wheezing, dyspnea, abdominal pain, diarrhea, and hypotension. However, in several studies the types of reactions were not specified and were described as "Not specified," "Mild systemic reaction," "Mild-moderate systemic reaction," "Systemic reaction," "Systemic reaction requiring Epinephrine," "unspecified symptoms," and "pulmonary reactions." The calculated risk differences based on the number of patients who developed systemic allergic reactions ranged from zero to 0.319.

Bronchoconstriction was reported in patients receiving SCIT as follows: "Bronchospasm," "wheezing," "asthma," and "pulmonary reactions" were specifically reported in 15 patients receiving SCIT in seven RCTs: 1/37,[52] 2/18,[55] 2/17,[39] 1/15,[57] 3/30 (two receiving cluster and one in the conventional arm),[61] 4/18,[62] and 2/36.[18] Only one study reported pulmonary reactions in the control arm: 3/17.[62]

Adults. Systemic allergic reactions were described in eight studies, including 205 patients treated with SCIT compared with 152 patients treated with placebo injections and 18 patients treated with pharmacotherapy. In two studies there were specifically no systemic allergic reactions reported. The rate of systemic allergic reactions ranged from zero to 44 percent (4 out of 9 patients receiving SCIT for cat, calculated risk difference 0.319).[35] Out of the patients receiving SCIT, 46 patients were receiving an accelerated SCIT protocol (rush or cluster protocol).

There were 36 patients receiving SCIT who developed systemic allergic reactions, as compared to 6 patients receiving placebo injections. Out of these 36 patients, 7 patients were receiving an accelerated protocol.[54, 55] The description of the nature and severity of these systemic allergic reactions varied greatly from study to study.

Children. Three studies reported systemic allergic reactions. Two studies used multiple-allergen SCIT. One of those studies compared multiple-allergen SCIT to pharmacotherapy and reported that nine children (11%) in the SCIT arm had an immediate systemic reaction.[28] Of those nine children, one had mild respiratory involvement (grade 2) and eight had a skin rash (grade 1); all reactions were successfully treated in the clinic and did not require additional observation or hospitalization. The reactions and subsequent treatment were not described in further detail.[28] The other study compared multiple-allergen SCIT with placebo and reported systemic allergic reactions to injections in 21 of the 61 children in the SCIT group (34%) and in 4 of the 60 children in the placebo group (7%) (P =0.001). In this study (n=121), there were 114 total systemic allergic reactions (in 21 of the 61 children receiving SCIT and 4 of the 60 children receiving placebo), 52 of which were treated with adrenergic drugs; however, neither the severity of the reactions nor the type of adrenergic drugs was specified, and there were no dropouts due to reactions to SCIT. All 52 responded to treatment without clinical sequelae.[32] In one study that compared 3 years versus 5 years of HDM SCIT, two patients with asthma in the 5-year arm had an asthma episode within 30 minutes of receiving a maintenance dose that resolved with a bronchodilator. The following dose was adjusted in both patients and the authors comment that long-term tolerance was confirmed in every patient.[18] One study specifically commented that there were no systemic allergic reactions.[48]

Summary and description of events in non-RCTs

Systemic allergic reactions were described in 13 studies (see Appendix G), 11 were case series and two were single case reports.[21, 67] The rate of systemic allergic reactions ranged from 0.6 percent of patients and 0.1 percent of injections[26] to 23.9 percent of patients.[19] In the latter study, 16 of 67 children (24%) receiving HDM SCIT developed "non-fatal systemic reactions." [19] Reported systematic reactions consisted of urticaria, asthma, flushing, nasal congestion, nasal itching, wheezing, chest tightness, bronchospasm, vasculitis, and anaphylaxis. However, in several studies the types of reactions were not specified and were described as "Non-specified systemic symptoms," "systemic reactions," "systemic effects," and "non-fatal systemic reactions."

In the studies where systemic allergic reactions and numbers of patients treated were reported, 5,692 patients were treated with SCIT, 52 patients were treated with pharmacotherapy, and no patients received placebo injections. Of the patients who received SCIT, 311 were being treated with a cluster regimen,[20, 21, 24] and 836 were being treated with a rush or ultra-rush regimen.[25, 66, 70]

Adults. Systemic allergic reactions were described in five studies of adults, two of which were single case reports.[21, 67] The rate of systemic allergic reactions ranged from 1.5 percent of patients[20] to 11 percent of patients;[64] in the latter study, patients were treated with HDM and animal SCIT, and the highest rate of systemic reaction was in patients with asthma but without seasonal rhinitis (11%) (as

compared with patients with asthma and seasonal rhinitis, where the rate of systemic allergic reactions was 3%). In the studies where systemic allergic reactions and numbers of patients treated were reported, the total number of patients treated with SCIT was 379 patients, with no patients receiving placebo injections or pharmacotherapy. Out of the patients received SCIT, 184 were being treated with a cluster regimen[20, 21] and 18 were being treated with a rush or ultra-rush regimen.[66]

Excluding case reports, there were 20 patients receiving SCIT who were reported to have systemic allergic reactions. Six of these patients were receiving an accelerated SCIT protocol. The case reports described one patient who developed anaphylaxis treated with epinephrine, and one patient who developed leukocytoclastic vasculitis that occurred repeatedly after SCIT injections.

Children. One study that included 67 children with asthma and allergic rhinitis sensitized to HDM who received HDM SCIT for 2 years documented that systemic allergic reactions occurred in 16 of 67 (23.8%) of children with asthma (27/2045 or 1.32% of total injections). All children in this study completed the initial phase of SCIT. Not all patients had asthma in this study and the systemic allergic reactions were not described further for children with asthma, specifically.[19]

Anaphylaxis

Summary and description of events in RCTs

Only one RCT specifically reported anaphylaxis, reporting that there were no anaphylaxis events in 33 patients who received HDM SCIT.[31] This RCT was conducted in 65 people and was considered at medium risk of bias.

Upon review of the nature of reactions in all of the SCIT RCTs, four of the remaining 25 RCTs had patients with reactions we considered consistent with anaphylaxis.[39, 52, 54, 60] (See Appendix E, Table E4.A for details.) One trial compared different forms of SCIT, reporting that one out of 12 patients receiving unmodified SCIT to grass developed urticaria and bronchospasm compared to none of the 11 patients in the modified SCIT arm.[60] In another trial, at high risk of bias, one patient in the placebo group (n=40) received a HDM SCIT injection by mistake, and developed bronchospasm and hypotension requiring epinephrine.[52]

One RCT, at high risk of bias due to lack of allocation concealment and masking of outcome assessors, reported a high rate of anaphylaxis with three of 20 patients receiving rush HDM SCIT having a reaction consistent with anaphylaxis and none of the 10 patients receiving placebo injections having such a reaction (risk difference of 0.15).[54] The rush SCIT protocol was delivered over the course of 3 to 4 days, starting at 30 BU of D pter. Once maintenance was reached, patients received weekly injections of 3000 BU. Four patients experienced a “systemic reaction” during the rush protocol, and three of these patients required epinephrine injections. The underlying asthma severity in these patients was not reported. No systemic allergic reactions occurred while patients were on maintenance SCIT, and no systemic allergic reactions occurred in the placebo group.

Finally, one RCT, judged to be at low risk of bias, randomized 50 patients to receive either HDM SCIT (15 patients), HDM SCIT in addition to oral vitamin D (17 patients), or pharmacotherapy only (18 patients).[39] One patient in the SCIT-alone group experienced a systemic reaction within 20 minutes after injection of vial 4 during the buildup phase and was treated with epinephrine. Two patients in the SCIT+Vitamin D group developed mild asthma attacks and were treated with inhaled beta-2 agonist. The underlying asthma severity in these patients was not described. The risk difference, comparing the SCIT groups versus placebo, is 0.03.

Overall, the reports of systemic allergic reactions consistent with anaphylaxis varied greatly (from 0 to 15 additional cases of anaphylaxis per 100 people treated with SCIT). We are unable to draw

conclusions on whether SCIT increased risk of anaphylaxis, primarily because the RCTs did not directly measure or report anaphylaxis (indirectness) and were not powered to assess such effects (imprecision). See Table 4. Summary of the strength of evidence for the safety of subcutaneous immunotherapy for details.

Adults. As described above, one RCT reported three out of 20 patients receiving rush HDM SCIT were treated with epinephrine due to reactions consistent with anaphylaxis.[54] One out of 12 patients receiving SCIT to grass developed urticaria and bronchospasm.[60]

Children. There were no RCTs of SCIT assessing or reporting anaphylaxis in the pediatric population.

Summary and description of events in non-RCTs

A case series with a total of 658 patients, reported no cases of anaphylaxis in 339 patients (2712 doses) receiving cluster SCIT and no cases of anaphylaxis in 319 patients (2552 doses) receiving conventional dosing SCIT with multiple allergens.[20]

One case series reported specifically on the incidence of anaphylaxis in patients with mixed-age groups.[69] In this study, anaphylaxis was classified as "mild, moderate, or severe" based on symptoms. Reactions were classified as uniphasic (symptoms occurred within 5-30 minutes and resolved gradually) or biphasic (initial symptoms resolved then the re-emerged within several hours). There was a total of 453 patients receiving SCIT for allergic rhinitis, asthma, or venom allergy; 133 patients had asthma. A total of 21,022 injections were given and 131 anaphylactic reactions were recorded in 76 out of the 453 patients (120 uniphasic and 11 biphasic); 65 of these reactions were treated with epinephrine. The total incidence of anaphylaxis was calculated as 1.3%. Out of these 131 reactions, 63 (48%) occurred in patients who had asthma; however, the severity of systemic allergic reactions in patients with underlying asthma was not described. Following WHO criteria for assessing case reports, we determined that it was likely that SCIT caused the anaphylaxis reactions reported in this case series (causality).

Bronchoconstriction was reported in patients receiving SCIT as follows. One case series reported one participant out of 18 presenting "Bronchospasm grade 2" after receiving treatment with HDM SCIT.[66] Another study reported one case of shortness of breath and hypotension during buildup, out of 144 patients who received SCIT.[72]

Adults. A case series with a total of 658 patients (5264 doses with multiple allergens) (cluster vs. conventional) reported no cases of anaphylaxis.[20] One case report described a patient receiving cluster grass SCIT, who presented chest tightness with wheezing, requiring epinephrine.[21]

Children. There were no non-RCTs of SCIT assessing anaphylaxis in the pediatric population.

Deaths

Summary and description of events in RCTs

No deaths were reported in the RCTs.

Summary and description of events in non-RCTs

There was one case report [65] of death occurring in a 17-year-old female with moderate persistent asthma who had received SCIT in childhood for 4 years and stopped due to a skin reaction. The authors report that, 12 hours after initiation of new regimen, she complained of abdominal pain, vomiting, and diarrhea without fever. Two days later, she developed an acute respiratory failure and was referred to the

ICU. She had markedly elevated CPK, elevated troponin, leukopenia, thrombocytopenia, and bilateral interstitial markings on chest X-ray. On day four, she developed hypoxic coma leading to intubation and mechanical ventilation, followed by shock and acute renal impairment. By day five, she developed multi-organ failure and died. The authors considered immunological mechanism secondary to manipulation or the way the dose was escalated and considered causality probable. Following WHO criteria for assessing case reports, we also determined that the likelihood of SCIT causing this death (causality) was possible, as the event was related to intervention but was not dose-related.

Variation per setting

Of the 26 RCTs, SCIT was provided in the clinic setting in 24 studies, and two studies did not specify the location. There were no studies reporting administration of SCIT at home. Therefore, in all the studies where location was mentioned, SCIT was provided in the clinic setting. There is insufficient evidence to analyze any variation in adverse effects of SCIT by the clinic or home setting.

Table 4. Summary of the strength of evidence for the safety of subcutaneous immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Anaphylaxis	5 RCTs[31, 39, 52, 54, 60] N=245 6 cases	Medium	Inconsistent	Indirect	Imprecise	Undetected	Unable to draw conclusions	Insufficient
	1 Non-RCT[69] 1 case series[20] 1 case report[21] N=792 55 cases	Likely (Likelihood of causality)						
Death	No RCTs or Non-RCTs						Unable to draw conclusions	Insufficient
	1 case report[65] 1 case series[72] N=145 1 case	Possible (Likelihood of causality)						

Key Question 3. What is the evidence for the efficacy of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

Key Points

- SLIT improves asthma symptoms, as measured by validated instruments (high SOE).
- SLIT improves disease-specific quality of life and decreases use of long-term control medications (specifically, ICS), and improves FEV_1 (moderate SOE).
- SLIT may decrease quick-relief medication use (short-acting bronchodilators) and may improve disease-specific quality of life (low SOE).
- There is insufficient evidence on the effect of SLIT on systemic corticosteroid use or health care utilization.

- There is insufficient evidence about the efficacy of SLIT in children.

Overall Study Characteristics

We identified 18 RCTs regarding the efficacy of SLIT for asthma. The articles were published between 2001 and 2016, with 75 percent of the articles originating from Europe. Eleven studies included only adults (12 years of age and older),[74-84] four studies included mixed adult/children populations,[85-88] and three studies included only children.[89-91] Patients were monosensitized in 12 studies, polysensitized in one study,[78] and one study did not clearly report sensitization status.[84] Four studies included both polysensitized and monosensitized patients.[74-76, 85] The majority of studies treated HDM allergy; the next most commonly treated allergies in these studies were birch and grass. No study used multiple allergens.

We provided details about the studies, patient characteristics, and interventions in Appendix F and components in the assessment of risk of bias in Appendix I.

Asthma Symptoms

Asthma symptom control outcomes were reported in four SLIT RCTs,[74, 75, 77, 78] which included a total of 1,193 patients, with all studies including adult patients. Clinically and statistically significant improvement in scores was found in three of four studies.[75, 77, 78] Three studies were low risk of bias, and the fourth had medium risk of bias.

Three studies used HDM in comparison to placebo and utilized the ACQ to evaluate asthma symptoms.[74, 75, 78] The treatment duration for all three HDM studies was 1 year, with daily maintenance dosing ranging from 1 SQ-HDM to 12 SQ-HDM or 300IR for the daily dose. Two studies used tablets,[74, 75] and one used aqueous drops.[78] One of the three HDM studies was performed in patients with mild to moderate persistent asthma and demonstrated statistically significant improvement in asthma symptoms with SLIT with a daily maintenance dose of 300 IR drops.[78] This study compared the percentage of patients with an ACQ score of <0.75 at the end of the study based on treatment versus placebo; raw data were not reported by the authors, so whether they achieved the minimal clinically important difference (MCID) could not be determined.[92] They found statistically significant improvement in their subgroup analysis of 180 moderate persistent asthmatics (percentage improvement 56% vs. 40%, $P<0.039$); this effect was not found in the mild asthmatics.[78] The second RCT found a trend for a non-statistically significant improvement in asthma symptoms with a decrease of 0.41 in ACQ score in the 6 SQ-HDM treatment group, compared with no change in score in the control group.[75] The decrease in ACQ did not meet the MCID. The third HDM study was performed in patients with moderate to severe asthma and did not demonstrate statistically significant improvement ($P=0.22$).[74]

The fourth study of asthma symptoms used birch allergen with a maintenance dose of 100 AU tablet 5 days per week for 3 years plus daily inhaled budesonide 400 µg daily and the ACT to assess asthma symptoms.[77] The comparator group was treated with inhaled budesonide (800 µg daily, 1600 µg daily, or 400 µg inhaled budesonide plus montelukast 10 mg daily). Treatment with birch allergen for 3 years, in this study, resulted in a statistically significant improvement of ACT scores (mean post value 24 in SLIT arm, vs. 18 in other arms, $P<0.05$); the improvement exceeded the MCID for the ACT.[92]
There is high strength of evidence that SLIT improves asthma symptoms, based on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall low risk of bias. See Table 5. Summary of the strength of evidence for the efficacy of sublingual immunotherapy for details.

Quality of Life

Three RCTs, all of HDM allergen with a total of 1,120 patients, examined the impact of SLIT on disease-specific quality of life using the AQLQ.[74, 75, 78] Two studies were low risk of bias, and one study

was medium risk of bias. All three studies included only adult patients and each compared SLIT with placebo.

The three RCTs did not demonstrate statistically significant improvement (*P* =0.89, *P* reported as "not significant" for 2 of the studies). The largest study (n=877) reported that scores in both SLIT groups and the placebo group improved, but there was no statistically significant difference between SLIT and placebo.[74] Two studies included mild to moderate asthmatics, and one study included moderate to severe asthmatics. Two of the three RCTs used tablets,[74, 75] and one used aqueous drops.[78] All studies treated for 1 year, with daily maintenance dosing ranging from 1 SQ-HDM to 12 SQ-HDM or 300IR for the daily dose. The RCT that reported statistically significant changes in AQLQ in the treatment group pre- versus post-treatment used a 6 SQ-HDM tablet, but no significant differences were reported when the treatment group was compared to controls.[75]

Heterogeneity in the study populations and how quality of life was measured prevents further synthesis. Each study reported improvement in AQLQ in both the SLIT and placebo groups. The use of SLIT may improve disease-specific quality of life with asthma, based on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall low risk of bias (low SOE). See Table 5. Summary of the strength of evidence for the efficacy of sublingual immunotherapy for details.

Medication Use

Quick-relief medications. Five studies of SLIT included data on quick-relief medication (SABA) outcomes.[77, 82-84, 90] Four studies reported quick-relief medication outcomes in doses of SABA over 3 months, with three studies demonstrating statistically significant decrease in the need for SABA.[77, 82, 83] The fifth study reported the reduction in doses of SABA used over a 6-month period.[84] The studies were performed in patients with mild to moderate asthma and included a total of 298 patients. The risk of bias was low for one study, medium for two studies, and high for the remaining study. The high risk of bias was due to lack of allocation concealment and blinding.[83] Two studies were performed in adults with birch allergy, with 5 years of continuous treatment (5 drops of 10,000 AU maintenance dose 3 times per week; cumulative annual dose for 100 micrograms of Bet v 1) or 3 years of pre/co-seasonal treatment (1000 AU tablet maintenance dose 5 days per week).[77, 82] The first birch SLIT study measured SABA use in doses during 3-month pollen seasons per year over 5 years; it found that the SLIT group decreased SABA intake on average by 16.1 doses, compared with the control group treated with montelukast, which had a decrease on average of 3.6 doses (*P*=0.019).[82] The second birch SLIT study measured SABA use over 3-month pollen seasons per year for 3 years; it found that the SLIT group decreased SABA intake on average by 10.1 doses, compared with the control groups treated with inhaled budesonide (800 or 1600 µg, or inhaled budesonide 400 µg daily plus montelukast 10 mg daily), which had decreases of 0.7, 2.9, or 4.5 doses on average, respectively (*P*<0.001).[77] One study was performed with grass mix for 5 years (maintenance dose 3 times per week, 5 drops of 10,000 RU/ml; cumulative annual does of 70 micrograms of Phl p 1). The third study was grass mix study which measured doses of SABA over 3-month pollen seasons per year for 5 years and found an average decrease of 17.9 doses in the SLIT group, compared with an average decrease of 9.4 doses in the control group treated with 800 micrograms daily of inhaled budesonide (*P*=0.01).[83]

The fourth study was performed in children with HDM (20 drops of 300 IR/ml maintenance dose) and measured puffs of SABA per day; it did not find a significant change comparing SLIT to the placebo group after treatment (*P*=0.951).[90] The fifth study was performed in adults (maintenance dose 710 UBE/ml 3 times/week) and measured the reduction in SABA doses. The study found a 50 percent reduction in the treatment group, compared to a 21 percent reduction in the placebo group (P<0.03).[84]

Overall, we found low SOE that SLIT may decrease the use of quick-relief medications, based on a body of evidence that is consistent, imprecise, direct, and with an overall medium risk of bias. See Table 5. Summary of the strength of evidence for the efficacy of sublingual immunotherapy for details.

Long-term control medications. Four studies of SLIT reported long-term control medication use and included a total of 1,308 patients. All studies treated mild to moderate persistent asthmatics with HDM and evaluated the use of ICS compared to placebo.[75, 78, 86, 90] Two studies were low risk of bias and two were medium risk of bias. Two studies were performed in adults,[75, 78] one in mixed-age populations,[86] and one in children.[90] Treatment duration ranged from 6 to 24 months, with dosing ranging from 1 SQ HDM to 12 SQ HDM, 100 IR, or 300 IR. The two studies performed in adults demonstrated significant decreases in the used of ICS with treatment using a daily maintenance dose of 300 IR drops or 6 SQ-HDM tablets.[75, 78] In the first of these two studies, the authors measured absolute decrease in daily inhaled budesonide dose in micrograms, with the SLIT group decreasing by 218.5 micrograms on average, compared with the placebo group, which decreased by 126.5 micrograms on average (P=0.004).[78] The second study reported the difference between placebo and SLIT in change from baseline in daily ICS use in micrograms as 327 (P<0.0001).[75] The third study that included mixed-age populations used a maintenance dose of 300 IR tablet, reported no statistically significant differences between SLIT and control.[86] The fourth study found no significant improvement in ICS use measured in puffs per day when comparing SLIT to placebo (P=0.215).[90]

Four large studies with low to medium risk of bias demonstrated statistically significant improvement comparing SLIT to controls. We found moderate strength of evidence that SLIT decreases the use of long-term control medications (inhaled corticosteroids). The strength of evidence was based on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall medium risk of bias. See Table 5. Summary of the strength of evidence for the efficacy of sublingual immunotherapy for details.

Systemic corticosteroids. One study reported on the effects of SLIT on systemic corticosteroid use.[90] This study included only children and is discussed in the pediatric section below. See Table 5. Summary of the strength of evidence for the efficacy of sublingual immunotherapy for details.

Asthma Exacerbations

Three studies reported on the effects of SLIT on asthma exacerbations using HDM in 1,498 adult patients with mild to moderate persistent asthma.[74, 75, 84]There were no children-only or mixed-aged population studies. One study, which used maintenance doses of 6 SQ-HDM or 12 SQ-HDM for 6 months in comparison with placebo, showed a statistically significant improvement in all of the following outcomes with the higher dose: time to asthma exacerbation, time to first asthma exacerbations with deterioration in asthma symptoms or nocturnal awakening, time to first exacerbation with deterioration in lung function, time to first asthma exacerbation and use of SABAs, and time to first severe asthma exacerbations. These were reported as hazard ratios with SLIT compared with placebo, with the placebo group as reference. The hazard ratios for the 12 SQ-HDM dose in this study are as follows: time to first asthma exacerbation, 0.69 (P=0.03); time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings, 0.64 (P=0.03); time to first asthma exacerbation with deterioration in lung function, 0.52 (P=0.02); time to first exacerbation with increased use of SABA, 0.52 (P=0.03); and time to first severe asthma exacerbation, 0.69 (P=0.02). The hazard ratios for the 6 SQ-HDM dose in this study are as follows: time to first asthma exacerbation, 0.72 (P=0.45); time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal

awakenings, 0.72 (*P*=0.17); time to first asthma exacerbation with deterioration in lung function, 0.62 (*P*=0.03); time to first exacerbation with increased use of SABA, 0.62 (*P*=0.09); time to first severe asthma exacerbation, 0.72 (*P*=0.03).[74] However, the second study, which utilized 1 SQ-HDM, 3 SQ-HDM, or 6 SQ-HDM maintenance dose for 1 year in comparison with placebo did not find a statistically significant improvement in the number of asthma exacerbations. The authors did not report the data for asthma exacerbations in this article.[75] The third study, which used maintenance doses of 710 UBE/ml of HDM three times per week, reported the total number of exacerbation at the end of the study.[84] The SLIT group had 71 exacerbations, compared with the placebo group, which had 123 (P<0.001).

Health Care Utilization

There were no studies of the effect of SLIT on health care utilization.

Pulmonary Physiology

***PEF*.** PEF was reported in five studies,[80, 86, 88-90] including a total of 341 patients. One study included only adults, two studies included only children, and two studies included mixed-age populations. The risk of bias was low in three studies and medium in two. All studies compared SLIT with placebo. Three studies were of HDM and two of grass pollen. While none of the studies demonstrated statistically significant improvement when compared with controls, three studies showed minimal improvement in those treated with SLIT,[86, 88, 90] and one study showed improvement only in the evening measurements.[89]

FEV_1. FEV_1 was the most commonly reported outcome, reported in 11 studies.[75, 77, 78, 80, 83, 84, 86, 88-91] Six of these studies included adults only,[75, 77, 78, 80, 83, 84] three studies included children only,[89-91] and two studies included mixed-age populations.[86, 88] The total number of patients in these studies was 1,694 and all had mild to moderate asthma. Seven studies were of HDM, two of grass mix, one of birch, and one of timothy grass.

When considering seasonal allergens, three of four pollen allergen studies found statistically significant improvement in FEV_1. One trial of grass mix SLIT versus control (treated with montelukast alone), at a dose of 5 drops of 10,000RU/ml 3 times per week for 5 years, reported an increase from an average of 78.5% to 96.2% of predicted FEV_1 in the SLIT group, compared with a change in control group of 76.4% to 81.2% (p<0.0001).[83] The second study, of birch allergen, was performed with a dose pre/co-seasonal 1000AU tablets 5 days a week for 3 years, and reported that mean FEV_1 improved from 85.2 to 103.3 in the SLIT group, compared with 3 control groups treated with budesonide alone, which improved from 88.3 to 90.3, 87.0 to 92.4, and 86.2 to 96.5, respectively (p <0.05 for SLIT compared to any of the control groups).[77] The third pollen study demonstrating statistically significant change was of grass mix over 6 months (maintenance dose of 43,800 IR three times per week), and demonstrated mean percent predicted FEV_1 in the treatment group improved from 92.9 to 100.4, compared with the placebo group, which improved from 87.9 to 88.2 (P=0.005).[88]

One HDM study demonstrated statistically significant improvement in FEV1, with the treatment group improving from 2.16 to 2.86 (percentage increase after salbutamol), compared with the placebo group, which improved from 2.58 to 2.81 (P<0.03).[84] The maintenance dose used in this study over 6 months was 710 UBE/ml.

The three pediatric studies noted a statistically significant improvement in FEV_1 in the SLIT arm but there was no statistically significant difference between arms.[89-91] Of the remaining three studies, demonstrated a non-statistically significant improvement in those treated with SLIT (numbers not reported).

The risk of bias was medium in five studies, low in five studies, and high in one study. SLIT may improve FEV_1, based on evidence that is precise, direct, consistent, and with a medium overall risk of bias (moderate SOE). See Table 5. Summary of the strength of evidence for the efficacy of sublingual immunotherapy for details.

FEV_1/FVC. There were no studies of the effect of SLIT on FEV_1/FVC.

FVC. One study reported on the effect of HDM SLIT on FVC in children,[90] and one study reported on the effect of HDM in adults.[84] Neither study found any statistically significant effects on FVC.

Airway Hyperresponsiveness

Methacholine challenge. Four studies reported methacholine challenge results, including two birch studies in adults with mild asthma,[77, 83] one study of grass mix in a mixed-age population,[88] and one HDM study in a mixed-age population with severe asthma,[85] There were no studies of children only. The studies included a total of 233 patients. Both birch studies demonstrated significant improvement in AHR after treatment with SLIT. The first birch study reported methacholine dose in micrograms causing a 20 percent fall in FEV_1 from baseline (PD_{20}), with the change in dose in the SLIT group improving by 592.9 after treatment, compared with the control group, which was treated with montelukast alone, of 190.1 (P=0.001).[83] The second birch study reported methacholine dose in micrograms causing a 20 percent fall in FEV_1 from baseline, with the SLIT group improving from 166.8 to 997.1 after treatment, compared with three control groups: budesonide 800 micrograms (from 226 to 520.0 µg of methacholine PD_{20}), budesonide 1600 micrograms (from 199.8 to 644.9), and budesonide 400 micrograms plus montelukast (from 165.7 to 728.7) (SLIT vs. all treatment arms $P<0.05$). The grass mix study (6-month treatment with a maintenance dose of 710 UBE/ml 3 times per week) demonstrated improvement that did not reach statistical significance in the treatment group with improvement from 3.51 to 4.05 Mg/ml methacholine, compared with the placebo group improvement from 4.35 to 4.0 (P=0.058).[88] The HDM study reported increases in cumulative methacholine dose in micrograms causing a reduction of 20 percent of the baseline FEV_1 for the SLIT group and an improvement from 626.4 to 1277.7 after treatment (p=0.001), compared with an improvement from 616.1 to 860.3 for the control group, which was treated with non-specified pharmacotherapy (P=0.08); however, this study did not make a direct statistical comparison of SLIT to SCIT for the methacholine challenge outcome (PD_{20}). The maintenance dosing used for the studies included the following: HDM, 1000 AU 2 times per week for 1 year; birch, 5 drops of 10,000AU/ml 3 times per week for 5 years; and birch, 1000 AU 5 days per week pre/co-seasonal 5 days per week. Two of four small studies with medium to high risk of bias demonstrated statistically significant improvement compared with controls.

Allergen challenge. There were no studies of the effect of SLIT on allergen challenge.

Exercise challenge. There were no studies of the effect of SLIT on exercise challenge**.**

Compliance

Three HDM studies reported on compliance in mild to moderate persistent asthmatics. The three studies involved adults only and included 1,022 patients.[75, 76, 78] Compliance in these trials ranged from 90 to 99 percent. The first study reported compliance as mean compliance with study drug, the second study reported compliance as the number of non-compliant patients, and the third study reported compliance by determining the number of unused SLIT packs.

Immunological Outcomes

Skin testing. Three placebo-controlled SLIT trials reported allergen skin testing results for HDM.[78, 86, 93] Two studies using HDM SLIT tablets demonstrated statistically significant reduction in skin wheal diameter when comparing SLIT baseline and post-therapy values and mean differences between SLIT and placebo groups.[78, 86]

Immunoglobulin E. Six SLIT aqueous or tablets versus placebo RCTs reported HDM-specific IgE levels.[78, 86, 87, 89, 90, 93] Only one study reported a statistically significant effect: an increase in HDM-specific IgE levels after SLIT tablets compared to placebo ($P<0.001$).[86]

Immunoglobulin G4. Four RCTs using SLIT reported HDM-specific IgG4 levels.[74, 78, 86, 89] Three studies reported statistically significant increases in specific IgG4 levels after SLIT compared with placebo.[74, 78, 86, 89] One study comparing two doses of HDM SLIT tablets versus placebo along with ICS in 834 HDM allergic asthmatics measured IgG4 levels for both Der p1 and Der f. Those studies reported significant increases in both Der p1/Der f1 specific IgG4 at both doses when compared with placebo ($P<0.001$).[74] Two other studies also reported significant increases in specific IgG4 using aqueous and tablet forms of SLIT ($P<0.01$ and $P=0.026$, respectively).[86, 89]

Variation per Setting

Ten studies of SLIT did not specify setting,[75, 80-83, 86, 87, 89-91] four reported administration at home,[76, 77, 79, 85] and two reported administration at the clinic.[74, 78] The body of evidence is insufficient to draw conclusions on any variation per setting.

Variation per Population

Adults

Asthma symptoms. In the studies done on adults only, there was no variation compared with the full body of evidence in asthma symptoms. (See description above.)

Quality of life. In the studies done on adults only, there was no variation compared to the full body of evidence in quality of life. (See description above.)

Medication use. In the studies done on adults only, there was variation compared with the full body of evidence in the long-term control medication use. The two studies involving adults only demonstrated significant decrease in the use of ICS with treatment using a maintenance dose of 300 IR or 6 SQ-HDM.[75, 78] This was not demonstrated in the two other studies, of children only and mixed-age populations. No studies evaluated quick-relief medications or systemic corticosteroids use in adults only.

Asthma exacerbations. In the studies done on adults only, there was no variation compared with the full body of evidence in asthma exacerbations. (See description above.)

Health care utilization. There were no studies of the effect of SLIT on health care utilization in adults

Pulmonary physiology. In the studies done on adults only, there was no variation compared with the full body of evidence in pulmonary physiology. Five studies, including 1,520 patients with mild to

moderate asthma treated with HDM, reported on pulmonary physiology.[75, 77, 78, 80, 83] (See results in the section above.)

Airway hyperresponsiveness. In the studies done on adults only, there was no variation compared with the full body of evidence in airway hyperresponsiveness when using methacholine challenge. (See description above.)

Compliance. Three adult-only HDM studies reported compliance outcomes in a total of 1,022 mild to moderate persistent asthmatics.[75, 76, 78] Compliance in these trials ranged from 90 to 99 percent. The first reported compliance as mean compliance with study drug, the second study reported compliance as the number of non-compliant patients, and the third study reported compliance by determining the number of unused SLIT packs. Compliance was similar in the placebo arms.

Children

Three studies, including 216 children, reported on the efficacy of SLIT in children 5 to 12 years of age with asthma. All studies enrolled children with mild to moderate persistent asthma. All studies used HDM SLIT in children who were monosensitized to HDM and compared SLIT to placebo.[89-91]

Asthma symptoms. There were no studies of the effect of SLIT on asthma symptom outcomes using ACT, ACQ, or P-ACT scores in children.

Quality of life. There were no studies of the effect of SLIT on asthma quality of life using the AQLQ, PAQLQ, or school or work absences in children.

Medication use. One trial of HDM SLIT versus placebo in 110 children with mild to moderate persistent asthma reported on the use of asthma-specific medications after a 24-week intervention.[90] This study found no difference in the use of quick-relief medication (Beta-agonists puffs per day) within or between groups. It also found no difference within or between groups for the use of long-term control medications (ICS puffs per day) or in the use of systemic corticosteroids (tablets per day). Overall strength of evidence is insufficient, based on a single small RCT with medium risk of bias.

Asthma exacerbations. There were no studies of the effect of SLIT on asthma exacerbations in children.

Health care utilization. There were no studies of the effect of SLIT on health care utilization in children.

Pulmonary physiology

PEF. Two studies reported on PEF as an outcome in children. One study included 20 patients and noted an improvement in evening, but not morning, PEF values compared with baseline in the SLIT arm.[89] The second study included 110 patients and demonstrated that PEF did improve significantly at followup compared with baseline in only the SLIT group.[90] Neither study noted a significant difference between arms.[89, 90]

FEV_1. Three studies, including 216 children, reported FEV_1 values.[89-91] All three studies noted a statistically significant improvement in FEV_1 in the SLIT arm, but there was no statistically significant difference between arms.[89-91] The overall strength of evidence is low that SCIT improves FEV_1 in children based on three RCTs with medium risk of bias, with consistent but imprecise results.

FEV_1/FVC. There were no studies of FEV_1/FVC in children only.

FVC. One study reported FVC values and found that children in the SLIT arm had significant improvement at the end of treatment, but there was no significant change in the placebo arm. There was no significant difference between arms.[90]

Airway hyperresponsiveness. There were no studies of the effect of SLIT on airway responsiveness in children.

Compliance. There were no studies of the effect of SLIT on compliance in children.

Table 5. Summary of the strength of evidence for the efficacy of sublingual immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Asthma Symptoms: ACT	4 RCTs [74, 75, 77, 78] N=1193	Low	Consistent	Direct	Precise	Undetected	SLIT improves asthma symptoms	High
QOL: AQLQ	3 RCTs[74, 75, 78]N=1120	Low	Consistent	Direct	Precise	Undetected	SLIT may improve asthma QOL	Low
Medication Use: Quick-relief medication	5 RCTs [77, 82-84, 90] N=298	Medium	Consistent	Direct	Imprecise	Undetected	SLIT may reduce the need of quick-relief medication	Low
Medication Use: Long-term control medication	4 RCTs[75, 78, 86, 90] N=1409	Medium	Consistent	Direct	Precise	Undetected	SLIT reduces the need for long-term control medication	Moderate
Medication Use: Systemic Corticosteroids use	1 RCT[90] N=110	Medium	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Health care Utilization	No RCTs	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology: FEV_1	10 RCTs[75, Stelmach, 2009#1335, 77, 78, 80, 83, 84, 86, 89-91] N=1694	Medium	Consistent	Direct	Precise	Undetected	SLIT improves pulmonary function (FEV_1)	Moderate

Key Question 4. What is the evidence for the safety of sublingual immunotherapy (SLIT) in the treatment of asthma?

Key Points

- Local reactions to SLIT were frequent (some reactions occurring in up to 80% of patients in RCTs); however, reactions also commonly occurred with placebo (risk differences ranged from -0.03 to 0.765).
- Systemic allergic reactions to SLIT were frequent (some reactions occurring in up to 22% of patients in RCTs), with only a few reports of anaphylaxis and no reports of deaths (risk differences ranged from -0.03 to 0.06).
- Although rates of anaphylaxis with SLIT compared to no treatment could not be determined (no cases reported in RCTs, insufficient evidence), three case reports suggest that rare cases may occur with SLIT treatment. Two of the three reports of anaphylaxis secondary to SLIT were in patients who received multiple-allergen therapy.
- No deaths secondary to SLIT therapy were reported (moderate SOE).

Overall Study Characteristics

Our search identified a total of 33 articles on 30 unique studies/populations reporting safety data. Of the included studies, 20 were RCTs (23 articles[74-80, 84-91, 94-101]), while 10 were either cohort, case-control, or case reports.[102-111]

We provided details about the studies, patient characteristics, and interventions in Appendix G and components in the assessment of risk of bias in Appendix I.

Summary and Description of Characteristics in RCTs

Ten RCTs enrolled adults, six enrolled mixed-age populations,[85-88, 98, 99] and four enrolled children only.[89-91, 100] Thirteen used GINA criteria to identify asthmatics,[74-77, 79, 84, 89-91, 94, 95, 97-99, 101] while the other half used a positive methacholine challenge, bronchodilator reversibility, or did not describe the methods used. Asthma severity ranged from mild to severe persistent, with two studies specifying the recruitment of poorly-controlled patients.[74, 77] Allergy was diagnosed using SPT and IgE in all studies but one in which diagnostic criteria was not specified.[101] Patients were monosensitized in 13 studies[77-80, 86-91, 98, 99, 101] and polysensitized in two studies.[97, 100] Four studies included both polysensitized and monosensitized patients,[74-76, 85] and one was unclear about monosensitization versus polysensitization.[84] All studies examined single-allergen therapy, with allergens including HDM, birch, and grass. Five studies compared different doses of SLIT and included a placebo arm,[74-76, 80, 94, 95, 98] while the remaining compared SLIT versus placebo, control, or standard asthma pharmacotherapy.[77, 78, 85-87, 89-91, 96, 97, 99-101] Studies variably reported on treatment for adverse events or discontinuation of SLIT therapy due to adverse events, and many did not report whether adverse events were considered drug-related. Two studies took place in a combined clinic and home setting,[87, 97, 98] three in the home,[74, 76, 79] and the remainder did not specify setting. (See Appendix G, Table G1.A for patient characteristics and Table G3.A for SLIT dosing characteristics.)

Adults. Nine studies included adults only,[74-78, 80, 84, 94-96, 101] and one reported results separately for adults.[98] Seven studies used GINA criteria for asthma identification.[74-77, 79, 84, 94, 95, 98] In these studies, asthma severity ranged from mild to severe persistent, and two studies specified recruitment of poorly-controlled patients.[74, 77] Just over half of the studies of adults included polysensitized patients. HDM, birch, and grass allergens were represented. Five trials compared different doses of SLIT and included a

placebo arm,[74-76, 80, 94, 95, 98] while the remaining studies compared a SLIT versus placebo, control, or standard asthma pharmacotherapy.[77-79, 84, 97] Four studies took place in the clinic,[74, 78, 97, 98] three at home,[76, 77, 79] and two did not specify setting.

Children. Four studies, including 270 children, reported safety data for the use of SLIT. All studies included patients with mild to moderate persistent asthma. Three studies, including 216 patients, compared HDM SLIT to placebo in patients who were monosensitized to HDM.[89-91] One study evaluated ultra-rush high dose birch pollen SLIT in patients with tree pollen allergy.[100]

Summary and Description of Characteristics in Non-RCTs

We included 10 non-RCTs, of which five included adults only (4 case reports,[102-105] 1 retrospective cohort[111]), two included mixed-age populations,[106, 107] and three included children only.[108-110] Two studies described asthma diagnosis criteria: one based on American Thoracic Society criteria,[108] and the other using bronchodilator reversibility for criteria.[109] Asthma severity ranged from mild intermittent to moderate persistent and was not specified for five of the studies.[102, 103, 105, 109, 110] Asthma control was also variably described. Eight studies used SPT for diagnosis, with five adding IgE criteria[103, 104, 106, 107, 111] and two which did not specify atopic criteria.[105, 110] Patients were monosensitized in three studies[108, 109 118, 110] and polysensitized in three studies.[102-104] Two studies included both polysensitized and monosensitized patients,[107, 111] two studies did not clearly report sensitization status,[105, 106] and one study did not report sensitized allergen.[105] Three case reports examined administration of multiple-allergen SLIT,[102, 103, 105] while the others examined single-allergen SLIT with HDM, grass, or pollen. Studies variably reported on treatment for adverse events or discontinuation of SLIT therapy due to adverse events. Three studies took place at least partially in the home,[102, 105, 109] the other studies took place in clinic or hospital or were not specified. (See Appendix G, Table G1.Bfor Study characteristics and Table G3.B for Intervention characteristics.)

Adults. Four adult non-RCTs were case reports,[102-105] and the fifth was a retrospective cohort.[111] Four included polysensitized patients,[102-104, 111] and two of those were given multiple-allergen SLIT.[102, 103] Patients in one study in which allergic status was not specified also received multiple-allergen SLIT.[105] Two studies occurred in the home,[102, 105] one in the clinic,[103] and two were not specified[104, 111] (See Appendix G, Table G1.B Study characteristics.)

Children. Three studies reported safety data for the use of SLIT in children with asthma.[108-110] All studies were case reports, included monosensitized patients to HDM, and had patients who received single-allergen SLIT.

Local Reactions

Summary and description of events in RCTs

Local events, including pruritus and/or swelling of the mouth, tongue, or lip, were reported in ten RCTs including roughly 2,500 patients,[74, 75, 78-80, 86, 88, 90, 91, 95, 98] with risk differences between SLIT therapy and placebo ranging from -0.336 to 0.252. Throat irritation was reported in five studies including roughly 1,700 patients,[74, 75, 79, 80, 95, 98] with risk differences ranging from -0.089 to 0.004. Abdominal pain, nausea, vomiting, and other gastrointestinal complaints were reported in six studies including roughly 1,500 patients,[74, 78, 86, 88, 97, 98] with risk differences ranging from -0.004 to 0.384. Also reported were local rashes in three studies with roughly 750 patients.[78, 97, 100] Frequency of local reactions was not consistently dose-dependent. Participants in trials reporting local reactions had mild to

moderate asthma in thirteen studies, with one study including patients with moderate to severe asthma.[74] Only two of the included studies took place in the home.[74, 79] (See Appendix G, Table G5.A- Local reactions for further detail.)

Adults. Six of the eight RCTs reporting pruritus and/or swelling of the mouth, tongue, or lip,[74, 75, 78-80, 95, 98] all of the five studies reporting throat irritation,[74, 75, 79, 80, 98] four of the six studies reporting abdominal pain, nausea, vomiting, and other gastrointestinal complaints,[74, 78, 97, 98] and two of the three studies reporting local rashes[78, 97] were either exclusively conducted in adults or reported results separately in an adult population. The risk difference in the adult population was therefore similar to those in the overall population. (Summary above.)

Children. One study comparing birch SLIT versus placebo in 116 patients, reported local reactions, including application site itching and paresthesia. The number of reactions was not included.[100] Another study comparing HDM SLIT versus placebo in 110 patients reported local reactions (tongue disorder, vomiting, abdominal pain, and circumoral paresthesia) in 5 children (10 incidences) in the SLIT group.[90] One study found that there were no relevant local side effects in 86 children.[91] One study did not comment on local reactions.[89]

Summary and description of events in non-RCTs

Local reactions were all related to gastrointestinal events, reported in three studies encompassing 79 patients. Reports included abdominal pain, nausea, vomiting, general malaise, and eosinophilic esophagitis.[104, 106, 110] (See Table G4.B.4 Local reactions).

Adults. Abdominal pain, nausea, and vomiting was noted in one case report of a polysensitized adult female receiving single-allergen (HDM) therapy at home.[104] No other local reactions were documented in non-RCTs.

Children. One pediatric case report documented a diagnosis of eosinophilic esophagitis related to HDM SLIT therapy.[110]

Systemic Allergic Reactions

Summary and description of events in RCTs

Reported systemic events included lower respiratory symptoms in eight RCTs including approximately 2,100 patients,[74-76, 80, 86, 97-99] with risk differences between SLIT and placebo ranging from -0.089 to 0.002. Bronchospasm was not specifically addressed, though lower respiratory symptoms included asthma exacerbation or “aggravation” and chest tightness, which are often symptoms of bronchospasm. Mucosal irritation (other than mouth or gastrointestinal tract) was reported in five studies including approximately 1,800 patients,[74, 75, 78, 97, 98] with risk differences of -0.07 to 0.035. Cutaneous systemic allergic reactions were reported by one study in 2 of 78 patients and resolved without treatment.[77] This study was also the only RCT conducted in the home setting that reported systemic allergic reactions. All participants in studies reporting systemic effects had mild to moderate asthma. One study did not specify asthma severity.[74] Incidence of systemic allergic reactions was not consistently associated with higher dose. (See Appendix G, Table G5.A Systemic allergic reactions).

Adults. Four of five studies documenting lower respiratory symptoms[74, 80, 97, 98] demonstrated an identical range of risk difference between SLIT versus placebo to that described above for all studies. All other studies included in the systemic allergic reactions to SLIT were adult studies.

Children. No RCTs of children only reported systemic allergic reactions to SLIT. One study commented that there were no systemic allergic reactions in 86 patients treated with HDM SLIT or placebo.[91]

Summary and description of events in non-RCTs

Lower respiratory symptoms were reported in five studies,[105-109] with asthma severity ranging from mild intermittent to moderate persistent. The symptoms included descriptions of wheezing requiring beta agonists and "worsening" of asthma, all of which may be consistent with bronchospasm, though bronchospasm was not specifically reported as an outcome. One pediatric case report documented a diagnosis of eosinophilic esophagitis related to HDM SLIT therapy.[110] Two of the studies reported SLIT administered at least part of the time in the home. (See Appendix G, Table G5.B Systemic allergic reactions.)

Children. Three studies reported safety data for the use of SLIT in children with asthma.[108-110]

Adults. One case was reported of a 16 year-old female with mild intermittent asthma and HDM allergy.[105]

Children. One case was reported of a 6-year-old male with persistent asthma and HDM allergy. Asthma symptoms were well controlled on daily fluticasone. PEF was 75 percent predicted and FEV_1 was 85 percent predicted and was reversible with bronchodilator. HDM SLIT was initiated (D far;D pter=50:50, 300 IR/ml). Following the induction phase, when the patient reached maintenance dosing (8 pumps), he developed wheezing within 2 minutes of his dose; symptoms persisted for 25 minutes and resolved with beta agonist (grade 2 reaction). He continued HDM SLIT at a reduced maintenance dose (4 pumps) and completed 3 years of therapy.[109] Another case reported of a 10-year-old female with asthma of unspecified severity and unspecified controlled status, who received a standardized mix of D far;D pter=50:50, at 300 IR/ml concentration, presented with reflux and vomiting 6 weeks after starting SLIT. Symptoms did not respond to treatment. Histopathology confirmed a diagnosis of eosinophilic esophagitis which resolved after discontinuation of SLIT.[110] Another retrospective case series reported no significant side effects in 39 pediatric patients with mild to moderate asthma receiving 3 years of HDM SLIT.[107]

Anaphylaxis

Summary and description of events in RCTs

No cases of anaphylaxis were reported among RCTs. Six studies[74-76, 86, 97, 100] specifically reported no episodes of anaphylaxis with HDM SLIT administered in the clinic setting or the home. Dose ranged up to 12 SQ, and included patients were either monosensitized or polysensitized with mild to severe persistent asthma (See Appendix G, Table G6.A Anaphylaxis for further detail.)

Adults. Three studies in adults[74-76] specifically reported no episodes of anaphylaxis with HDM SLIT administered in the clinic setting or the home. Dose ranged up to 12 SQ, and included patients were either monosensitized or polysensitized with mild to severe persistent asthma.

Children. No RCTs with children only reported anaphylactic reactions to SLIT.

Summary and description of events in non-RCTs

Three case reports, all in adults, reported anaphylactic reactions to SLIT therapy. The first was a 16-year-old female who received multi-allergen SLIT and developed anaphylactic shock.[105] The second was a polysensitized 25-year-old female who received multi-allergen SLIT and developed flushing, hoarseness, dyspnea, dizziness, and mild hypotension.[103] The last was a polysensitized, 31-year-old female who received multi-allergen SLIT and developed anaphylaxis.[102] Asthma severity and control were not identified in any of the cases. For one case, SLIT was discontinued; for another case, SLIT was maintained at a low dose; and, for a third case, the ultimate therapy decision was not noted. All three received aqueous SLIT: two in a home setting and one in a clinic setting. Following WHO criteria for assessing case reports, we determined that it was certain that SLIT caused these reactions of anaphylaxis (causality) in two cases[102, 105] and likely caused this reaction in one case,[103] with the main difference being that this reaction was not time-related. (See Appendix G, Table G6.B Anaphylaxis.)

Death

Three RCTs, including 934 patients in the SLIT arm and 489 in the placebo arm,[74, 78, 99] specifically reported that no deaths occurred during the study. There is moderate strength of evidence that SLIT does not increase the risk of death compared to placebo, based on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall medium risk of bias.

No deaths were reported in any of the non-RCTs evaluated.

Other

See Appendix G, table G8.B for reactions that were not otherwise classified. These included studies for which no serious reactions were reported, specific reactions were not specified, or reactions could not be categorized and it was unclear that the reaction was mechanistically related to SLIT therapy.

Conclusions

Most reported reactions were local with few systemic reactions noted. Occurrence did not differ systematically by setting of administration: home versus clinic versus other. Most studies looked at single-allergen therapy with HDM extract, which was generally well tolerated. Dose of SLIT did not demonstrate a clear association with risk of adverse events in all studies, though a subgroup of individual studies did report an association. One study comparing adult and child populations noted that adverse events tended to occur at lower doses in children than in adults.[98] No episodes of anaphylaxis were reported in RCTs, and three case reports of anaphylaxis were found among those who were polysensitized and/or treated with multiple allergen extracts. RCTs did not consistently report medication use or SLIT discontinuation in response to adverse events, though several studies did one or both. Of the three case reports of anaphylaxis, only one required a definite discontinuation of therapy (one followed a modified protocol of dosing and the other was not reported). No reports of death secondary to SLIT were found. See Table 6. Summary of the strength of evidence for the safety of sublingual immunotherapy for details.

Table 6. Summary of the strength of evidence for the safety of sublingual Immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusions	SOE
Anaphylaxis	6 RCTs[74-76, 86, 97, 100] N=1772 No cases No Non-RCTs	Medium	Inconsistent	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
	3 case reports[102, 103, 105]	2 Certain 1 Likely (Likelihood of causality)					Unable to draw conclusions	
Death	3 RCTs specifically reported no deaths[74, 78, 99] N=4231 Events 0	Medium (1 low, 1 medium, 1 high)	Consistent	Direct	Precise	Undetected	SLIT does not increase the risk of death	Moderate

Subcutaneous Versus Sublingual Immunotherapy

Key Points

- There is insufficient evidence to assess the relative efficacy of SCIT versus SLIT.
- There is insufficient evidence to assess the relative safety of SCIT versus SLIT.

Overall Study Characteristics

We included six studies published between 1989 and 2016 that reported on the efficacy and safety of SCIT versus SLIT.[112-118] The studies included 267 patients; all studies used SPT for allergy diagnosis, included monosensitized patients, and used HDM as allergen, except for one study that included polysensitized patients and used multiple allergens.[118]

We provided details on the studies, patient characteristics, and interventions in Appendix H and components in the assessment of risk of bias in Appendix I.

Asthma Symptoms

One study of SCIT versus SLIT aqueous HDM therapy reported asthma symptoms using ACT.[113] The study included 90 adult and pediatric patients. Asthma severity was not specified. The study reported that both the SCIT and SLIT arms had statistically significant improvement when comparing pre- and post-treatment scores and when compared to treatment with a combination inhaled steroid and short-acting bronchodilator (pre/post improvement in scores: SCIT 5.91, SLIT 4.29, control 4.27). However, the article did not report a direct comparison of ACT score for the SCIT to SLIT treatment groups.

The strength of evidence is insufficient to draw conclusions on the efficacy of SLIT versus SCIT on asthma symptoms.

Quality of Life

No SCIT versus SLIT studies that met inclusion criteria for this review reported on quality of life.

Medication Use

No SCIT versus SLIT studies that met inclusion criteria for this review reported on medication use.

Asthma Exacerbations

No SCIT versus SLIT studies that met inclusion criteria for this review reported on asthma exacerbations.

Health Care Utilization

No SCIT versus SLIT studies that met inclusion criteria for this review reported on health care utilization.

Pulmonary Physiology

One RCT of SCIT versus SLIT for HDM in comparison to medication alone reported pulmonary physiology outcomes in 90 mixed-aged patients in the form of PEF and FEV_1.[113] Asthma severity was not specified. The study reported that both the SLIT and SCIT arms had statistically significant improvement when comparing pre- and post-treatment PEF and FEV_1 and when compared to treatment with a combination inhaled steroid and short-acting bronchodilator. However, the study did not report a direct comparison of the SCIT to SLIT treatment groups for these pulmonary physiology measures. The strength of evidence is insufficient to draw conclusions on the efficacy of SLIT or SCIT of pulmonary function.

Airway Hyperresponsiveness

Methacholine Challenge. One HDM study including adults only reported methacholine challenge results in 90 patients treated with SCIT, SLIT aqueous immunotherapy, or placebo/pharmacotherapy.[112, 115] The study did not specify asthma severity. The study reported non-statistically-significant changes in AHR after treatment with 1 year of treatment in any of the groups. The publications did not report a direct comparison of results of those treated with SCIT with those treated with SLIT, nor was the specific data on the methacholine challenge values reported.

Allergen Challenge. One HDM study of mixed-age patients with mild persistent asthma reported bronchial provocation results with HDM after 1 year of treatment with SCIT (0.2-0.8 ml of 5000 TU/ml monthly), SLIT (28 drops of 100 TU/ml 3 times per week), or placebo. The total number of patients in this study was 32. There was a statistically significant improvement pre- versus post-treatment in the SCIT group only (P=0.003). However, when comparing SCIT to SLIT patients, there was no statistically significant difference in HDM bronchial provocation.[114]

Exercise Challenge. No SCIT versus SLIT studies that met inclusion criteria for this review reported on exercise challenge.

Immunological Outcomes

Four studies compared HDM-specific IgE levels between patients receiving SCIT versus SLIT.[112, 113, 115, 117] Two studies reported individual statistically significant decreases in HDM-specific IgE at baseline and after SCIT or SLIT compared with placebo.[113, 117]

Two RCTs reported HDM-specific IgG4 levels over 1 year comparing SCIT, SLIT, and placebo.[114, 115] One trial found that only SCIT was associated with an increase in HDM-specific IgG4 compared with either SLIT or SCIT.[114] Another RCT compared four groups: SCIT, SLIT, SCIT in addition to SLIT, and pharmacotherapy and reported HDM-specific IgG4 increases in only the SCIT and SCIT+SLIT groups when compared with pharmacotherapy alone.[115]

Safety of SCIT Versus SLIT

Local Reactions

Three of the five RCTs reported local reactions.[112, 113, 117] In two studies the incidence of reactions at the site of AIT application were comparable for SCIT and SLIT (13% vs. 10%)[112] and one out 30 patients presented grade 2 events in each arm.[113] Incidence was higher for SLIT in one study (oral itching was reported in only one of 16 patients in the SLIT arm)[117] and higher for SCIT in a second study (10 out 27 patients receiving SCIT presented Grade 1 events compared to 3 out of 30 receiving SLIT).[113] (See Appendix H.)

Systemic Allergic Reactions

Four of five RCTs reported systemic events.[112, 113, 115, 117] Respiratory symptoms were reported only for SCIT,[112, 115, 117] with an incidence ranging from 6 to 18 percent (1 or 2 patients). Gastrointestinal events (mild nausea) were reported for only one patient receiving SLIT.[112] One study reported events as unspecified systemic allergic reactions; events were higher for SCIT than SLIT (2 patients vs. 1 out of 30 in each arm).[113] (See Appendix H.)

Anaphylaxis

One study reported a case of anaphylactic reaction to SCIT therapy. One out of 16 patients receiving SCIT presented flushing, wheezing, and dyspnea requiring adrenaline, and required treatment discontinuation. All patients receiving SLIT (n=16) and pharmacotherapy (n=16) were able to complete the study.[117]

Safety in Non-RCTs

We included one case series that compared SCIT versus SLIT.[118] It reports on two cases of adolescents (14 years of age and 13 years of age) receiving SCIT, who presented painful local reactions at the site of injection, significant enough to discontinue therapy. The patients were started on SLIT looking for a better safety profile. However, neither of these patients tolerated treatment; they both developed respiratory reactions and asthma worsening. Both patients required treatment discontinuation. (See Appendix H.)

Death

No deaths were reported in any of the studies evaluated.

See Table 7 for details.

Table 7. Summary of the strength of evidence for SCIT versus SLIT

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Asthma Symptoms: ACT	1 RCT[113] N=90	Medium	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Quality of Life: AQLQ	No studies	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Medication Use	No studies	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Health care Utilization	No studies	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology: FEV1	1 RCT[113] N=90	Medium	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Anaphylaxis	1 RCT[117] N=16	Low	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Death	No studies	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient

FEV_1= Forced Expiratory Volume

Discussion

In this systematic review addressing the efficacy and safety of SCIT and SLIT in the treatment of allergic asthma, we identified a total of 61 RCTs and 29 non-RCTs. Of those studies focusing on SCIT only, there were 31 RCTs focused on efficacy and 44 articles reporting data on the safety of SCIT. Patients in the included SCIT studies had mild to moderate asthma in most studies. However, in many studies the diagnosis of asthma was not specified and, in the majority, the status of asthma control prior to treatment with SCIT was not specified. Several studies described an accelerated SCIT protocol.

For asthma related outcomes, our current report abstracted data exclusively from RCTs, with 31 studies of the efficacy of SCIT meeting inclusion criteria. Of the SCIT asthma outcomes that were the focus of our current report, we found moderate strength of evidence that SCIT reduces the need for long-term control medications. We also found that SCIT may improve quality of life, reduce the use of quick-relief medication, reduce the need for systemic corticosteroids, and improve FEV_1 (low SOE). We found insufficient evidence to make conclusions about the effect of SCIT on asthma symptoms, and for health care utilization. Overall, our systematic review found that SCIT was beneficial for the majority of asthma-related outcomes assessed in this report.

Regarding adverse reactions to SCIT, we found that local reactions are frequent, occurring in up to one-third of patients receiving AIT injections; however, reactions also commonly occurred with placebo injections in more than one-tenth of patients but infrequently required a change in the SCIT dosing. Systemic allergic reactions to SCIT are relatively common and were reported in up to 33 percent of adult patients. Seldom were reactions consistent with anaphylaxis requiring treatment with injectable epinephrine (of the total 180 systemic allergic reactions reported in RCTs, we determined that six cases were consistent with anaphylaxis and there was one case reported from the 165 reported in the non-RCTs.) SCIT in patients with asthma generally has a favorable safety profile; however, our review found that systemic allergic reactions do occur, some of which require treatment with injectable epinephrine. According to published practice guidelines, it is essential that patients in these studies are carefully monitored in a medically supervised setting where a trained allergist and appropriate emergency equipment are immediately available to recognize and treat systemic allergic reactions.[119, 120]

The efficacy of SLIT for asthma was assessed in 18 RCTs. Similar to the SCIT articles identified in our report, the patients in the SLIT studies generally had mild to moderate asthma. In several SLIT efficacy studies that were included in our review, the diagnosis of asthma and asthma control prior to treatment was not clearly stated. We found high strength of evidence that SLIT reduces asthma symptom outcomes. There was moderate grade evidence for the benefit of SLIT in reducing the use of long-term control medications (inhaled corticosteroids) and improving FEV_1. SLIT may also reduce the need for quick-relief medication and improve disease-specific quality of life (low SOE). There was insufficient evidence to draw conclusions on the effect of SLIT on systemic corticosteroid use and health care utilization. Overall, our systematic review finds SLIT beneficial for the majority of asthma-related outcomes included in this systematic review.

We found that local adverse events were common with use of SLIT, occurring in up to 40 percent of patients, but that systemic and life-threatening events were reported in only a few studies. Recent alterations in grading of systemic versus local reactions, with a more liberal definition of systemic allergic reactions prior to the 2017 World Allergy Organization (WAO) update,[121] may lead to an overestimation of systemic allergic reactions. It is important to note that all reported anaphylaxis events (3 case reports) occurred in patients receiving multiple-allergen therapy, perhaps signaling that this form of therapy poses higher risk for systemic adverse effects.[122] Furthermore, the rate of adverse events did not show a consistent relationship with SLIT dose. Of note, the package insert for SLIT tablets approved by the FDA does recommend that an epinephrine auto-injector device be prescribed for patients taking

SLIT tablets,[123] and this is supported by our systematic review, which found systemic reactions can occur with SLIT.

Our current systematic review is the most up-to-date evidence report on the efficacy of AIT for asthma. Our current findings are consistent with our prior JHU EPC evidence report and other prior systematic reviews and support the efficacy of SCIT and SCIT for asthma in the allergic patient. The Cochrane review of SCIT concluded that it resulted in significant reduction in asthma symptoms and the need for asthma medications, as well as improvement in allergen-specific bronchial hyper-reactivity.[8] Our prior evidence report similarly concluded that there was high strength of evidence that SCIT reduces asthma symptoms and medication use.[10] Both of these reviews noted the significant heterogeneity between the studies, as we found. In contrast, we could not draw conclusions about the effect of SCIT on asthma symptoms, as we limited our review to studies that used validated tools to measure asthma symptoms and identified none. A 2015 Cochrane review found there was low quality evidence supporting the use of SLIT in changing ICS use and very low quality evidence regarding bronchial provocation.[9] This Cochrane review further noted that the largely non-validated asthma symptom scores, medications scores, and available data for quality of life precluded meaningful synthesis of these outcomes. Our prior evidence report examined SLIT in aqueous form only, and concluded that SLIT reduced asthma symptoms.[10] This review expanded our scope to consider SLIT in tablet form and came to similar conclusions.

Limitations

We found considerable heterogeneity in the outcomes reported, and in the measurement of outcomes, that precluded quantitative pooling of the data. Many studies did not report relevant statistical information on continuous variables (such as confidence interval, standard deviation, and standard error) and some studies did not report results between arms, also limiting our ability to synthesize the evidence. We found considerable heterogeneity in the outcomes reported, and in the measurement of outcomes, that precluded quantitative pooling of the data. Many studies did not report relevant statistical information on continuous variables (such as confidence interval, standard deviation, and standard error) and some studies did not report results between arms, also limiting our ability to synthesize the evidence. While heterogeneity of study methods and outcome precluded quantitative meta-analysis, because the general mechanism of immunotherapy is the same across targeted allergens, we pooled these results qualitatively. In addition, it was not feasible to make direct comparisons between different allergen targets due to insufficient data and lack of studies for specific allergens.

It was a challenge to align some study findings with the age categories defined in asthma guidelines. National asthma guidelines recommend distinct treatment for children 5 to 11 years of age and consider treatments for children 12 years of age and older to be the same as for adults. When we evaluated studies that included children and youth (i.e., younger than 18 years of age) we found very few studies had set enrollment criteria to restrict populations that would fit neatly into either of the groups defined by the guidelines. Furthermore, data were not reported in the studies to allow abstraction of subgroups that fit distinctly into these categories. Thus, a study that enrolled, for example, patients between 5 to 15 years of age would have findings relevant to both age groups (5 to 11 years of age and 12 years of age and older); for the purposes of this review, these studies were reported as mixed-age groups. As a result, there was some information that could inform the overall question of immunotherapy efficacy but could not be used in subgroup analyses of children only or adults only.

We found extreme variability in the dosing and treatment schedules from study to study. The doses were reported in varying units (e.g., BU, IR, SQ-U, micrograms, BAU, STU, etc.). Some studies used conventional schedules; some studies used rush or ultra-rush schedules. These variations made it very

hard to compare outcomes across studies. In several studies, major allergen content was not reported and the study length varied from weeks to months. There was also variability from study to study in the use of standardized and non-standardized allergens. In addition, almost all of the SCIT and SLIT studies were performed using a single allergen; therefore, we were unable to perform an analysis of multi-allergen immunotherapy.

There was much variability across studies in methods and criteria used for asthma diagnosis, as well as grading of asthma severity and control status. Also, some studies did not provide information about baseline asthma severity or control. These issues may affect the ability to generalize the findings to certain patients with asthma and limited our ability to determine whether asthma health status at the beginning of treatment affects the observed outcomes.

Unfortunately, there were some studies of SLIT and SCIT that could not be included in the analysis, either because validated measures of outcomes were not used (e.g., use of a non-standardized "symptom score" or "medication score"), or because patients without asthma were also included in the study but results were not presented separately for those with asthma. For example, some studies enrolled patients with allergic rhinitis and/or asthma which did not allow us to assess the impact of immunotherapy specifically on asthma.

We tried to grade all adverse events using the WAO classification; however, many descriptions of the reactions (or the lack of description) significantly limited our ability to classify the adverse events. Studies reporting adverse events used different grading systems, no formal grading system at all, and, in some cases, no descriptions of events: this made classification difficult for both SCIT and SLIT. All the studies included were published before the most recent WAO classification,[121] and even before the initial 2010 grading system;[124] therefore, classification of what was considered as local or systemic events and severity differed greatly, and may lead to overestimation or underestimation of events.

Only a small number of articles described some of the systemic reactions as "anaphylactic" reactions. However, upon review of the systemic allergic reactions described, several of these reactions would be consistent with anaphylaxis, based on the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) criteria for diagnosis of anaphylaxis.[125]

Applicability

The results of this review are applicable to patients with inhalant allergy (as confirmed by skin or allergen specific in vitro testing) and asthma treated with allergen-specific immunotherapy. Most studies were performed in adults or mixed-aged populations, with merely 12 studies of children only. For some outcomes in this report, a limited number of allergens were studied. The applicability of results to allergens that have not been studied is unclear. Almost all trials used a single allergen for immunotherapy; therefore, we cannot comment on the comparative effectiveness of multiple-allergen immunotherapy. These studies were done almost exclusively in patients with mild to moderate persistent asthma, with a paucity of studies in those with severe persistent asthma. The dose and duration of treatment varied considerably in these studies. Half of the studies were with HDM allergen (46 of the 89 studies); the number of studies of other allergens that met inclusion criteria for this review were limited or very diverse. Many of the studies were performed with extracts manufactured outside of the United States and subject to different standardization methods; therefore, caution does need to be applied when considering the applicability of our results to allergens that have undergone different standardization processes.

Future Research Needs

We were limited in our ability to synthesize results owing to lack of studies for specific populations, interventions, and outcomes; substantial heterogeneity; and limited reporting. We detail below specific areas for future research.

Population

- The overwhelming majority of studies that met inclusion criteria for this review included patients with mild to moderate asthma; there is a need to investigate the safety and efficacy of immunotherapy in patients with severe asthma.
- Not all studies provided information about asthma severity or control of study patients. Because severity and control are potentially important modifiers of treatment effect, studies are needed that clearly report the severity and control of enrolled patients.
- There were few studies conducted in children only, and few studies of all ages that reported outcomes for children separately. To inform asthma treatment guidelines, investigators should consider including only children 5 to 11 years of age in studies, or, if a broader age is studied, reporting separately findings on children 5 to 11 years of age and older.

Intervention and Comparison

- There is a specific need for studies investigating the efficacy and safety of multiple-allergen regimens for SCIT or SLIT. Multiple-allergen treatment is frequently used in the United States, but most of the studies include single-allergen regimens. There is increasing discussion in the scientific community about the clinical use and efficacy of single-allergen versus multiple-allergen therapy, and there is a lack of studies which compare these head-to-head.
- For both SCIT and SLIT, additional studies are needed to assess compliance/adherence, and the effect compliance may have on management.
- Immunotherapy dosing quantity, frequency, and formulation varied substantially and details were often lacking. Standardized methods and reporting of therapy would be helpful.
- Most studies we identified were of HDM allergen; additional studies of the efficacy of SCIT or SLIT treatment with other allergens would be useful.

Outcomes

- For both SCIT and SLIT, studies are needed that address health care utilization.
- Many studies used non-validated scoring of outcomes. For instance, we found no trials of SCIT that assessed asthma symptoms using a validated tool. Future studies would benefit from standardized methods and validated instruments to report outcomes such as asthma symptoms and adverse events.

Conclusion

SCIT reduces the need for long-term control medication and may improve asthma-specific quality of life, use of quick-relief medications, systemic corticosteroids use, and FEV_1. SLIT improves asthma symptoms, reduces long-term control medication use, improves disease-specific quality of life, and may reduce the need for quick-relief medication and improve FEV_1. Local and systemic allergic reactions to SCIT and SLIT are common but infrequently required changes in treatment. Life-threatening events (such as anaphylaxis) are reported rarely. There is insufficient evidence on the comparative effectiveness of SCIT versus SLIT or for differential effects by patient age, type of allergen, or setting.

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Appendix A. Detailed Electronic Database Search Strategies

PubMed
(immunotherapy[mesh] OR immunotherap*[tiab]) AND (asthma[mh] OR asthma[tiab]) NOT (“occupational diseases” [mh]) NOT (animals[mh] NOT humans[mh])

1. immunotherapy [mh]
2. immunotherap*[tiab]
3. 1 OR 2
4. asthma [mh]
5. asthma [tiab]
6. 4 OR 5
7. “occupational diseases” [mh]
8. 6 NOT 7
9. 3 AND 8
10. (animals[mh] NOT humans[mh])
11. 9 NOT 10
12. 11 AND (2005 to present [date-publication]

Embase
(‘immunotherapy’/exp OR immunotherapy) AND (‘asthma’/de OR asthma)

1. ‘immunotherapy’/exp OR immunotherapy
2. ‘asthma’/de OR asthma
3. 1 AND 2
4. 3 AND (2005 to present)

Cochrane Central Register of Controlled Trials (CENTRAL)
"immunotherapy" AND "asthma" in Title, Abstract, Keywords, Publication Year from 2005 to 2017 in Trials'

Appendix B. Glossary and List of Definitions

Glossary

AIT	Allergen Immunotherapy
SCIT	Subcutaneous Immunotherapy
SLIT	Sublingual Immunotherapy
µg	microgram
BU	Biological units
SQU	Standard quality units
PNU	Protein Nitrogen Unit
AU	Allergy unit
Ag/ml	major protein unit; Antigen per ml
TU	Treatment units
wt/vol	Weight to volume
SE	Specific units of short-term immunotherapy
IR	Index of reactivity unit
ACT	Asthma Control Test
ACQ	Ashtma Control Questionnaire
P-ACT	Pediatric- Asthma Control Test
QOL	Quality of life
AQLQ	Asthma Quality of Life Questionnaire
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
PEF	Peak Expiratory Flow Rate
Ig	Immunoglobulin

List of Definitions

Objective Tests

a) Spirometry (FEV1;FVC;FEV1/FVC ratio)
b) PEF [peak expiratory flow rate]: as opposed to formal spirometry (which is performed in a physician's office), the patient can use a home peak flow meter (hand-held device) to check his/her peak flow readings on a regular basis.
c) Methacholine challenge: research tool in which a chemical irritant substance is inhaled into the airways in a controlled fashion to induce asthma symptoms. It can be used to diagnose asthma, characterize the severity of asthma, and/or assess the patient's response to treatment.
d) Allergen challenge testing: research tool in which allergen is introduced into the airways in a controlled fashion to reproduce allergen-induced asthma symptoms and characterize the patient's allergic response and response to treatment.

e) Exercise challenge: research tool in which intense exercise is used to trigger asthma symptoms, spirometry tests before and after to provide evidence of exercise-induced bronchoconstriction.

a) Medications Long term control medications: Long term control medications are used daily to achieve and maintain control of persistent asthma. The most effective are those that attenuate the underlying inflammation characteristic of asthma. Long term control medications include corticosteroids, cromolyn sodium and nedocromyl, immunomodulators, leukotriene modifiers, long-acting bronchodilators and methylxanthines. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf

b) Quick-relief medication: Quick-relief medications are used to treat acute symptoms and exacerbations. They include the following: short-acting beta agonists (SABA), anticholinergics and systemic corticosteroids. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf

c) Systemic corticosteroids: There are potent anti-inflammatory medications, usually used in oral forms, for treatment of asthma. They can be used in the short term for quick relief or long term as long term control medications. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf

d) Placebo: Any dummy medication or treatment. Although placebos originally were medicinal preparations having no specific pharmacological activity against a targeted condition, the concept has been extended to include treatments or procedures, especially those administered to control groups in clinical trials in order to provide baseline measurements for the experimental protocol. https://www.drugs.com/article/placebo-effect.html

Medications for asthma care

https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report

a) Corticosteroids: anti-inflammatory medications that reduce airway hyperresponsiveness, inhibit inflammatory cell migration and activation, and block late phase reaction to allergen
   i. Inhaled corticosteroid (ICS): beclomethasone dipropionate (QVAR, Vanceril, Beclovent)), budesonide (Pulmicort), flunisolide (Aerobid), mometasone, fluticasone propionate (Flovent), triamcinolone acetonide (Azmacort)
   ii. Systemic corticosteroids: Prednisone, Prednisolone (Prelone, Pediapred), Methylprednisolone (Medrol, Solu-Medrol), Triamcinolone (Kenalog).

b) Leukotriene antagonist (LTRA): A class of drugs designed to prevent leukotriene synthesis or activity by blocking binding at the receptor level. Montelukast (Singulair), zafirlukast (Accolate), zileuton (Zyflo)

c) $Beta_2$ agonists; Inhaled bronchodilators that relax smooth muscle.
   i. Short acting beta agonists (SABAs) - duration of bronchodilation of less than 12 hours after a single dose; albuterol, levalbuterol, pirbuterol.
   ii. Long acting beta agonist (LABAs) – duration of bronchodilation of at least 12 hours after a single dose; salmeterol and folmoterol

d) Cromolyn (Cromolyn sodium): A chromone complex that acts by inhibiting the release of chemical mediators from sensitized mast cells. It is used in the prophylactic treatment of

both allergic and exercise-induced asthma, but does not affect an established asthmatic attack.

e) Anticholinergics: Inhibit muscarinic cholinergic receptors and reduce vagal tone in the airway. Ipatropium is used as an alternative to SABAs or as added treatment.
f) Methylxantines: bronchodilators that relax smooth muscle. Sustained-release theophylline is a mild to moderate bronchodilator used as adjunctive therapy.
g) Immunomodulators: Omalizumab is an anti-IgE monoclonal antibody, therefore it prevents binding of IgE to its receptor in basophils and mast cells (prevents sensitization)

Efficacy measures

a) Asthma symptoms: Recorded self-assessment of asthma signs and symptoms through validated scores. Validated scores included in this review are ACT, ACQ and P-ACT http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/act.php
b) Medication use: Need of daily medications. Reduction in long term control medication and quick relief medication.
c) Quality of life (QOL): Asthma Quality of Life Questionnaire (AQLQ): There are 32 questions in the AQLQ addressing 4 domains (symptoms, activity limitation, emotional function and environmental stimuli). The activity domain contains 5 'patient-specific' questions. This allows patients to select 5 activities in which they are most limited and these activities will be assessed at each follow-up. Patients are asked to think about how they have been during the previous two weeks and to respond to each of the 32 questions on a 7-point scale (7 = not impaired at all - 1 = severely impaired). The overall AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. (Includes strenuous activities (such as hurrying, exercising, running upstairs, sports), moderate activities (such as walking, housework, gardening, shopping, climbing stairs), social activities (such as talking, playing with pets/children, visiting friends/relatives), work-related activities, and sleeping. http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/aqlq.php

Mechanistic Terms

a) Immunoglobulins (Ig): Multi-subunit proteins which function in immunity. They are produced by B lymphocytes from the immunoglobulins genes. They are comprised of two heavy chains (immunoglobulins heavy chains) and two light chains (immunoglobulins light chains) with additional ancillary polypeptide chains depending on their isoforms. The variety of isoforms includes monomeric or polymeric forms, and transmembrane forms (B-Cell antigen receptors) or secreted forms (antibodies). They are divided by the amino acid sequence of their heavy chains into five classes; Immunoglobulin A (IgA), Immunoglobulin D (IgD), Immunoglobulins E (IgE), Immunoglobulin G (IgG), Immunoglobulin M (IgM), and various subclasses.
    - IgG: The major immunoglobulin isotype class in normal human serum. There are several isotype subclasses of IgG, for example, IgG1, IgG4, IgG2A, IgG2B.
    - IgE: An immunoglobulin associated with mast cells. Overexpression has been associated with allergic hypersensitivity.
    - All other immunologic parameters, such as T-Lymphocytes (Lymphocytes responsible for cell-mediated immunity), cytokines (IL4/IL5/IL10/etc, non-

antibody proteins that act as intercellular mediators) are not included as outcomes in this review.

b) Sensitization: chain of cellular responses to induce an allergic response to a specific allergen. The allergen causes a chain of immunological responses; development of specific B and T cells, differentiation and clonal expansion of specific T-helpers and production of cytokines, with final induction of IgE production, and demonstrating a positive allergy skin test or positive specific IgE testing to that allergen. http://www.nature.com/nri/journal/v6/n10/fig_tab/nri1934_F1.html
    - Monosensitized: Patients who tested positive to only one allergen (or one family of related allergens) after being tested with a panel of allergens
    - Polysensitized: Patients who tested positive to multiple allergens after being tested with a panel of allergens

Safety terms

http://osp.od.nih.gov/sites/default/files/resources/Reporting_Guidelines.pdf

a) Adverse events (AE): An injury caused by medical management–rather than by the underlying disease–which prolongs hospitalization, produces a disability, or both. Etiology: Drug effects, wound infections, technical complications, negligence, diagnostic mishaps, therapeutic mishaps, and events occurring in the emergency room.
b) An adverse event is any undesirable experience associated with the use of a medical product in a patient. (Food and Drug Administration, 2009: http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm)
c) Serious adverse events (SAE): The event is serious and should be reported when the patient outcome is: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, or requires intervention to prevent permanent impairment or damage. (Food and Drug Administration, 2009)
d) When a particular condition causes the immune system to overreact, it is referred to as hypersensitivity reaction that triggers the production of IgE. These reactions may be damaging, uncomfortable, or occasionally fatal. https://www.aaaai.org/conditions-and-treatments/conditions-dictionary/hypersensitivity-reactions
e) Anaphylaxis: An acute hypersensitivity reaction (Type I IgE mediated allergic immediate reaction) due to exposure to a previously encountered antigen. The reaction may include rapidly progressing urticaria, respiratory distress, vascular collapse, systemic shock, and death. http://www.worldallergy.org/professional/allergic_diseases_center/anaphylaxis/anaphylaxissynopsis.php

Appendix C. List of Excluded Articles

Immunotherapy tablets improve asthma control in patients with dust mite sensitisation. Clinical Pharmacist. 2016;8(6).
No original data

Aasbjerg K, Dalhoff KP, Backer V. Adverse Events During Immunotherapy Against Grass Pollen-Induced Allergic Rhinitis - Differences Between Subcutaneous and Sublingual Treatment. Basic and Clinical Pharmacology and Toxicology. 2015;117(2):73-84.
No original data

Abbas AR, Jackman JK, Bullens SL, et al. Lung gene expression in a rhesus allergic asthma model correlates with physiologic parameters of disease and exhibits common and distinct pathways with human asthma and a mouse asthma model. Am J Pathol. 2011 Oct;179(4):1667-80. doi: 10.1016/j.ajpath.2011.06.009. PMID: 21819959.
Study is about efficacy but does not have a comparator group or is not an RCT; Does not apply to any key question

Abreu C, Resende I, Cunha L, et al. Eosinophilic esophagitis and profilin allergy. Allergy: European Journal of Allergy and Clinical Immunology. 2016;71((Abreu C.; Resende I.; Cunha L.; Falcão H.) Imunoalergology, Centro Hospitalar do Porto, Porto, Portugal):633.
Abstract – conference proceeding

Acquistapace F, Agostinis F, Castella V, et al. Efficacy of sublingual specific immunotherapy in intermittent and persistent allergic rhinitis in children: an observational case-control study on 171 patients. The EFESO-children multicenter trial. Pediatr Allergy Immunol. 2009 Nov;20(7):660-4. doi: 10.1111/j.1399-3038.2009.00860.x. PMID: 19320852.
Not allergic asthma

Adamic K, Zidarn M, Bajrovic N, et al. The local and systemic side-effects of venom and inhaled-allergen subcutaneous immunotherapy. Wien Klin Wochenschr. 2009;121(9-10):357-60. doi: 10.1007/s00508-009-1172-0. PMID: 19562302.
Mixed population; Not allergic asthma

Agache I, Ciobanu C. Risk factors and asthma phenotypes in children and adults with seasonal allergic rhinitis. Phys Sportsmed. 2010 Dec;38(4):81-6. doi: 10.3810/psm.2010.12.1829. PMID: 21150146.
Not allergic asthma; Does not apply to any key question

Agostinis F, Foglia C, Bruno ME, et al. Efficacy, safety and tolerability of sublingual monomeric allergoid in tablets given without up-dosing to pediatric patients with allergic rhinitis and/or asthma due to grass pollen. Eur Ann Allergy Clin Immunol. 2009 Dec;41(6):177-80. PMID: 20128231.
Mixed population – does not report asthma patients separately

Agostinis F, Foglia C, Landi M, et al. The safety of sublingual immunotherapy with one or multiple pollen allergens in children. Allergy. 2008 Dec;63(12):1637-9. doi: 10.1111/j.1398-9995.2008.01742.x. PMID: 19032238.
Mixed population – does not report asthma patients separately

Agostinis F, Tellarini L, Canonica GW, et al. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. Allergy. 2005 Jan;60(1):133. doi: 10.1111/j.1398-9995.2004.00616.x. PMID: 15575951.
Other: Survey data on safety

Ahmetaj LN, Mehic B, Gojak R. Prospective and comparative clinical study of blood risk factors in patients with allergic asthma on immunotherapy. Allergy: European Journal of Allergy and Clinical Immunology. 2016;71((Ahmetaj L.N.) Department of Allergology-Immunology, Medical Faculty, University Clinical Center of Kosova, Prishtina, Albania):335.
Study is about efficacy but does not have a comparator group or is not an RCT

Ajduk J, Marinic I, Aberle N, et al. Effect of house dust mite immunotherapy on transforming growth factor beta1-producing T cells in asthmatic children. Ann Allergy Asthma Immunol. 2008 Apr;100(4):314-22. doi: 10.1016/s1081-1206(10)60592-3. PMID: 18450115.
Study is about efficacy but does not have a comparator group or is not an RCT

Akmanlar N, Altintas DU, Guneser KS, et al. Comparison of conventional and rush immunotherapy with der PI in childhood respiratory allergy. Allergol Immunopathol (Madr). 2000 Jul-Aug;28(4):213-8. PMID: 11022267.

Mixed population – does not report asthma patients separately

Aksoy F, Yildirim YS, Veyseller B, et al. Serum levels of advanced oxidation protein products in response to allergen exposure in allergic rhinitis. Ear Nose Throat J. 2012 Aug;91(8):E32-5. PMID: 22930093.
Not allergic asthma

Al-Asad K, Al-Nazer S, Al-Faqih A, et al. Evaluation of a sublingual immunotherapy solution in olive-induced respiratory allergy in Jordan: a retrospective observational study. J Asthma Allergy. 2017;10:23-30. doi: 10.2147/jaa.s96153. PMID: 28280371.
Mixed population – does not report asthma patients separately

Alexander C, Tarzi M, Larche M, et al. The effect of Fel d 1-derived T-cell peptides on upper and lower airway outcome measurements in cat-allergic subjects. Allergy. 2005 Oct;60(10):1269-74. doi: 10.1111/j.1398-9995.2005.00885.x. PMID: 16134993.
Does not include SCIT or SLIT

Alvarez-Cuesta E, Berges-Gimeno P, Gonzalez-Mancebo E, et al. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study. Allergy. 2007 Jul;62(7):810-7. doi: 10.1111/j.1398-9995.2007.01365.x. PMID: 17573730.
Mixed population – does not report asthma patients separately

Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, et al. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. J Allergy Clin Immunol. 1994 Mar;93(3):556-66. PMID: 8151058.
Mixed population – does not report asthma patients separately

Amar SM, Harbeck RJ, Sills M, et al. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. J Allergy Clin Immunol. 2009 Jul;124(1):150-6 e1-5. doi: 10.1016/j.jaci.2009.04.037. PMID: 19523672.
Mixed population – does not report asthma patients separately

Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol. 2006 Jan;117(1):169-75. doi: 10.1016/j.jaci.2005.10.010. PMID: 16387602.
Mixed population – does not report asthma patients separately

Angelini F, Pacciani V, Corrente S, et al. Dendritic cells modification during sublingual immunotherapy in children with allergic symptoms to house dust mites. World J Pediatr. 2011 Feb;7(1):24-30. doi: 10.1007/s12519-011-0242-3. PMID: 21191773.
Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population – does not report asthma patients separately

Anolik R, Schwartz AM, Sajjan S, et al. Patient initiation and persistence with allergen immunotherapy. Ann Allergy Asthma Immunol. 2014 Jul;113(1):101-7. doi: 10.1016/j.anai.2014.04.008. PMID: 24814759.
Does not apply to any key question; Mixed population – does not report asthma patients separately

Antico A, Pagani M, Crema A. Priming-like effect and successful desensitization after anaphylactic shock by latex sublingual immunotherapy. Eur Ann Allergy Clin Immunol. 2007 Oct;39(8):259-61. PMID: 18237003.
Food allergy/aeroallergen not related to asthma; Other: latex slit

Antolín-Amérigo D, Rodríguez-Rodríguez M, Barbarroja-Escudero J, et al. Factors related to adverse reactions in SCIT cluster initiation schedules. Allergy: European Journal of Allergy and Clinical Immunology. 2016;71((Antolín-Amérigo D.; Rodríguez-Rodríguez M.; Barbarroja-Escudero J.; Sánchez-González M.J.; Belinchón-Moreno T.; Alvarez-Mon M.) Departamento de Medicina y Especialidades Médicas, Hospital Universitario Príncipe de Asturias, Universidad de Alcalá, Alcaláde Henares, Madrid, Spain):327-8.
Abstract – conference proceeding

Antolín-Amérigo D, Sánchez-González MJ, Barbarroja-Escudero J, et al. SCIT adherence after adverse reactions in cluster initiation schedules. Allergy: European Journal of Allergy and Clinical Immunology. 2016;71((Antolín-Amérigo D.; Sánchez-González M.J.; Barbarroja-Escudero J.; Belinchón-Moreno T.; Alvarez-Mon M.; Rodríguez-Rodríguez M.) Departamento de Medicina y Especialidades Médicas, Hospital Universitario Príncipe de Asturias, Universidad de Alcalá, Alcaláde Henares, Madrid, Spain):337-8.
No original data; Abstract

Antonova LP, Romanov VV, Averbakh MM. Experience with bronchomunal used in the combined treatment of patients with bronchial asthma and chronic obstructive pulmonary disease. Problemy tuberkuleza i bolezneĭ legkikh. 2008; (4), #Pages#

Does not include SCIT or SLIT

Ariano R, Incorvaia C, La Grutta S, et al. Safety of sublingual immunotherapy started during the pollen season. Curr Med Res Opin. 2009 Jan;25(1):103-7. doi: 10.1185/03007990802591673. PMID: 19210143.
Not allergic asthma

Ariano R, Panzani RC, Mistrello G. Efficacy of sublingual coseasonal immunotherapy with a monomeric allergoid in Cupressaceae pollen allergy--preliminary data. Eur Ann Allergy Clin Immunol. 2005 Mar;37(3):103-8. PMID: 15918297.
Mixed population – does not report asthma patients separately; Does not apply to any key question

Arvidsson MB, Lowhagen O, Rak S. Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. Allergy. 2004 Jan;59(1):74-80. PMID: 14674937.
Not allergic asthma

Astafieva N, Kobzev D, Gamova I, et al. Allergic sensitization to Cannabis ruderalis: Prevalence, clinical and immunologic characteristics, subcutaneous immunotherapy. Allergy: European Journal of Allergy and Clinical Immunology. Conference: 35th Annual Congress of the European Academy of Allergy and Clinical Immunology, EAACI 2016. Austria. Conference Start: 20160611. Conference End: 20160615; 2016. p. 173.
Abstract – conference proceeding

Aydogan M, Eifan AO, Keles S, et al. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomised trial. Respir Med. 2013 Sep;107(9):1322-9. doi: 10.1016/j.rmed.2013.06.021. PMID: 23886432.
Not allergic asthma

Bag O, Can D, Karaarslan U, et al. The long-term outcomes of persistent childhood allergic asthma: a cross-sectional study from western Anatolia: childhood persistent asthma in western Anatolia. Allergol Immunopathol (Madr). 2013 Sep-Oct;41(5):315-9. doi: 10.1016/j.aller.2012.05.008. PMID: 23137869.
Does not include SCIT or SLIT

Bahceci Erdem S, Nacaroglu HT, Karaman S, et al. Risk of systemic allergic reactions to allergen immunotherapy in a pediatric allergy clinic in Turkey. Int J Pediatr Otorhinolaryngol. 2016 May;84:55-60. doi: 10.1016/j.ijporl.2016.02.032. PMID: 27063754.
Mixed population – does not report asthma patients separately

Bahceciler NN, Arikan C, Taylor A, et al. Impact of sublingual immunotherapy on specific antibody levels in asthmatic children allergic to house dust mites. Int Arch Allergy Immunol. 2005 Mar;136(3):287-94. doi: 10.1159/000083956. PMID: 15722639.
Study is about efficacy but does not have a comparator group or is not an RCT

Baiardini I, Puggioni F, Menoni S, et al. Patient knowledge, perceptions, expectations and satisfaction on allergen-specific immunotherapy: a survey. Respir Med. 2013 Mar;107(3):361-7. doi: 10.1016/j.rmed.2012.11.004. PMID: 23218454.
Survey

Barasona Villarejo MJ, García Nuñez I, Moreno Aguilar C. Descriptive study of a population with two subcutaneous immunotherapy simultaneously. Allergy: European Journal of Allergy and Clinical Immunology. 2016;71((Barasona Villarejo M.J.; Moreno Aguilar C.) Allergology, Hospital Reina Sofía, Córdoba, Spain):333.
Abstract – conference proceeding

Bavishi AA, Grammer LC, Pongracic J, et al. Diurnal variations in subcutaneous allergen immunotherapy reactions. Ann Allergy Asthma Immunol. 2017 Jan;118(1):103-7. doi: 10.1016/j.anai.2016.10.007. PMID: 27864091.
Mixed population – does not report asthma patients separately; Does not apply to any key question

Beitia JM, Lopez-Matas MA, Alonso A, et al. Allergenic profile to Phleum pratense and immunological changes induced after grass allergen-specific immunotherapy. Int Arch Allergy Immunol. 2014;165(1):9-17. doi: 10.1159/000365866. PMID: 25277364.
Mixed population – does not report asthma patients separately

Ben Ameur S, Kamoun F, Ben Bey A, et al. Allergenic profile and control level in asthmatic children in Sfax. Revue Francaise d'Allergologie. 2016;56(7-8):509-14.
Does not include SCIT or SLIT

Bergmann KC, Okamoto Y, Ambroisine L, et al. Efficacy and safety of 300IR and 500IR doses of house dust mite sublingual immunotherapy tablet in subjects with house dust mite-associated allergic rhinitis in two phase II/III studies. Allergy: European

Journal of Allergy and Clinical Immunology. 2016;71((Bergmann K.-C.) Allergy-Centre-Charité, Berlin, Germany):341.
Abstract – conference proceeding

Bernaola G, Corzo JL, Dominguez-Ortega J, et al. Sublingual immunotherapy: factors influencing adherence. J Investig Allergol Clin Immunol. 2012;22(6):458-9. PMID: 23101200.
Does not apply to any key question

Bernardini R, Campodonico P, Burastero S, et al. Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study. Curr Med Res Opin. 2006 Aug;22(8):1515-22. doi: 10.1185/030079906x115711. PMID: 16870076.
Not allergic asthma; Other: latex

Bernstein DI, Murphy KR, Nolte H, et al. Efficacy of short-ragweed sublingual immunotherapy tablet MK-3641 in monosensitized and polysensitized subjects. Allergy, Asthma and Clinical Immunology. 2014;10(2).
Not allergic asthma

Berto P, Passalacqua G, Crimi N, et al. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. Ann Allergy Asthma Immunol. 2006 Nov;97(5):615-21. PMID: 17165269.
Study is about efficacy but does not have a comparator group or is not an RCT; Other: retrospective

BilgiçEltan S, Keskin O, Kücükosmanoglu E, et al. Gaziantep university clinic of pediatric allergy specific immunotherapy in patients with multiple allergen frequency and multiple allergen immunotherapy. Allergy: European Journal of Allergy and Clinical Immunology. 2016;71((BilgiçEltan S.; Keskin O.; Kücükosmanoglu E.; Karakus H.; Sonmez S.) Pediatric Allergy Immunology, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey):334.
Not allergic asthma

Blaiss M, Maloney J, Nolte H, et al. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol. 2011 Jan;127(1):64-71, e1-4. doi: 10.1016/j.jaci.2010.11.034. PMID: 21211642.
Mixed population – does not report asthma patients separately

Blume SW, Yeomans K, Allen-Ramey F, et al. Administration and Burden of Subcutaneous Immunotherapy for Allergic Rhinitis in U.S. and Canadian Clinical Practice. J Manag Care Spec Pharm. 2015 Nov;21(11):982-90. doi: 10.18553/jmcp.2015.21.11.982. PMID: 26521110.
Other: no safety data and not an RCT

Bouchaud G, Braza F, Chesne J, et al. Prevention of allergic asthma through Der p 2 peptide vaccination. J Allergy Clin Immunol. 2015 Jul;136(1):197-200 e1. doi: 10.1016/j.jaci.2014.12.1938. PMID: 25680456.
Animals or in vitro

Bozek A, Kolodziejczyk K, Bednarski P. The relationship between autoimmunity and specific immunotherapy for allergic diseases. Hum Vaccin Immunother. 2015;11(12):2764-8. doi: 10.1080/21645515.2015.1087627. PMID: 26431066.
Mixed population – does not report asthma patients separately

Bozek A, Kolodziejczyk K, Krajewska-Wojtys A, et al. Pre-seasonal, subcutaneous immunotherapy: A double-blinded, placebo-controlled study in elderly patients with an allergy to grass. Annals of Allergy, Asthma and Immunology. 2016;116(2):156-61.
Not allergic asthma

Bozek A, Kolodziejczyk K, Warkocka-Szoltysek B, et al. Grass pollen sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis. Am J Rhinol Allergy. 2014 Sep-Oct;28(5):423-7. doi: 10.2500/ajra.2014.28.4091. PMID: 25198030.
Mixed population – does not report asthma patients separately

Bozek A, Kozlowska R, Jarzab J. The safety of specific immunotherapy for patients allergic to house-dust mites and pollen in relation to the development of neoplasia and autoimmune disease: a long-term, observational case-control study. Int Arch Allergy Immunol. 2014;163(4):307-12. doi: 10.1159/000361022. PMID: 24776522.
Mixed population – does not report asthma patients separately

Buczylko K, van der Werf JF, Boot D, et al. Accelerated Up-Dosing of Subcutaneous Immunotherapy with a Registered Allergoid Birch Pollen Preparation. Int Arch Allergy Immunol. 2017 Apr 06;172(3):183-6. doi: 10.1159/000464103. PMID: 28380494.
Mixed population – does not report asthma patients separately

Bush RK, Swenson C, Fahlberg B, et al. House dust mite sublingual immunotherapy: results of a US trial. J Allergy Clin Immunol. 2011 Apr;127(4):974-81 e1-7. doi: 10.1016/j.jaci.2010.11.045. PMID: 21333346.

Not allergic asthma

Bussmann C, Maintz L, Hart J, et al. Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. Clin Exp Allergy. 2007 Sep;37(9):1277-85. doi: 10.1111/j.1365-2222.2007.02783.x. PMID: 17845407.
Mixed population – does not report asthma patients separately

Cadario G, Ciprandi G, Di Cara G, et al. Comparison between continuous or intermittent schedules of sublingual immunotherapy for house dust mites: effects on compliance, patients satisfaction, quality of life and safety. Int J Immunopathol Pharmacol. 2008 Apr-Jun;21(2):471-3. PMID: 18547495.
Not allergic asthma

Caimmi D, Barber D, Hoffmann-Sommergruber K, et al. Understanding the molecular sensitization for Cypress pollen and peach in the Languedoc-Roussillon area. Allergy. 2013 Feb;68(2):249-51. doi: 10.1111/all.12073. PMID: 23205629.
Does not include SCIT or SLIT

Calderon MA, Cox LS. Monoallergen sublingual immunotherapy versus multiallergen subcutaneous immunotherapy for allergic respiratory diseases: a debate during the AAAAI 2013 Annual Meeting in San Antonio, Texas. J Allergy Clin Immunol Pract. 2014 Mar-Apr;2(2):136-43. doi: 10.1016/j.jaip.2013.12.008. PMID: 24607039.
No original data

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No original data

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately; Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Not allergic asthma

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No original data; Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Not allergic asthma; Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Survey

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Does not apply to any key question; Mixed population – does not report asthma patients separately

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No original data; Abstract

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No original data

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Does not apply to any key question; No original data

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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No original data

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Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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No original data

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Not allergic asthma

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not apply to any key question

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No original data

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Other: does not evaluate outcomes of interest

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Not allergic asthma

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Other: not in English – could not get appropriate translation

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Not allergic asthma

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No original data; Abstract

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No original data

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Other: followup of eligible trial CAS

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Does not apply to any key question

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Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not apply to any key question

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Study is about efficacy but does not have a comparator group or is not an RCT

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Abstract – conference proceeding

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Type of immunotherapy not specified

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Mixed population – does not report asthma patients separately

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Does not include SCIT or SLIT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Not allergic asthma

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Abstract – conference proceeding

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No original data; Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Abstract – conference proceeding

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Abstract – conference proceeding

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Not allergic asthma

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Study is about efficacy but does not have a comparator group or is not an RCT

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Not allergic asthma

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Other: pooled data

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Abstract – conference proceeding

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Animals or in vitro

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Mixed population – does not report asthma patients separately

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Not allergic asthma

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Not allergic asthma

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Other: not an RCT – post hoc analysis of a previously excluded paper

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Mixed population – does not report asthma patients separately

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No original data

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Mixed population – does not report asthma patients separately

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Not allergic asthma

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not apply to any key question

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No original data

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Mixed population – does not report asthma patients separately

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No original data

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Not allergic asthma

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not include SCIT or SLIT

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No original data

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not include SCIT or SLIT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not apply to any key question

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Not allergic asthma

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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No original data

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Mixed population – does not report asthma patients separately

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Does not apply to any key question

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Mixed population – does not report asthma patients separately

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Mixed population – does not report asthma patients separately

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Study is about efficacy but does not have a comparator group or is not an RCT

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Animals or in vitro

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Abstract – conference proceeding

Appendix D. KQ1- What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

(Organization in tables first by population; adults-mixed population- children. Within each category by comparator SCIT vs placebo- SCIT vs pharmacotherapy- SCIT vs SCIT. Within each subcategory by allergen; HDM-grass- weed- trees- animal-multiple allergen)

Table D1 – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Garcia-Robaina, 2006[1] Gallego, 2010[2] Europe	SCIT Placebo	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Positive SPT IgE ≥ 2	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic
	Bousquet, 1985[3] France	SCIT Placebo	Asthma diagnosis criteria- pulmonary tests (reversible bronchoconstriction to B agonist or significant sensitivity to methacholine and positive BPT with Dp) Severity NS Control status NS (baseline FEV1 required to be within 20% predicted)	SPT and IgE Positive SPT (clinic specific) IgE RAST class 3-4	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic
	Ameal, 2005[4] Europe	SCIT Placebo	Asthma diagnosis criteria GINA Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Wheal size (10HEP)	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic
	Vidal, 2011[5] Europe	SCIT Placebo	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Wheal > 3mm; IgE ≥ class 2	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter)	Clinic
	Olsen, 1997[6] Europe	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE NS	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Kohno, 1998[7] Asia	SCIT Placebo	Asthma diagnosis criteria -Bronchial response to histamine Severity NS Control status -Controlled (no need of ICS)	SPT and IgE NS	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D far)	Single allergen Dust mite (D far)	Clinic
	Chakraborty, 2006[8] Asia	SCIT Placebo	Asthma diagnosis criteria NS Severity NS Control status NS	SPT and IgE wheal >3mm	Monosensitized Grass (P sylvestris)	Single allergen Grass (P sylvestris)	Not specified

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Creticos, 1996[9] US	SCIT Placebo	Asthma diagnosis criteria Methacholine challenge Severity moderate to severe Control status uncontrolled (dependent of ICS)	SPT NS	Monosensitized Ragweed	Single allergen Ragweed	Clinic
	Ohman, 1984[10] US	SCIT Placebo	Asthma diagnosis criteria- positive bronchial challenge to cat Severity NS Control status -Controlled (no need of ICS)	SPT NS	Mono vs Polysensitized unclear* All patients sensitized to cat	Single allergen Cat	Clinic
	Van Metre, 1988[11] US	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE SPT +2 IgE significant	Mono vs Polysensitized unclear* All patients sensitized to cat	Single allergen Cat	Clinic
	Garcia-Ortega, 1993[12] Europe	SCIT Pharmacotherapy	Asthma diagnosis criteria-- positive bronchial challenge to dust mite Severity NS Control status NS	SPT and IgE SPT NS IgE RAST class 2	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic
	Blumberga, 2011[13] Blumberga, 2006[14] Europe	SCIT HDM Placebo	Asthma diagnosis GINA criteria Severity moderate persistent Control status NS	SPT and IgE positive SPT (>3 mm) and allergen-specific IgE class 2	Polysensitized (72% of patients were sensitized to Timothy, 65% to dog, 52% to cat and 35% to birch pollen)	Single allergen Dust mite	Clinic
Mixed age	Wang, 2006[15] Asia	SCIT Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate Control status – Controlled (stable dose of ICS)	SPT and IgE NS	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic
	Maestrelli, 2004[16] Europe	SCIT Placebo	Asthma diagnosis criteria NS Severity mild to moderate per GINA Control status – NS (excluded if FEV1<70, 2+ asthma attacks in past 12m)	SPT and IgE SPT NS IgE class 3	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Ibero, 2006[17] Europe	SCIT Placebo	Asthma diagnosis per mild moderate criteria Severity mild and moderate Control status NS	SPT and IgE	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Van Bever 1992[18] Europe	SCIT Placebo	Asthma diagnosis criteria-(FEV >70%) Severity All severities Control status stable	SPT and IgE RAST	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D far)	Single allergen Dust mite (HDM)	Clinic
	Altintas,1999[19] Asia	SCIT vs SCIT vs Placebo	Asthma diagnosis criteria NS Severity Mild to moderate Control status – Poorly controlled	SPT and IgE	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D far)	Single allergen Dust mite (D pter)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Hill,1982[20] Australia	SCIT (rush) VS. Placebo	Asthma diagnosis criteria NS Severity NS Control status NS	SPT and IgE NS	Polysensitized and Monosenstized All patients sensitized to Grass (Rye) 18 patients also to Dust mite (D pter)	Single allergen Grass (Rye)	Clinic
	Valovirta, 1984[21] Valovirta, 2006[22] US	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE SPT +3 IgE class 2	Polysensitized Birch, Timothy, *Cladosporium*, HDM, cat	Single allergen Dog	Clinic
	Bousquet, 1988[23] France	SCIT Pharmacotherapy	Asthma diagnosis criteria- pulmonary tests (reversible bronchoconstriction to B2 and positive BPT) Severity NS Control status NS	SPT and IgE Positive SPT (clinic specific) IgE RAST class 3-4	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D far)	Single allergen Dust mite (D pter)	Clinic
	Baris, 2014[24] Asia	SCIT Pharmacotherapy	Asthma diagnosis GINA criteria (FEV changes) Mild and moderate Control status NS	SPT and IgE NS	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D far)	Single allergen Dust mite (HDM)	Clinic
	Kilic, 2011[25] Asia	SCIT Pharmacotherapy	Asthma diagnosis GINA criteria Severity Mild persistent and moderate persistent Control status NS	SPT > 3mm	Monosensitized Molds	Single allergen Molds *Alternaria*	Not specified
	Lozano, 2014[26] Europe	SCIT Pharmacotherapy	Asthma diagnosis NS Mild persistent and moderate persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic
	Zielen, 2010[27] Europe	SCIT Pharmacotherapy (ICS alone)	Asthma diagnosis criteria GINA Severity NS Well controlled	SPT and IgE SPT >5mm; IgE of class 2 or greater (10.7 kU/l)	Polysensitized pollen, animal, house dust mite (D pter-D far), and mold allergens	Single allergen Dust mite (D pter)	Clinic
	Pifferi, 2002[28] Europe	SCIT No treatment	Asthma diagnosis per doctor criteria Severity NS Control status NS	SPT SPT (EAACI)	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Dreborg, 1986[29] Europe	SCIT Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate Control status – Controlled (stable dose of ICS)	SPT and IgE SPT 2 + IgE RAST class 1 or greater	Monosensitized *Cladosporium*	Single allergen *Cladosporium*	Clinic
	Hui, 2014[30] Asia	SCIT OTHER (desensitization vaccine)**	Asthma diagnosis per Breathing Group of Pediatric Academy; Chinese Medical Association Mild persistent Control status NS	SPT and IgE SPT "positive" and/or allergen-specific IgE in serum (>0.35kUA/l)	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Not specified

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Arroabarren, 2015[31] Europe	SCIT SCIT (3 vs 5 y)	GINA criteria Mild persistent and moderate persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (D pter-D far) And Polysensitized (latex, food, tree, grass, weed, mold, cat, dog)	Single allergen Dust mite (D pter)	Clinic
Children	Adkinson, 1997[32] Limb, 2006[33] US	SCIT Placebo	Asthma diagnosis physician diagnosed Severity Moderate to severe Control status – Controlled (stable dose of ICS)	SPT and IgE	Polysensitized Dust mite (D pter -D far) Trees (white oak) Weeds (ragweed, English plantain), Grass (Grass mix, Bermuda grass) Molds (*Alternaria, Aspergillus, Cladosporium*)	Multiple allergens	Clinic
	Alzakar, 2010[34] Asia	SCIT Pharmacotherapy	Asthma diagnosis criteria GINA and EPR Excluded severe asthma Control status NS	SPT and IgE Wheal > 3mm; Allergen specific IgE of 0.35 EU/mL	Polysensitized *Alternaria, Cladosporium, Penicillium*, grass mix, feather mixture, dog, horse, cat, *Aspergillus, Fagacae, Betulaceae*, plantain, Bermuda grass, *Chenopodium*, mugwort, *Oleaceae* and dust mite (D pter-D far)	Multiple allergens	Clinic
	Tsai, 2010[35] Asia	SCIT Pharmacotherapy	Asthma diagnosis criteria GINA Severity moderate and severe persistent Control status NS	SPT and IgE Not specified	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic

SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified -Not described D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*

***** Authors did not report sensitization status

****** the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table D2 – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease
Adults	Garcia-Robaina, 2006[1] Gallego, 2010[2]	64	SCIT Placebo	24 +/- 9 24 +/- 8	47/53 37/63	32/5 32/5	NR
	Bousquet, 1985[3]	30	SCIT (Rush) Placebo	29 +/- 5 (Range 18-41) 27 +/- 6 (Range 19-42)	65/35 70/30	20/0 10/0	6.3 9.1
	Ameal, 2005[4]	63	SCIT Placebo	23 (14-48)	47/53	32/3 31/5	NR
	Vidal, 2011[5]	45	SCIT Placebo	26 (14-42) 28 (16-52)	57/43 58/42	21/2 24/1	NR
	Olsen, 1997[6]	31	SCIT Placebo	32 (Range 18-56) 40.7 (Range 22-64)	NR	NR	NR

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease
	Kohno, 1998[7]	16	SCIT Placebo	25.8 26.3	75/25 66/34	8/0 6/2	NR
	Chakraborty, 2006[8]	14	SCIT Placebo	32.22 32.59	NR	8/0 6/0	NR
	Creticos, 1996[9]	90	SCIT Placebo	36 +/- 10 35 +/- 10	51/49 50/50	37/8 53/16	At least 1
	Ohman, 1984[10]	17	SCIT Placebo	26 (Range 22-31) 30 (Range 24-48)	NR NR	9/0 8/0	NR
	Van Metre, 1988[11]	22	SCIT Placebo	Range 21-52 Range 21-52	N 5/6 N 5/6	11/1 11/0	NR
	Garcia-Ortega, 1993[12]	36	SCIT Pharmacotherapy	Range 13-45 Range 13-45	Entire study N 16/20	18/NR 18/NR	NR
	Blumberga, 2011[13] Blumberga, 2006[14]	54	SCIT HDM Placebo	29 +/- 11 28 +/- 7	42/58 39/61	26/6 28/6	14.8 14.1
Mixed age	Wang, 2006[15]	132	SCIT Placebo	Range 6-45	56/44 61/39	64/2 65/1	7.1 +/- 0.81 7.3 +/- 0.79
	Maestrelli, 2004[16]	95	SCIT Placebo	20 +/- 8 23 +/- 10	61/39 71/29	41/8 31/15	1
	Ibero, 2006[17]	30	SCIT Placebo	10 (8-15) 12 (8-16)	66/34 60/40	15/NR 15/NR	NR
	Van Bever, 1992[18]	18	SCIT Placebo	9 (7-11) 12 (8-22)	NR	9/0 9/2	NR
	Altintas,1999[19]	35	Aluminum Hydroxide SCIT Calcium Phosphate SCIT Aqueous SCIT Placebo	10.8 +/- 3.7 10.0 +/- 3.7 11 +/- 4 11 +/- 3	80/20 60/40 55/45 60/40	10/ NR 10/ NR 9/ NR 5/ NR	NR
	Hill,1982[20]	20	SCIT Placebo	Range 9-14 Range 9-14	Entire study 65/35	11/NR 9/NR	3 3
	Valovirta, 1984[21] Valovirta, 2006[22]	27	SCIT Placebo	11 (Range 5-18) 10.5 (Range 5-16)	60/40 58/42	15/0 12/0	NR
	Bousquet, 1988[23]	215	SCIT (Rush) Pharmacotherapy	24 +/- 13(Range 3-72) 24 +/- 11(Range 3-72)	Entire study 68.0/32.0	171/NR 44/NR	12 9.8
	Baris, 2014[24]	55	SCIT + Vit D SCIT alone Pharmacotherapy	9.2 +/- 2 8.8 +/- 1 7.9 +/- 3	38/62 47/53 50/50	17/0 15/0 18/0	NR
	Kilic, 2011[25]	24	SCIT Pharmacotherapy	10.1 +/- 2.2 (7-13) 10.1+/- 2.1 (8-14)	NR	12/3 12/5	NR
	Lozano, 2014[26]	43	SCIT Pharmacotherapy	Median 9 (6-12) Median 9 (6-12)	48/52 55/45	21/1 20/2	1
	Zielen, 2010[27]	66	SCIT Pharmacotherapy (ICS alone)	Median 9 (6-17) Median 11 (6-16)	66/34 69/31	33/0 33/4	2
	Pifferi, 2002[28]	29	SCIT Control	11 +/- 3 10 +/- 2	Entire Study 55/45	15/0 14/4	NR

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease
	Dreborg, 1986[29]	30	SCIT Placebo	11 (Range 5-17) 11 (Range 5-17)	NR	16/NR 14/NR	NR
	Hui, 2014[30]	90	SCIT Desensitization vaccine*	10.1 +/- 2.2 9.8 +/- 1.5	56/44 49/51	43/5 45/4	3.5
	Arroabarren, 2015[31]	63	5-year IT 3-year IT	9.26 (NR) 8.9 (NR)	NR	36/NR 27/NR	NR
Children	Adkinson, 1997[32]	121	SCIT Placebo	9 +/- 2 9 +/- 2	80/20 76/24	61/8 60/3	> 1 > 1
	Alzakar, 2010[34]	242	SCIT Pharmacotherapy	9.8 +/- 1.7 (7-12) 10 +/- 1.5 (7-12)	55/45 60/40	105/20 137/25	NR
	Tsai, 2010[35]	40	SCIT Pharmacotherapy	8.6 +/- 2.9 8.3 +/- 2.4	70/30 35/65	20/0 20/0	6 months

NR: Not reported * the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table D3 – Intervention Characteristics SCIT

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major Allergen Content	Duration of Treatment
Adults	Garcia-Robaina, 2006[1] Gallego, 2010[2]	SCIT Placebo	Both (B2 and ICS)	0.1, 0.3 and 0.5 ml weekly for 3 weeks and then 0.5 ml monthly	NR	Monthly for 12 months	35 µg /ml D. pter + 28 µg /ml D. far	54 weeks
	Bousquet, 1985[3]	SCIT Rush Placebo	NR	3000 BU (=to 0.1 ml of 1/100 w/v)	NR	Weekly	NR	7 weeks not clearly stated)
	Ameal, 2005[4]	SCIT Placebo	Only rescue (B2)	0.5 mL of 70 µg/mL	NR	Monthly	14.25 µg of Der p 1/ml and 8.61 of Der p 2	12 months
	Vidal, 2011[5]	SCIT Placebo	Both (NS)	0.8ml	NR	Monthly	4.8 µg DP1, 3.2 µg DP2	4 months
	Olsen, 1997[6]	SCIT dust mite alum-precipitated Placebo	Only rescue medication	100000 SQ-U (after 15 weeks)	NR	3 weeks for one dose; every 6 weeks thereafter	7 µg Der p 1 or 10 µg Der f 1	1 year
	Kohno, 1998[7]	SCIT dust mite Rush Bronchodilators	conventional therapy	0.15-0.30 ml of 1/10 wt/vol	NR	Weekly for 2 months then every 2 weeks for 6 months	1 mg dust mite extract = 9.8 ng of major allergens Der1 and Der2 (5.4 ng was *D far)*	6 months
	Chakraborty, 2006[8]	SCIT Placebo	NR	1:2500 wt/vol	NR	Conventional Weekly	0.5 µg	2 years
	Creticos, 1996[9]	SCIT Ragweed Placebo	Only rescue medication	0.5 mL of 1:10 dilution (actual mean dose in year = 4 µg of Amb a1)	NR	Every 2 weeks for 3 months thereafter every 4 weeks	10 µg of Amb a1	2 years

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major Allergen Content	Duration of Treatment
	Ohman, 1984[10]	SCIT Cat Placebo	NR	0.3 ml of extract containing 13 units of cat allergen 1per ml or 300 µg/ml of cat albumin)	10.9 units cat allergen or 272 µg of cat albumin	Weekly	13 units of cat allergen 1 U/ml or 300 µg /ml of cat albumin)	6 weeks
	Van Metre, 1988[11]	SCIT Cat Placebo	conventional therapy	1.0 mL of 4 .56 FDA units of Fel d 1 per mL.	NR	Biweekly	4 .56 FDA units of Fel d 1	At least 1 year
	Garcia-Ortega, 1993[12]	SCIT Dust mite Cluster Pharmacotherapy	conventional therapy (bronchodilators/ usual care)	100000 SQ	2000000 SQ	Every 15 days	NR	7 months
	Blumberga, 2011[13] Blumberga, 2006[14]	SCIT HDM Placebo	Both Salbutamol and ICS)	100000 SQ-U w 6 weeks	20 SQ-U	Conventional	0.01ug	3 years
Mixed age	Wang, 2006[15]	SCIT dust mite alum-precipitated Placebo	Only rescue medication	100000 SQ-U	NR	6 weeks	9.8 µg Der p1	1 year
	Maestrelli, 2004[16]	SCIT dust mite Placebo	conventional therapy	7 BU (adults) 6 BU (children)	NR	every 3 weeks	6 µg /ml major antigens Der1 + Der2)	3 years
	Ibero, 2006[17]	SCIT Placebo	Both (NS)	42.5 µg	216.75 µg	Monthly	NR	4 months
	Van Bever 1992[18]	SCIT Cluster Placebo	conventional therapy	1000 BU	16497 BU	Every 4 weeks	NR	1 year
	Altintas, 1999[19]	SCIT Dust mite Adsorbed Aluminum SCIT Dust mite Adsorbed calcium	NR	50000 -100000 SQ (targeted) 60000 to 100000 SQ (actual) 6 -10 IR 10 IR ≡ 1000w/v)	NR	Every 4 weeks	NR	2 years
	Hill, 1982[20]	SCIT Rye grass Rush Placebo	conventional therapy (NS)	75-1000PNU = 1 PNU of rye pollen	NR	Every 2 weeks until the start of the season; then every 4 weeks until the end of season	NR	8 months
	Valovirta, 1984[21] Valovirta, 2006[22]	SCIT Dog alum-precipitated Placebo	NR	100,000 SQ U Range from 8000 to 50000 in 4/15 subjects)	NR	6 weeks	NR	1 year
	Bousquet, 1988[23]	SCIT Dust mite Pharmacotherapy	conventional therapy not specified	3000 BU	NR	Weekly for 6 weeks; then every 2 weeks for 1 year	NR	1 year
	Baris, 2014[24]	SCIT + Vit D SCIT alone Pharmacotherapy	Both	NR	NR	Buildup NS. Maintenance monthly	NR	2 months

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major Allergen Content	Duration of Treatment
	Kilic, 2011[25]	SCIT Pharmacotherapy	conventional therapy (as part of study NS)	NR	NR	Buildup NS. Maintenance monthly	NR	12 months
	Lozano, 2014[26]	SCIT Pharmacotherapy	Both (LTRA, LABA, ICS)	10,000 AUeq	NR	Monthly	4 µg Der p1, 15 µg Der p2	8 months
	Zielen, 2010[27]	SCIT Pharmacotherapy (ICS alone)	Both (ICS)	0.6 mL of strength B= 10,000 TU/ml	NR	6 weeks	7 ug Der p 1 6 ug Der p 2	2 years
	Pifferi, 2002[28]	SCIT HDM Control	conventional therapy not specified	800 U	24758.33 U (mean)	4 -6 weeks	NR	3 years
	Dreborg, 1986[29]	SCIT *Cladosporium* Placebo	conventional therapy	100000 BU (reached after 18 weeks	NR	Every 4 weeks	NR	10 months
	Hui, 2014[30]	SCIT Desensitization vaccine*	Both (NS)	100,000 U/ml	1,025,000 U/ml	every 4-6 weeks	NR	51 weeks
	Arroabarren, 2015[31]	SCIT 3 years SCIT 5 years	Both (NS)	Mix of conventional and cluster	NR	Monthly	3.6 µg Der P1 per dose	3 years vs 5 years
Children	Adkinson, 1997[32]	SCIT Placebo	Both (NS)	4.3 µg Der p1- 5 µg Der f1- 26 µg Amb a1 38 µg group 1 0.7 mL of concentrate	NR	Biweekly for 24 months, every 3 weeks after 24 months	common dust mites, short ragweed, grass mix (timothy, orchard, perennial ryegrass) *alternaria alternata*, Bermuda grass, English plantain, white oak, *cladosporium* herbarum, *aspergillus fumigatus*	27 months
	Alzakar, 2010[34]	SCIT Pharmacotherapy	conventional therapy (beclomethasone + aminophylline as part of study)	0.5 of stock standardized extracts	NR	Every 15 days then every 4-6 weeks	Single or multiple allergen SCIT (HDM, grass, trees, mold, pets)	12 months
	Tsai, 2010[35]	SCIT Pharmacotherapy	Both (SABA, LTRAs, ICS, LABAs and oral corticosteroids) modified in stepwise manner per GINA guidelines	initial dose of 0.5 AU/mL weekly and increased 25-100% weekly until optimal maintenance dose reached	NR	Biweekly	D pter and D far (10,000 AU/mL)	3 months

NR: Not reported BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg: microgram
Ag/ml: major protein unit TU: Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy LTRA: Leukotriene receptor antagonist
LABA:Long acting Beta agonist SABA:Short acting Beta agonist
*****the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table D4 – Asthma control
No study reported on Asthma control using ACT, ACQ or P-ACT scores

Table D5 – Quality of Life
Asthma Specific Quality of Life – Asthma Quality of Life Questionnaire (AQLQ)
No study reported on Asthma QOL using Pediatric Asthma Specific Quality of Life – Asthma Quality of Life Questionnaire (PAQLQ)- School/Work Absences

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Value pre	Value post	Comparative Values
Kilic, 2011[25]	*Alternaria* Mild and moderate	SCIT Pharmacotherapy	9 7	12 months	Median (IQR) 3.8 (2.73-5.21) 4.91 (3.91-5.82)	Median (IQR) 6.52 (5.78-7) 5.86 (4.21-7)	SCIT pre vs post *P* = 0.002 Control pre vs post *P*=0.01 SCIT vs Control post *P*= 0.09
Lozano, 2014[26]	Dust mite Mild and moderate	SCIT Pharmacotherapy	21 20	8 months	4.9 5.14	6.4 5.42	SCIT vs Pharm post *P*=0.488
Garcia-Robaina, 2006[1] Gallego, 2010[2]	Dust mite Mild asthma	SCIT Placebo	32 32	54 weeks	Median 22 23	Median (IQR) 7.44 [5.78-9.11] 11.44 [9.67-13.22]	SCIT vs placebo post % improvement 34.95 (*P* = 0.043)I
Ameal, 2005[4]	Dust mite Mild and moderate	SCIT Placebo	29 26	12 months	Median (IQR) 17 [13-30] 27 [15-36]	Median (IQR) 4 [1-8] 10.50 [5-17]	SCIT vs placebo post *P* = 0.0025

NR: Not reported NS: Not significant

Table D6 – Medication Use
A. Quick Relief Medications

Study	Allergen and Ashma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Olsen, 1997[6]	Dust mite Severity NS	SCIT Placebo	16 15	12 months	Asthma rescue medication consumption (inhaled beta-2 agonists) Mean number of puffs per week (percentage decrease)	27 52	14 (46%) 46 (NR)	SCIT pre post *P*<0.05 Placebo pre vs post *P* NS

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted

B. Long term Control Medications

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Garcia-Robaina, 2006[1] Gallego, 2010[2]	Dust mite Mild asthma	SCIT Placebo	32 32	54 weeks	Inhaled corticosteroids (beclomethasone), Weeks free of inhaled corticosteroids per patient	NR	Median-IQR 13 [3.5-30.5] 6 [1-18.5]	SCIT vs placebo pre vs post *P* < 0.001
Olsen, 1997[6]	Dust mite Severity NS	SCIT Placebo	16 15	12 months	Inhaled steroid consumption Mean number mg per week (percentage decrease)	4.7 1.4	2.9 (38%) 2.6 (NR)	SCIT pre vs post *P*<0.05 Placebo pre post *P* NS

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Baris, 2014[24]	Dust mite Mild and moderate	SCIT + Vit D SCIT alone Pharmacotherapy	17 15 18	12 months	Inhaled corticosteroids Rate of discontinuation	NA	3 (20%) 6 (35%) 0 (0)	SCIT with and without vitD vs pharmacotherapy alone *P*=0.002
Lozano, 2014[26]	Dust mite Mild and moderate	SCIT Pharmacotherapy	21 20	8 months	Inhaled corticosteroids Changes in the need for medication	N (%) 7 (33) 5 (25)	N (%) 4 (18) 5 (25)	NR
					LTRA's Changes in the need for medication	N (%) 7 (33) 5 (25)	N (%) 4 (18) 5 (25)	SCIT pre vs post *P*<0.046 Pharmacotherapy pre post p=0.158
					IC + LTRA Changes in the need for medication	N (%) 2 (10) 1 (5)	N (%) 1 (5) 1 (5)	NR
					IC + LABA Changes in the need for medication	N (%) 1 (5) 1 (5)	N (%) 1 (5) 3 (15)	NR
Hui, 2014[30]	Dust mite Mild asthma	SCIT desensitization vaccine*	43 45	3 years	Steroids dose Budesonide equivalents (µgs)	196.7 +/- 65.6 206.7 +/- 45	71.3 +/- 53.8 101.3 +/- 48.5	SCIT vs vaccine pre *P*= 0.081 SCIT vs vaccine post *P* = 0.027
Adkinson, 1997[32]	Multiple Moderate to severe	SCIT Placebo	61 60	30 months	Use of inhaled steroids (number of days in previous 60 days)	21.4+/-26 20.1+/-24.9	Change: -10.1+/-24 -5.4 +/-27.8	SCIT pre vs post *P* <0.001 Placebo pre vs post *P*=0.16 Mean difference in change (SCIT vs placebo)= 4.7 (95% CI -4.7 to 14) *P*=0.26

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted LTRA: Leukotriene receptor antagonist LABA:Long acting Beta agonist

* the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

C. Systemic Corticosteroids

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Pifferi, 2002[28]	Dust mite Severity NS	SCIT Control	15 14	3 years	systemic steroids (Days of therapy/year)	22 25	1 12	SCIT vs Control p <0.01
Adkinson, 1997[32]	Multiple Moderate to severe	SCIT Placebo	61 60	30 months	Use of oral steroids (number of days in previous 60 days)	5.3+/-13.3 4.4+/-10.8	-1.9+/-12.4 -1.7+/-12.1	SCIT pre vs. post *P*= 0.19 Placebo pre vs. post *P*= 0.75 Mean difference in change (placebo vs. SCIT)= 0.1 (95% CI -4.2 to 4.5) *P*=0.49

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted

Table D7 – Asthma Exacerbations

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Zielen, 2010[27]	Dust mite Severity NS	SCIT Pharmacotherapy (ICS alone)	32 33	2 years	Numbers of asthma exacerbations requiring oral steroids	NR	2 patients/ 2 events 1 patient/ 1 event	NR
Pifferi, 2002[28]	Dust mite Severity NS	SCIT Control	15 14	3 years	Rate of asthma exacerbations per year	8 8.5	1 4.5	SCIT vs Pharm *P* < 0.01

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted

Table D8 – Healthcare Utilizations

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Tsai, 2010[35]	Dust mite Moderate and severe	SCIT Pharmacotherapy	20 20	6 months	Outpatient visits Number of clinic visits in 6 months	NR	SCIT 17.25 +/- 4.6 Control: 12.4 +/- 5.87	Mean difference: SCIT vs Pharm 4.8, *P*= 0.006
					Number of ED visits or hospitalizations in 6 months	NR	SCIT 0.76 +/- 0.17 Control: 0.95 +/- 0.21	Mean difference SCIT vs Pharm -0.19 *P*=0.267
Adkinson, 1997[32]	Multiple Moderate to severe	SCIT vs. placebo	61 60	30 months	Number of office visits from baseline to follow up	0.05 +/- 0.28 0.03 +/-0.18	Change: -0.03 +/- 0.38 0 +/-0.26	SCIT pre vs. post: *P*= 0.75 Placebo pre vs post *P* >0.99 Mean difference change placebo vs. SCIT= 0.03 (95% CI -0.07 to 0.14) *P*=0.71
					Number of ED visits from baseline to follow up	0.08 +-0.33 0.03+-0.18	Change: -0.05 +-0.38 -0.02+-0.37	SCIT pre vs. post *P* >0.53 Placebo pre vs. post *P* >0.99 Mean difference change placebo vs. SCIT = 0.03 (95% CI -0.08 to 0.15) *P*=0.73
					Number of hospitalizations from baseline to follow up	0.11 +-0.64 0.2 +-0.90	Change: -0.11 +-0.64 -0.10 +- 0.77	SCIT pre vs. post *P*=0.5 Placebo pre vs. post *P*=0.63 Mean difference change placebo vs. SCIT = 0.01 (95% CI -0.24 to 0.27) *P*= 0.43

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted

Table D9 – Pulmonary Physiology
A. PEF

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Creticos, 1996[9]	Short ragweed Moderate to severe	SCIT Placebo	11 11	2 Year	Mean daily PEF during peak season (l/min)	454 444	480 +/-12 461 +/-13	SCIT vs Placebo post *P*=0.03
Kohno, 1998[7]	Dust mite Severity NS	SCIT Rush Bronchodilators	8 6	6 months	Morning PEF (L/min)	471.2 ±27.3 484.3 ± 30.5	506.2 ± 25.2 491.1 ± 26.8	SCIT pre vs post *P* < 0.03 B2 pre vs post *P* NS
Maestrelli, 2004[16]	Dust mite Mild and moderate	SCIT Placebo	41 31	3 years	Morning PEF scores (% predicted)	95 97	104 101	SCIT pre vs post *P*<0.05 Placebo pre vs post NS
Wang, 2006[15]	Dust mite Mild to moderate	SCIT Placebo	56 61	12 months	Morning PEF (l/min)	289.6 +/- 9.94 308.4 +/- 12.6	309.5 +/- 9.29 330.1 +/- 10.4	SCIT pre vs post *P*=0.02 Placebo pre vs post *P*=0.01 SCIT vs Placebo pre *P*=0.26 SCIT vs Placebo post *P*=0.14
					Evening PEF (l/min)	293.1 +/- 10.6 316 +/- 12.1	312.2 +/- 9.27 335.1 +/- 10.7	SCIT pre vs post *P*=0.02 Placebo pre vs post *P*=0.02 SCIT vs Placebo pre *P*=0.16 SCIT vs Placebo post *P*=0.11
Dreborg, 1986[29]	*Cladosporium* Mild to moderate	SCIT Placebo	16 14	6 months	Mean PEF	290 310	280 340	SCIT vs Placebo *P* NS
Kilic, 2011[25]	*Alternaria* Mild and moderate	SCIT Pharmacotherapy	9 7	12 months	PEF (%) Median IQR	76 [64-91] 74 [57-93]	96 [81-102] 101 [73-106]	SCIT pre vs post *P*=0.007 Pharm pre vs post *P*=0.02 SCIT vs pharm *P*=0.2
Zielen, 2010[27]	Dust mite Severity NS	SCIT + ICS ICS alone	32 33	2 years	Increase in morning PEF (L/min)	NR	Change from baseline (% +/- SD) +55 (49) +30 (44)	SCIT vs ICS alone *P* <0.05
					Mean PEF +/- SD (L/min)	296 +/-101 315 +/-91	315 +/- 116 345 +/-95	SCIT vs ICS *P* =0.0315
Hui, 2014[30]	Dust mite Mild asthma	SCIT Desensitization Vaccine*	43 45	3 years	Mean PEF	Mean +/- SD 63.3 +/- 5.4 62.3 +/- 5.1	91.3 +/- 5.8 81.6+/- 4.5	SCIT pre vs post *P* = 0.007
Tsai, 2010[35]	Dust mite Moderate to severe	SCIT Pharmacotherapy	20 20	6 months	PEF (% of predicted value)	83.15 ± 7.49 84.98 ± 5.5	84.3 ± 5.56 84.12 ± 4.72	Change pre vs post SCIT 1.15, *P* =0.056 Pharm -0.86, *P* = 0.099 Mean difference SCIT vs pharm At baseline -1.83, *P* = 0.39 At follow-up: 0.18, *P* = 0.92

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Adkinson 1997[32]	Multiple Moderate to severe	SCIT Placebo	61 60	30 months	PEF (% predicted)	81.9 ± 10.8 84.8 ± 8.6	(change from baseline) 2.5 ± 11.1 -1.4 ± 11.1	SCIT vs placebo Mean difference (95% CI) *P* Baseline: 2.9 (0.6 to 6.4), *P*=0.17 Change: -3.8 (-7.8 to 0.1), *P*=0.05

NS: Not significant SCIT vs placebo post data unless otherwise noted * the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

B. FEV_1

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Chakraborty, 2006[8]	Dust mite Severity NS	SCIT Placebo	8 6	2 years	FEV1 (% predicted)	Mean 78.56 74.5	Mean 92.61 78.91	SCIT pre vs post *P* <0 .001 Placebo pre vs post *P* >0.05
Wang, 2006[15]	Dust mite Mild to moderate	SCIT Placebo	64 65	12 months	FEV1 (% predicted)	87.96 ±1.43 87.97 ±1.74	NR NR	SCIT pre vs post *P* NS Placebo pre vs post *P* NS
Lozano, 2014[26]	Dust mite Mild and moderate	SCIT Pharmacotherapy	21 20	8 months	FEV1 (percentage of patients with FEV >80%)	99.01 99.1	NR	At 8-month, 100% of patients had an FEV1 >80%
Bousquet 1988[23]	Dust mite Severity NS	SCIT – Rush Pharmacotherapy	125 25	12 months	FEV1 (% predicted values) Mean +/- SD	82.3 +/- 23.2 85.6 +/- 26.1	98.6 +/- 16.3 83.4 +/- 18.9	SCIT pre vs post *P* <0.0001 Pharm pre vs post *P* NS SCIT vs B2 (post) *P*<0.0001
Kilic, 2011[25]	*Alternaria* Mild and moderate	SCIT Pharmacotherapy	9 7	12 months	FEV1 Median – IQR	73 [60-80] 75 [65-97]	96 [83-119] 85 [80-117]	SCIT pre vs post *P*= 0.008 Pharm pre vs post *P*= 0.02 SCIT vs pharm *P*= 0.009
Alzakar, 2010[34]	Multiple allergens Excluded severe asthma	SCIT Pharmacotherapy	85 112	12 months	FEV1 - Patients with improvement in pulmonary function test	NR	51/85 (60%) 21/112 (19%)	SCIT vs pharmacotherapy *P* =0 .0001

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted

C. FVC

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Wang, 2006[15]	Dust mite Mild to moderate	SCIT Placebo	64 65	1 year	FVC	94.15 +/-1.39 95.17 +/-1.71	NR NR	SCIT pre vs post *P* NS Placebo pre vs post *P* NS

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted

Table D10 - Airway Hyperresponsiveness (AHR)
A. Methacholine Challenge

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Maestrelli, 2004[16]	Dust mite Mild and moderate	SCIT Placebo	41 31	3 years	AHR- PD20 FEV1	µg methacholine (geometric mean (95%CI) 158 (91-274) 95 (44-203)	183 (104-322) 175 (101-305)	SCIT pre vs post = NS Placebo pre vs post = NS SCIT vs placebo post=NS *P* values not reported P values not reported
Pifferi, 2002[28]	Dust mite Severity NS	SCIT Control	15 14	3 years	AHR- PD20 FEV1 (ug)	(µg methacholine, cumulative dose) 93.5 ± 56.3 374.3 ± 505.5	997.7±974.0 388.5±516.4	P-values are not reported for SCIT vs.control dose of methacholine The authors calculated the ratio of the incidence of ''non-improvement'' of bronchial reactivity in the SIT to the control group (Relative Risk: 0.3, and 95% CI between 0.11 and 0.87) indicated the likelihood of non-improvement of the former was 1/3 of that of the latter
Zielen, 2010[27]	Dust mite Severity NS	SCIT + ICS ICS alone	32 33	2 years	AHR- PC20 FEV1	NR	NR	SCIT pre vs post NR Control pre vs post NR SCIT vs.control post: NR
Garcia-Ortega, 1993[12]	Dust mite Severity NS	SCIT Pharmacotherapy	18 18	7 months	AHR- PD20 FEV1	(Methacholine inhalatory units) 18±26 19±27	NR	SCIT pre vs post, *P* NS Pharm pre vs post NR SCIT vs control post, *P*=NS
Ohman, 1984[10]	Cats Severity NS	SCIT Placebo	9 8	17 weeks	AHR- PD 20 FEV1	Methacholine, Bronchoprovocation Units (Geometric Mean) 3.0 1.7	4.7 3.8	SCIT pre vs post, *P* NS Placebo pre vs post, *P* NS SCIT vs Placebo NR
Adkinson, 1997[32] Limb, 2006[33]	multiple allergen Moderate to severe	SCIT Placebo	61 60	30 months	AHR- PC 20 FEV1	methacholine, µg/ml (geometric mean, 95% CI) 0.23 ± 1.33 0.32 ± 0.32	0.41± 1.87 0.39 ± 1.51 (change from baseline)	SCIT pre vs post *P*= 0.008 Placebo pre vs post *P*=0.003 SCIT vs Placebo post, *P* > 0.99
Kilic, 2011[25]	*Alternaria* Mild and moderate	SCIT Pharmacotherapy	9 7	12 months	AHR- Methacholine challenge	Mean – IQR 0.49 [1.17-NR] 1.1 [1.52-NR]	Mean – IQR 4.07 [5.59-NR] 0.90 [2.53-NR]	SCIT pre vs post *P*= 0.002 SCIT vs pharm *P* = 0.03

NR: Not reported NS: Not significant PC20: Concentration of allergen causing a fall if 20% in FEV1 PD20: Dose of allergen causing a fall if 20% in FEV1

B. Allergen Challenge

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Garcia-Robaina, 2006[1] Gallego, 2010[2]	Dust mite Mild asthma	SCIT Placebo	32 32	56 weeks	AHR- Allergen challenge PD20 FEV1	No units Mean – IQR 10.05 [5.48-81] 43.5 [6.1-511]	Mean – IQR 111.06 [41.05-686] 41 [3.35- 311]	SCIT pre vs post *P* < 0.001 Placebo pre vs post *P* = 0.648 SCIT vs placebo *P* = 0.029
Ameal, 2005[4]	Dust mite Mild and moderate	SCIT Placebo	29 26	12 months	AHR- Allergen challenge PD20 FEV1	HEP/ml Median – IQR 2.56 [0.54-5.61] 2.77 [1.69-4.02]	Median – IQR 7.14 [4.29-14.38] 2.76 [1.5-10.81]	SCIT pre vs post *P* < 0.0001 Placebo pre vs post *P* = 0.9292 SCIT vs placebo pre *P* = 0.9173 SCIT vs placebo post *P* = 0.0029
Bousquet 1985[3]	Dust mite Severity NS	SCIT Placebo	20 10	7 weeks	AHR- Allergen challenge (PD20 FEV1)	µg of allergen solution 96.3±82.1 79.1±93.6	432±171 95.0±99.8	SCIT, pre vs post, *P*<0.01 Placebo, pre vs post,*P*=NS SCIT vs Placebo post *P*<0.01
Ibero, 2006[17]	Dust mite Mild and moderate	SCIT Placebo	15 15	4 months	AHR- Allergen challenge PC20 FEV1	HEP units llergen/ml Mean [IQR] 26 [9-43.2] 5.2 [2.6-7.8]	Mean [IQR] 309.4 [-39-657.8] 8 [2.6-13.4]	SCIT pre vs post *P* = 0.0054 Placebo pre vs post *P* > 0.05 SCIT vs. placebo, post p=0.0020
Olsen, 1997[6]	Dust mite Severity NS	SCIT Placebo	16 15	12 months	AHR- Allergen challenge (Dpt) PC 20 FEV1	SQ-Units/ml 25000 11000	37000 14000	SCIT, pre vs post, *P*=0.022 Placebo pre vs post, *P*=0.60 SCIT vs Placebo post, p=0.037
					AHR- Allergen challenge PC 20 FEV1	SQ-Units/ml 31000 29000	46000 20000	SCIT pre vs post, *P*=0.039 Placebo pre vs post, *P*=0.75 SCIT vs Placebo post, *P*=0.041
Van Bever 1992[18]	Dust mite All severities	SCIT Placebo	9 9	12 months	AHR- Allergen challenge PD 20 FEV1 Median PD 20 house dust mite (BU)	Median Biologic Units (BU) 238 303	477 385	SCIT pre vs post, *P*=0.04 Placebo, pre vs post, *P*=0.11 SCIT vs Placebo *P* = 0.24
Altintas, 1999[19]	Dust mite Mild to moderate	SCIT-Adsorbed aluminum SCIT-Adsorbed calcium SCIT-aqueous Placebo	10 10 9 5	2 years	BPT -Allergen bronchial provocation test)	Geometric mean SQ/ml 7244 4786 2137 4786	31622 39810 31153 7100	No significant difference among treatment groups, P>0.05 All SCIT vs Placebo P<0.05
Kohno, 1998[7]	Dust mite Severity NS	SCIT Pharmacotherapy (Bronchodilators NS)	8 6	6 months	AHR- Allergen challenge PC 20 FEV1	(wt/vol) Concentration of dust mite extract 1:303.7±1231 230.0±154.5	1:65.0±13.2 1:291.7±158.9	SCIT pre vs post, *P*<0.03 Pharm pre vs post, *P* NS SCIT vs. control post, NR

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Garcia-Ortega, 1993[12]	Dust mite Severity NS	SCIT Pharmacotherapy	18 18	7 months	Allergen bronchial provocation, PD-20 (inhalatory units; IU)	47±52 70±93	425±303 106±196	SCIT, pre vs post, *P*=0.01 Conventional pre vs post NS SCIT vs Conventional *P*=0.001
Ohman, 1984[10]	Cats Severity NS	SCIT Placebo	9 8	17 weeks	AHR- Allergen challenge PD 20 FEV1	BU geometric mean cumulative dose 4.27 8.8	20.7 12.3	SCIT pre vs post *P* <0.05 Placebo pre vs post, *P* NS SCIT vs Placebo,post *P* NS
Van Metre, 1988[11]	Cats Severity NS	SCIT Placebo	11 11	12 months	AHR- Allergen challenge PD 20 FEV1 Cat extract PD 20 (Comparison of the median ratios values of the measurements from baseline to1 year)	NR	2.8 0.80 Median ratio of allergen extract required for PD 20, post relative to pre treatment concentration	SCIT pre vs post NR Placebo pre vs post NR SCIT vs Placebo, *P*<0.01
Valovirta, 1984[21] Valovirta, 1986[22]	Dogs Severity NS	SCIT Placebo	15 12	12 months	Bronchial provocation test to dog dander extract	NR	40 17	SCIT, pre vs post, *P*<0.1 Placebo pre vs post NR SCIT vs Placebo, *P*=NS
Dreborg, 1986[29]	*Cladosporium* Mild to moderate	SCIT Placebo	16 14	10 week period during peak season	AHR- Allergen challenge positive defined as peak expiratory flow reduction of at least 15%	NR NR	NR NR	SCIT pre vs post, *P*<0.01 Placebo pre vs post, <0.05 SCIT vs control *P*<0.05
Creticos, 1996[9]	Short ragweed moderate to severe	SCIT Placebo	11 11	2 Year	AHR- Allergen challenge PD 20 FEV1 Amount of allergen causing 20% drop in FEV1(PD 20)	Logarithm of allergen dose -1.4 +/- 1.1 -1.5 =/- 1.3	-0.273 ± 0.045 -0.662 ±0.135	SCIT pre vs post NR Placebo pre vs post NR SCIT vs Control post , *P*=0.03

NR: Not reported NS: Not significant PC20: Concentration of allergen causing a fall if 20% in FEV1 PD20: Concentration of allergen causing a fall if 20% in FEV1
µg :migrogram SCIT vs placebo post data unless otherwise noted

C. Exercise Challenge

There were no studies reporting on exercise challenge

Table D11 – Immunologic Parameters
A. IgE

Study	Allergen and Asthma Severity	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Gallego, 2010[2]	Dust mite Mild and moderate	SCIT Placebo	1 year	Specific IgE to D pter (kUA/l)	Mean (SD) 44.8 (33.5) 49.6 (35.1)	Mean (SD) 39.5 (31.4) 43 (35)	SCIT pre vs post *P* =0.06 Placebo pre vs post *P* = 0008 SCIT vs placebo post NR
Hui, 2014[30]	Dust mite Mild and moderate	SCIT desensitization vaccine *	3 years	Specific IgE to D pter (kUA/l)	Mean (SD) 91.4 (29.1) 92.6 (24.5)	Mean (SD) 77.6 (26.4) 90.8 (20.5)	SCIT vs placebo at year 3 *P* = 0.003
Zielen, 2010[27]	Dust mite Severity NS	SCIT + ICS ICS alone	2 years	Specific IgE to D pter (kU/L)	Geometric means 16.29 14.46	Decrease in geometric means -22.9% + 2%	SCIT+ ICS vs ICS alone post *P*=0.0217
Baris, 2014[24]	Dust mite Mild and moderate	SCIT + Vit D SCIT alone Pharmacotherapy	12 months	Specific IgE Df. (kU/l)	50 +/- 34.1 49.6 +/- 34 54.1 +/- 38.6	35.8 +/- 33.4 41.7 +/- 30.1 72.7 +/- 33.4	SCIT+ Vit D pre vs post *P*=0.03 SCIT pre vs post *P*= NS Pharm pre vs post *P*= NS SCIT+Vit D vs. Pharm *P*=0.007 SCIT vs. Pharm *P*=0.036
Blumberga, 2011[13]	Dust mite Moderate	SCIT Placebo	1 year	Specific IgE to D pter (Δlog)	NR	Change from baseline – 95% CI 0.048 [-0.017,-0.11] -0.051 [-0.11, -0.0080]	SCIT vs placebo post P=0.028
Tsai, 2005[36]	Dust mite Moderate and severe	SCIT Control	1 year	Dpt-specific IgE (kU/l)	70.8 (35.97) 61.18 (38.87)	52.36 (37.84) 56.32 (38.56)	SCIT vs pharm post P < 0.005
Vidal, 2011[5]	Dust mite Mild and moderate	SCIT Placebo	15 weeks	Specific IgE to D pter kU/L	Median [IQR] 50 [72.5-NR] 29.1 [81.3-NR]	Median [IQR] 49.7 [116.3-NR] 20.5 [58.7-NR]	Difference [IQR] SCIT pre vs post -0.38 [28.9] Placebo pre vspost 3.2 [8.7] SCIT vs placebo Baseline values *P*= 0.73 Final values *P*=0.26 Differences *P*= 0.0425
Arroabarren, 2015[31]	Dust mite Mild and moderate	SCIT 3y SCIT 5y	3 vs 5 years	Evolution of specific IgE to D pter at 3 and 5 years	55 79.1	T(3) 64.2 and 60 T (5) 50 and 53.3	*P* at T(3) =0.656 *P* at T (5) =0.669
Kilic, 2011[25]	*Alternaria* Mild and moderate	SCIT Pharmacotherapy	12 months	Specific IgE to *alternaria* kU/L	Median [IQR] 26.4 [21.8-NR] 35.3 [19-NR]	Median [IQR] 8.17 [14.2-NR] 46.8 [28.4-NR]	SCIT pre vs post *P*=0.004 Pharm pre vs post *P*=0.05 SCIT vs pharm post *P* = 0.0001

Study	Allergen and Asthma Severity	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Adkinson, 1997[32] Limb, 2006[33]	Multiple allergen Moderate to severe	SCIT Placebo	27 months	Specific IgE to each allergen	Specific for each allergen	Specific for each allergen	Short term reduction of specific IgE ragweed (*P*=0.001), D far (*P*=0.03) and all allergens pooled together (*P*< 0.001) but not for long term
Alzakar, 2010[34]	Dust mites, mold, trees, animals, grass Excluded severe asthma	SCIT Pharmacotherapy (Beclomethasone + Aminophylline)	12 months	Number of patients with reduction in specific IgE (≤0.35 IU/ml)	NR NR	64 (75%) 9 (8%)	SCIT vs pharmacotherapy post *P* = 0.0001

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted

*the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

B. IgG4

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Baris, 2014[24]	Dust mite Mild and moderate	SCIT + vitamin D SCIT alone VIt D alone	12 months	Der p 1 specific IgG4 Unit NR	Mean 0.13 0.12 0.05	Mean 4.23 2.8 0.09	Pre vs post within arm *P* =0.002 *P* =0.002 *P* = 0.0002 Between arms not reported
Vidal, 2011[5]	Dust mite Mild and moderate	SCIT Placebo	15 weeks	Specific IgG4 to D pter Unit NR	Median [IQR] 0.12 [0.11-NR] 0.10 [0.17-NR]	Median [IQR] 0.40 [0.76-NR] 0.10 [0.21-NR]	Difference [IQR] SCIT pre - post 0. 21 [0.16] Placebo pre-post -0.02[0.25] SCIT vs placebo pre *P*= 0.55 SCIT vs placebo post *P*=0.001 Differences *P*= 0.0003
Zielen, 2010[27]	Dust mite Severity NS	SCIT + ICS ICS alone	2 years	Specific IgG4 to D pter Unit NR	NR	NR	SCIT vs ICS alone post Significantly increased *P*<0.0001
Gallego, 2010[2]	Dust mite Mild and moderate	SCIT Placebo	1 year	Der p 1 specific IgG4 Unit NR	NR NR	NR NR	SCIT pre vs post D pter *P*=002 Der p1 *P*=0.001 Der p2 *P*=0.048 Placebo pre vs post NR SCIT vs placebo NR
				Ratio of Specific IgE/Specific IgG4 (SD)	Median 94.8 (89.9) 103.3 (83)	Median 65.1 (54.3) 133 (204.6)	SCIT pre vs post *P* =0.02 Placebo pre vs post NR

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Altintas, 1999[19]	Dust mite Mild to moderate	SCIT Adsorbed Aluminum SCIT Adsorbed calcium SCIT aqueous Placebo	2 years	Specific IgG4 to Der P1	I: 6.3 +/- 1.6 II: 5.0 +/- 2.6 III: 10 +/- 1.7 IV: 7 +/- 2.2	I: 50.1 +/- 1.9 II: 14.4 +/- 1.6 III: 8.9 +/- 2.3 IV: 5.4 +/- 1.2	All SCIT vs. Placebo: *P*< 0.01 I vs. II and III: *P*<0.05 II vs III: *P* >0.05

NR: Not reported NS: Not significant

C. Allergy Skin Testing

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Hui, 2014[30]	Dust mite Mild and moderate	SCIT Control*	3 years	SPT (skin prick testing)	Mean (SD) 1.2 (0.5) 1.3 (0.5) *P* = 0.532	SPT results remained unchanged	No differences between groups were identified
Vidal, 2011[5]	Dust mite Mild and moderate	SCIT Placebo	15 weeks	Specific IgE to D pter kU/L	Median [IQR] 50 [72.5-NR] 29.1 [81.3-NR]	Median [IQR] 9.7 [116.3-NR] 20.5 [58.7-NR]	Difference [IQR] SCIT pre vs post -0.38 [28.9] Placebo pre vs post 3.2 [8.7] SCIT vs placebo pre *P*= 0.73 SCIT vs placebo post *P*=0.26 Differences *P*= 0.0425
				CTI Cutaneous tolerance index	NA	CTI -95% CI 2.81 [1.29-7.48] 1.03 [0.44-2.41]	SCIT vs placebo post Difference [95% CI] *P* 0.27 [0.11-0.56] P <0.05
Blumberga, 2011[13]	Dust mite Moderate	SCIT Placebo	3 years	Intradermal skin testing, Immediate-phase skin reactions	Mean 24 21	11 5	SCIT vs placebo at 3 years P = 0.0002
				Intradermal skin testing, Late-phase skin reaction	Mean 23 26	0 22	SCIT vs placebo at 3 years *P* < 0.0001
				Skin prick test titration HEP--the estimated HDM-allergen concentration that caused histamine equivalent skin reactions (HEP)	Mean 6 6	Mean 377 48	SCIT vs placebo at 3 years *P* <0.0001
Gallego, 2010[2]	Dust mite Mild and moderate	SCIT Placebo	54 weeks	HEP (dose of native allergen extract needed to produce the same wheal size as the positive control for Skin prick testing)	21.9 -0.31	NR NR	*P* = 0.029 NR

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Ibero, 2006[17]	Dust mite Mild and moderate	SCIT Pharmacotherapy	4 months	SPT (HEP mg- dose of native allergen extract needed to produce the same wheal size as the positive control for Skin prick testing)	10 HEP value (95% CI) 1.28 mg (0.25-2.35) 1.43 mg (-0.03-2.89)	HEP value (95% CI) 9.31 mg (-2.79-21.41) 0.29 mg (-0.08-0.67)	SCIT pre vs. post: *P*= 0.0164 Pharm pre vs. post *P*=0.286 SCIT vs. Pharm *P*=0.0012
Alzakar, 2010[34]	Dust mites, mold, trees, animals, grass Excluded severe	SCIT Pharmacotherapy (Beclomethasone + Aminophylline)	12 months	NR	NR NR	74 (87%) (7%)	SCIT vs pharm post *P* = 0.0001

NR: Not reported NS: Not significant SCIT vs placebo post data unless otherwise noted

* the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table D12. Compliance

Study	Allergen	Arms	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Adkinson, 1997[32]	Multiple allergen Moderate to severe	SCIT Placebo	30 months	Prescribed doses and doses recorded in diaries	NR	92.6% 93.6	Final comparative values NR

NR: Not reported NS: Not significant

Appendix E. KQ2- What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Organization in tables first by population; adults-mixed population- children. Within each category by comparator SCIT vs placebo- SCIT vs pharmacotherapy- SCIT vs SCIT. Within each subcategory by allergen; HDM-grass- weed- trees- animal-multiple allergen)

SECTION A SCIT Safety for RCTs

Table E1.– Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Garcia-Robaina, 2006[1] Gallego, 2010[2] Europe	SCIT Placebo	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Positive SPT IgE ≥ 2	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic
	Bousquet, 1985[3] France	SCIT Placebo	Asthma diagnosis criteria-pulmonary tests (reversible bronchoconstriction to B agonist or significant sensitivity to methacholine and positive BPT with Dp) Severity NS Control status NS (baseline FEV1 required to be within 20% predicted)	SPT and IgE Positive SPT (clinic specific) IgE RAST class 3-4	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic
	Ameal, 2005[4] Europe	SCIT Placebo	Asthma diagnosis criteria GINA Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Wheal size (10HEP)	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic
	Vidal, 2011[5] Europe	SCIT Placebo	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Wheal > 3mm; IgE ≥ class 2	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter)	Clinic
	Kohno, 1998[7] Asia	SCIT Placebo	Asthma diagnosis criteria -Bronchial response to histamine Severity NS Control status -Controlled (no need of ICS)	SPT and IgE NS	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D far)	Single allergen Dust mite (D far)	Clinic
	Garcia-Ortega, 1993[12] Europe	SCIT (cluster) Pharmacotherapy	Asthma diagnosis criteria- positive bronchial challenge to dust mite Severity NS Control status NS	SPT and IgE SPT NS IgE RAST class 2	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Chakraborty, 2006[8] Asia	SCIT Placebo	Asthma diagnosis criteria NS Severity NS Control status NS	SPT and IgE wheal >3mm	Monosensitized Grass (P sylvestris)	Single allergen Grass (*P Sylvestris*)	Not specified
	Creticos, 1996[9] US	SCIT Placebo	Asthma diagnosis criteria methacholine challenge Severity moderate to severe Control status uncontrolled (dependent of ICS)	SPT Not specified	Monosensitized Ragweed	Single allergen Ragweed	Clinic
	Ohman, 1984[10] US	SCIT Placebo	Asthma diagnosis criteria -positive bronchial challenge to cat Severity NS Control status -Controlled (no need of ICS)	SPT Not specified	Mono vs Polysensitized unclear* All patients sensitized to cat	Single allergen Cat	Clinic
	Van Metre, 1988[11] US	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE SPT +2 IgE significant	Mono vs Polysensitized unclear* All patients sensitized to cat	Single allergen Cat	Clinic
	Blumberga, 2011[13] Blumberga, 2006[14] Europe	SCIT Placebo	Asthma diagnosis GINA criteria Severity moderate persistent Control status NS	SPT and IgE positive SPT (>3 mm) and allergen-specific IgE class 2	Polysensitized (72% of patients were sensitized to Timothy, 65% to dog, 52% to cat and 35% to birch pollen)	Single allergen Dust mite	Clinic
	Casanovas, 2005[37] Europe	SCIT modified. SCIT unmodified	Asthma diagnosis GINA criteria Severity Mild persistent and moderate persistent Control status NS	SPT >3mm	Monosensitized Timothy grass	Single allergen Timothy grass	Clinic
Mixed age	Ibero, 2006[17] Europe	SCIT Placebo	Asthma diagnosis per mild moderate criteria Severity mild and moderate Control status NS	SPT and IgE	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Lozano, 2014[26] Europe	SCIT Pharmacotherapy	Asthma diagnosis NS Mild persistent and moderate persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic
	Baris, 2014[24] Asia	SCIT Pharmacotherapy	Asthma diagnosis GINA criteria (FEV changes) Mild and moderate Control status NS	SPT and IgE NS	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Zielen, 2010[27] Europe	SCIT Pharmacotherapy (ICS alone)	Asthma diagnosis criteria GINA Severity NS Well controlled	SPT and IgE SPT >5mm; IgE of class 2 or greater (10.7 kU/l)	Polysensitized pollen, animal, house dust mite (D pter-D far), and mold allergens	Single allergen Dust mite (D pter)	Clinic
	Altintas,1999[19] Asia	SCIT SCIT Placebo	Asthma diagnosis criteria NS Severity Mild to moderate Control status – Poorly controlled	SPT and IgE Values for baseline and follow-up	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Schubert 2009[38] Europe	SCIT cluster SCIT conventional	Asthma diagnosis GINA criteria Severity Mild to moderate Control status – Controlled (stable dose of ICS)	SPT and IgE Specific IgE with ELISA	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D pter)	Single allergen Dust mite (D pter)	Clinic
	Hui, 2014[30] Asia	SCIT Desensitization vaccine**	Asthma diagnosis per Breathing Group of Pediatric Academy; Chinese Medical Association Mild persistent Control status NS	SPT and IgE SPT "positive" and/or allergen-specific IgE in serum (>0.35kUA/l)	Monosensitized Dust mite (D pter)	Single allergen Dust mite (D pter)	Not specified
	Dreborg, 1986[29] Europe	SCIT Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate Control status – Controlled (stable dose of ICS)	SPT and IgE SPT 2 + IgE RAST class 1 or greater	Monosensitized *Cladosporium*	Single allergen *Cladosporium*	Clinic
	Roberts, 2006[39] Europe	SCIT Placebo	Asthma diagnosis criteria NS Severity Mild persistent moderate persistent and severe persistent Control status NS	SPT and IgE wheal >3mm IgE NS	Monosensitized Grass (Phleum pratense)	Single allergen Grass (*Phleum pratense*)	Clinic
	Valovirta,1984[21] Valovirta, 2006[22] US	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE SPT +3 IgE class 2	Polysensitized Birch, Timothy, *Cladosporium*, HDM, cat	Single allergen Dog	Clinic
	Arroabarren, 2015[31] Europe	SCIT SCIT (3 vs 5 y)	GINA criteria Mild persistent and moderate persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (D pter-D far) And Polysensitized (latex, food, tree, grass, weed, mold, cat, dog	Single allergen Dust mite (D pter)	Clinic
Children	Alzakar, 2010[34] Asia	SCIT Pharmacotherapy	Asthma diagnosis criteria GINA and EPR Excluded severe asthma Control status NS	SPT and IgE Wheal > 3mm; Allergen specific IgE of 0.35 EU/mL	Polysensitized *Alternaria*, *Cladosporium*, *Penicillium*, grass mix, feather mixture, dog, horse, cat, *Aspergillus*, *Fagacae, Betulaceae*, plantain, Bermuda grass, *Chenopodium*, mugwort, *Oleaceae* and dust mite (D pter-D far)	Multiple allergens	Clinic
	Tsai, 2010[35] Asia	SCIT Pharmacotherapy	Asthma diagnosis criteria GINA Severity moderate and severe persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Adkinson, 1997[32] US	SCIT Placebo	Physician diagnosis asthma Moderate to severe asthma	SPT and IgE	Polysensitized Dust mite (D pter -D far) Trees (white oak) Weeds (ragweed, English plantain), Grass (Grass mix, Bermuda grass) Molds (*Alternaria, aspergillus, cladosporium*)	Multiple allergens	Clinic

SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified- Not described D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*

***** Authors did not report sensitization status

****** the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table E2.A– Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (Range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Adults	Garcia-Robaina, 2006[1] Gallego, 2010[2]	64	SCIT Placebo	23.5 (9.3) 23.8 (7.7)	47/53 38/62	32/5 32/5	NR
	Bousquet, 1985[3]	215	SCIT (Rush) Placebo	24 +/- 13(Range 3-72) 24 +/- 11(Range 3-72)	Entire study 68.0/32.0	125/NR 25/NR	12 9.8
	Ameal, 2005[4]	63	SCIT Placebo	NR	NR	32/3 31/5	NR
	Vidal, 2011[5]	45	SCIT Placebo	25.9 28.3	57/43 58/42	21/2 24/1	NR
	Kohno, 1998[7]	16	SCIT Placebo	25.8 26.3	75/25 66/34	8/0 6/2	NR
	Garcia-Ortega, 1993[12]	36	SCIT Pharmacotherapy	Range 13-45 Range 13-45	Entire study N 16/20	18/NR 18/NR	NR
	Chakraborty, 2006[8]	14	SCIT Placebo	32.22 32.59	NR	8/0 6/0	NR
	Creticos, 1996[9]	90	SCIT Placebo	36 +/- 10 35 +/- 10	51/49 50/50	37/8 53/16	At least 1
	Ohman, 1984[10]	17	SCIT Placebo	26 (Range 22-31) 30 (Range 24-48)	NR NR	9/0 8/0	NR
	Van Metre, 1988[11]	22	SCIT Placebo	Range 21-52 Range 21-52	N 5/6 N 5/6	11/1 11/0	NR
	Blumberga, 2011[13] Blumberga,2006[14]	54	HDM SCIT Placebo	29.8 (10.7) 28.5 (7.1)	42/58 39/61	26/6 28/6	14.8 14.1
	Casanovas, 2005[37]	23	SCIT Unmodified SCIT Modified	28 34	50/50 45/54	12/NR 11/NR	2
Mixed age	Ibero, 2006[17]	30	SCIT Placebo	Median: 10 Range: 8-15 Median: 12 Range: 8-16	Entire study 63/47	15/NR 15/2	NR
	Lozano, 2014[26]	43	SCIT Combination	Median: 9 Range: 6-12 Median: 9 Range: 6-14	48/52 55/45	21/1 20/2	1

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (Range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
	Baris, 2014[24]	55	SCIT + Vit D SCIT Pharmacotherapy	9.2 (2.6) 8.8 (1.1) 7.9 (2.6)	29/81 47/53 50/50	17/1 15/2 18/2	NR
	Zielen, 2010[27]	66	SCIT + ICS ICS alone	Median: 9 Range: 6-17 Median: 11 Range: 6-16	66/34 69/31	33 32	Median: 3 Median: 2
	Altintas,1999[19]	35	Adsorbed Aluminum Hydroxide IT Adsorbed Calcium Phosphate SCIT Aqueous SCIT Placebo	10.8 +/- 3.7 10.0 +/- 3.7 11 +/- 4 11 +/- 3	80/20 60/40 55/45 60/40	10/ NR 10/ NR 9/ NR 5/ NR	NR
	Schubert 2009[38]	34	SCIT Cluster SCIT Classic	10 8.5	NR NR	20/2 14/2	NR
	Hui, 2014[30]	90	SCIT Desensitization vaccine*	10.1 (2.2) 9.8 (1.5)	53/47 49/51	45/5 45/4	3.5 3.4
	Dreborg, 1986[29]	30	SCIT Placebo	11 (Range 5-17) 11 (Range 5-17)	NR	16/NR 14/NR	NR
	Roberts, 2006[39]	37	SCIT Placebo	9.2 (4.4) 10.6 (2.9)	72/28 81/29	18/4 17/4	NR
	Valovirta, 1984[21] Valovirta, 2006[22]	27	SCIT Placebo	11 (Range 5-18) 10.5 (Range 5-16)	60/40 58/42	15/0 12/0	NR
	Arroabarren, 2015[31]	63	5-year IT 3-year IT	9.26 (NR) 8.9 (NR)	NR	36/NR 27/NR	NR
Children	Alzakar, 2010[34]	242	SCIT Pharmacotherapy	9.8 (1.7) 10 (1.5)	55/45 60/40	105 137	NR
	Tsai, 2010[35]	40	SCIT Pharmacotherapy	8.6 (2.99) 8.35 (2.43)	70/30 35/65	20/0 20/0	NR

SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified * the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table E3.A – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Garcia-Robaina, 2006[1] Gallego, 2010[2]	SCIT Placebo	Conventional and rescue therapy	12 administrations of 0.5mLvial 2 were administered in monthly intervals	NR	Monthly	20.35 µg Der p 1 and 12.30 mg Der p 2 per mg	54 weeks
	Bousquet 1985[3]	SCIT rush Placebo	NR	3000 BU (=to 0.1 ml of 1/100 w/v)	NR	Weekly	NR	7 weeks (not clearly stated)
	Ameal, 2005[4]	SCIT Placebo	Only rescue (B2)	0.5 mL of 70 µg/mL	NR	Monthly	14.25 µg of Der p 1/ml and 8.61 of Der p 2	12 months
	Vidal, 2011[5]	SCIT Placebo	Both NS	0.8ml	NR	Monthly	4.8 µg DP1, 3.2 µg DP2	4 months

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Kohno, 1998[7]	SCIT rush Bronchodilators	Conventional therapy	0.15-0.30 ml of 1/10 wt/vol	NR	Weekly for 2 months then every 2 weeks for 6 months	1 mg dust mite extract = 9.8 ng of major allergens Der1 and Der2 (5.4 ng was *D far)*	6 months
	Garcia-Ortega, 1993[12]	SCIT dust mite cluster Pharmacotherapy	Conventional therapy (bronchodilators/ usual care)	100000 SQ	2000000 SQ	Every 15 days	NR	7 months
	Chakraborty, 2006[8]	SCIT Placebo	NR	1:2500 wt/vol	NR	Conventional Weekly	0.5 µg	2 years
	Creticos, 1996[9]	SCIT Ragweed Placebo	Only rescue medication	0.5 mL of 1:10 dilution (actual mean dose in year = 4 µg of Amb a1)	NR	Every 2 weeks for 3 months thereafter every 4 weeks	10 µg of Amb a1	2 years
	Ohman, 1984[10]	SCIT Cat Placebo	NR	0.3 ml of extract containing 13 units of cat allergen 1 per ml or 300 µg/ml of cat albumin)	10.9 units' cat allergen or 272 µg of cat albumin	Weekly	13 units of cat allergen 1 U/ml or 300 µg /ml of cat albumin)	16 weeks
	Van Metre, 1988[11]	SCIT Cat Placebo	Conventional therapy	1.0 mL of 4 .56 FDA units of Fel d 1 per mL.	NR	Biweekly	4 .56 FDA units of Fel d 1	At least 1 year
	Blumberga, 2011[13] Blumberga, 2006[14]	HDM SCIT Placebo	Conventional and rescue therapy	100,000 SQ	20	6 weeks	NR	3 years
	Casanovas, 2005[37]	SCIT modified vs SCIT unmodified	NR	Target: 154 µg Actual: 154 µg	Target: 615.69 µg Actual: 615.69 µg	NR	Max concentration 308.50 µg/mL or 2464.90 Max concentration 2400 µg/mL or 24696 PNU/mL	11 weeks
Mixed age	Ibero, 2006[17]	SCIT Placebo	Conventional therapy and rescue medication	Target: 42.5 µg Actual: 42.5 µg	216.75 µg	Monthly	NR	4 months
	Lozano, 2014[26]	SCIT Pharmacotherapy	Both (LTRA, LABA, ICS)	10,000 AUeq	NR	Monthly	4 µg Der p1, 15 µg Der p2	8 months
	Baris, 2014[24]	SCIT + Vit D SCIT alone Pharmacotherapy	Both	NR	NR	Buildup NS Maintenance monthly	NR	12 months
	Zielen, 2010[27]	SCIT Pharmacotherapy (ICS alone)	Both (ICS)	0.6 mL of strength B= 10,000 TU/ml	NR	6 weeks	7 ug Der p 1 6 ug Der p 2	2 years

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Altintas, 1999[19]	SCIT Dust mite Absorbed Aluminum SCIT Dust mite Absorbed calcium	NR	50000 -100000 SQ (targeted) 60000 to 100000 SQ (actual) 6 -10 IR (10 IR ≡ 1/1000w/v)	NR	Every 4 weeks	NR	2 years
	Schubert, 2009[38]	SCIT dust mite cluster alum-precipitated SCIT dust mite conventional alum-precipitated	Conventional therapy	5000 TU after 6 weeks 5000 TU after 14 weeks	Either 30,825 TU or 33,825 TU 21, 325 TU	Every 2-4 weeks Every 2 weeks	NR	16 weeks
	Hui, 2014[30]	SCIT Desensitization vaccine*	Both (NS)	100,000 U/ml	1,025,000 U/ml	Every 4-6 weeks	NR	51 weeks
	Dreborg, 1986[29]	SCIT *Cladosporium* Placebo	Conventional therapy	100000 BU (reached after 18 weeks	NR	Every 4 weeks	NR	10 months
	Roberts, 2006[39]	SCIT *Cladosporium* Placebo	Conventional therapy and rescue therapy	Target: 100,000 SQ-U. Actual: 100,000 SQ-U.	NR	Every 6 weeks (+/- 2 weeks)	20	2 years
	Valovirta, 1984[21] Valovirta, 2006[22]	SCIT Dog alum-precipitated Placebo	NR	100,000 SQ U (Range from 8000 to 50000 in 4/15 subjects)	NR	6 weeks	NR	1 year
	Arroabarren, 2015[31]	SCIT 3 years SCIT 5 years	Both (NS)	Mix of conventional and cluster	NR	Monthly	3.6 µg Der P1 per dose	3 years vs 5 years
Children	Alzakar, 2010[34]	SCIT Pharmacotherapy	Conventional therapy (beclomethasone + aminophylline as part of study)	0.5 of stock standardized extracts	NR	Every 15 days then every 4-6 weeks	NR	12 months
	Tsai, 2010[35]	SCIT Pharmacotherapy	Both (NS)	NS	initial dose of 0.5 AU/mL weekly and increased 25-100% weekly until optimal maintenance dose reached	Biweekly	D pter and D far (10,000 AU/mL)	3 months

NR: Not reported BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg: microgram Ag/ml: major protein unit
TU: Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy LTRA: Leukotriene receptor antagonist LABA: Long acting Beta agonist
D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*
***** the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table E4.A - Anaphylaxis

Study	Allergen and Asthma Severity	Arms	N	Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Zielen, 2010[27]	Dust mite NS	SCIT + ICS ICS alone	33 32	No anaphylaxis occurred during the study	0	0	NA
Bousquet 1985[3]	Dust mite NS	SCIT rush Placebo	20 10	3 systemic reactions not specified, treated with Epinephrine*	3 0	NR	0.15
Baris, 2014[24]	Dust mite Mild and moderate asthma	SCIT + Vit D SCIT alone Pharmacotherapy	17 15 18	Systemic reaction not specified, treated with epinephrine*	0 1 0	NR	0.03
Casanovas, 2005[37]	Grass Mild and moderate asthma	SCIT modified vs SCIT unmodified	11 12	Urticaria, conjunctivitis, and bronchospasm treated with epinephrine*	0 1	NR	NA
Creticos, 1996[9]	Ragweed Moderate to severe asthma	SCIT Placebo	37 40	Bronchospasm and hypotension requiring epinephrine (was in the placebo group but received immunotherapy by mistake)*	0 1	NR	NA

*Not defined as anaphylaxis but symptoms and treatment are consistent with anaphylaxis

Table E5.A – Local Reactions

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Garcia-Robaina, 2006[1] Gallego, 2010[2]	Dust mite Mild and Moderate asthma	SCIT Placebo	32 32	erythema <5cm	2 2	NR NR	0
Ameal, 2005[4]	Dust mite Mild and Moderate asthma	SCIT Placebo	29 26	cutaneous (wheal)	2 3	NR NR	-0.046
Vidal, 2011[5]	Dust mite Mild and Moderate asthma	SCIT Placebo	21 24	Not specified	3 (14.3%) 3 (12.5%)	10 4	0.018
Ohman, 1984[10]	Cat Severity NS	SCIT Placebo	9 8	2 patients/3 reactions: Large local reaction required modifications of the immunotherapy schedule classified as severe	2 (22%) 0	N0.317 to 0,4R	0.222
Van Metre, 1988[11]	Cat Severity NS	SCIT Placebo	11 (336 injections)	local reactions: Induration > 5 cm Reactions reported during first year of IT – no reactions reported for placebo arm	Reaction rate (7.7 reactions/ 100 injections)	26	NA
Casanovas, 2005[37]	Timothy Grass Mild and Moderate asthma	SCIT unmodified SCIT modified	12 11	Immediate local reactions	NR NR	3 6	NA
				Delayed local reactions	NR NR	18 12	NA

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Lozano, 2014[26]	Dust mite Intermittent, Mild and Moderate asthma	SCIT Pharmacotherapy	21 20	Local AEs requiring dose modification	0 0	NR NR	0
Baris, 2014[24]	Dust mite Mild and Moderate asthma	SCIT + vitamin D SCIT alone Pharmacotherapy	17 15 18	Local urticarial plaques at their injection sites	6 7 0	NR NR NR	0.013
Ibero, 2006[17]	Dust mite Mild and Moderate asthma	SCIT Placebo	15 13	Pain and heat over a 24-hour period after the first 2 injections	1 0	1 0	0.067
				Pain immediately after the second maintenance dose	1 0	1 0	0.067
				Induration (1 cm in diameter) and pruritus after the third maintenance dose	1 0	1 0	0.067
Zielen, 2010[27]	Dust mite Severity NS	SCIT + ICS ICS alone	33 32	most frequent symptoms were application site itching and application site paresthesia	11 (33.3%) 0	NR NR	0.333
Schubert 2009[38]	Dust mite Mild and Moderate asthma	cluster schedule classic schedule	20 (341 injections) 10 (151 injections)	Local events classified as mild Redness: 97 (28%), Swelling <5cm: 57 (16%), Swelling > 5cm: 22 (6%), painful swelling >3h: 8 (2%) Redness: 40 (26%), Swelling <5cm: 20 (13%), Swelling > 5cm: 17 (11%), painful swelling >3h: 3 (2%)	events per patient 9.25 8	185 (54%) 80 (53%)	NA SCIT vs SCIT
Dreborg, 1986[29]	*Cladosporium* Mild and Moderate asthma	SCIT vs Placebo	16 14	Local reactions >10cm	NR	4 0	NA
Roberts, 2006[39]	Grass Mild, Moderate and Severe asthma	SCIT Placebo	18 17	Episodes of pruritus, pain, or swelling	NR NR	13 11	NA
Hui, 2014[30]	Dust mite Mild and Moderate asthma	SCIT Desensitization vaccine*	45 45	local induration, induced cough and urticaria	NR	202/ 1735 (11.7%) injections	NA
Tsai, 2010[35]	Dust mite Moderate and Severe asthma	SCIT Pharmacotherapy	20 20	Local red swelling at injection site	8 0	NR NR	0.4
Valovirta, 1984[21] Valovirta, 2006[22]	Dog Severity NS	SCIT Placebo	15 12	309: 227<1cm, 71 1-3cm, 11>3cm 251: 163<1cm, 82 1-3cm, 6>3cm	309 251	events per patient 20 21	-0.317

NR: Not reported * the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table E6.A – Systemic Reactions

Study	Allergen and Asthma Severity	Arms	N	Duration of SCIT Treatment	Time During SCIT When Reaction Occurred	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Garcia-Robaina, 2006[1] Gallego, 2010[2]	Dust mite Mild and Moderate asthma	SCIT Placebo	32 32	54 weeks	Not specified	Hoarseness	0 0	NR NR	0
Bousquet, 1985[3]	Dust mite Severity NS	SCIT (Rush) Placebo	20 10	7 weeks	Not specified	4/20 developed a "systemic reaction" (unspecified) No reactions in control group	4 (20%) 0	NR	0.2
Ameal, 2005[4]	Dust mite Mild and Moderate asthma	SCIT Placebo	29 26	12 months	Not specified	Pruritus (1 pt) Urticaria (1 pt) Note: occurred 12 hours later in patient known to have urticaria "Delayed mild reaction" (3 pts) Note: control reactions NS	5 3	NR	0.057
Vidal, 2011[5]	Dust mite Mild and Moderate asthma	SCIT Placebo	21 24	4 months	Not specified	"Mild-Moderate reaction" in 1 event "unlikely related to SCIT" (7 events) 1 probable reaction (5 unlikely)	6 (28.6%) 5 (11.1%)	8 6	0.077
Kohno, 1998[7]	Dust mite Severity NS	SCIT Placebo	8 6	6 months	Not specified	2 patients dropped out of the study due to respiratory infection	2 0	NR	0.25
Chakraborty, 2006[8]	Grass Severity NS	SCIT Placebo	8 6	2 years	Not specified	Respiratory AE	0 0	NR NR	0
Creticos, 1996[9]	Ragweed Moderate and Severe asthma	SCIT Placebo	37 40	2 years	Not specified	5 events "mild reactions that resolved spontaneously"	NR NR	NR NR	NA
						9 events systemic reactions: rhinitis, urticaria, angioedema (or combination of these): required antihistamines or epinephrine	7 1	14 1	0.164
						1 patient Bronchospasm + hypotension (Allergen given by mistake)	2 0	NR	0.054

Study	Allergen and Asthma Severity	Arms	N	Duration of SCIT Treatment	Time During SCIT When Reaction Occurred	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Ohman, 1984[10]	Cat Severity NS	SCIT Placebo	9 8	16 weeks	Not specified	Rhinoconjunctivitis, asthma, itching, facial swelling and hives. "all were mild and responded promptly to treatment" Note: skin test titer, bronchial reactivity, and sensitivity of white blood cells to allergen did not predict reliably those subjects who would have reactions to immunotherapy	4 (44%) 1 (12.5%)	10 2	0.319
Garcia-Ortega, 1993[12]	Dust mite Severity NS	SCIT (cluster) Pharmacotherapy (bronchodilators/ usual care)	18 18	7 months	Not specified	Mild reactions: 2 wheezing classified as moderate 1 generalized urticaria classified as moderate	3 (16%) 0	NR NR	0.167
						Generalized urticaria classified as moderate	5% 0	NR	0.028
Casanovas, 2005[37]	Timothy Grass Mild and Moderate asthma	SCIT unmodified SCIT modified	12 11	11 injections total	Highest maintenance dose	Immediate reactions: Group A 1 Perioral itching 1 Nasal-ocular symptoms, dyspnea, dizziness, cough 1 Urticaria, rhinoconjunctivitis, bronchospasm Group B 1 Palatal itching	NR	4 (114 injections) 1 (121 injections)	NA SCIT vs SCIT
						Delayed systemic reactions: Group A 1 "unspecified symptoms" 1 Naso-ocular symptoms, abdominal pain, diarrhea, headache 1 Rhinoconjunctivitis 1 Urticaria, headaches, pharyngeal discomfort Group B: 1 headache and nasal obstruction	NR	8 (114 injections) 1 (121 injections)	NA SCIT vs SCIT

Study	Allergen and Asthma Severity	Arms	N	Duration of SCIT Treatment	Time During SCIT When Reaction Occurred	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Lozano, 2014[26]	Dust mite Intermittent, Mild and Moderate asthma	SCIT Pharmacotherapy	21 20	8 months	Not specified	Systemic AEs requiring dose modification	0 0	NR	0
Baris, 2014[24]	Dust mite Mild and Moderate asthma	SCIT + vitamin D SCIT alone Pharmacotherapy	17 15 18	12 months	Not specified	2 mild asthma 1 "systemic reaction" within 20 minutes after injection of vial 4, requiring Epinephrine	2 1 0	NR NR NR	0.093
Ibero, 2006[17]	Dust mite Mild and Moderate asthma	SCIT Placebo	15 13	4 months	After 2nd or 3rd dose	1 mild rhinitis and asthma 1 mild dyspnea No meds were needed to treat any of the reactions	2 0	2 0	0.133
Zielen, 2010[27]	Dust mite Severity NS	SCIT + ICS ICS alone	33 32	2 years	Not specified	Cough, rhinitis	2 (6.1%) 0	NR	0.061
Schubert 2009[38]	Dust mite Mild and Moderate asthma	cluster schedule classic schedule	20 (341 injections) 10 (151 injections)	16 weeks	Not specified	Reactions classified as mild 12 reactions: 10 cough-2 dyspnea 7 reactions: 6 cough-1 dyspnea	0.7 events per patient 0.8 events per patient	12 reactions (3.5% of injections) 7 reactions (4.6% of injections)	NA SCIT vs SCIT
						Bronchial asthma - classified as moderate	0.3 events per patient 0.2 events per patient	2 reactions (0.6% of injections) 1 reaction (0.7% of injections)	NA SCIT vs SCIT
Roberts, 2006[39]	Grass Mild, Moderate and Severe asthma	SCIT Placebo	18 17	2 years	Not specified	pulmonary reactions that responded to bronchodilators	4 3	4 3	0.046
						Others: Eczema, urticaria, rhinoconjunctivitis	NR	21 9	NA
Hui, 2014[30]	Dust mite Mild and Moderate asthma	SCIT desensitization vaccine *	45 45	51 weeks	During dose increasing phase	NS and not divided by group	NR	1/ 1735 injections (0.05 %)	NA
Alzakar, 2010[34]	Dust mite, Grass, Mold, pets, and Trees Excluded severe asthma	SCIT Pharmacotherapy Beclomethasone + Aminophylline	85 112	12 months	Not specified	1 "mild respiratory involvement" 8 "skin rash" Did not specify if these are treatment or control groups	9 (11%)	NR	NA
Arroabarren, 2015[31]	Dust mite Mild and Moderate asthma	5-year IT 3-year IT	36 NR	3 or 5 years	Not specified	2 subjects with asthma had an asthma episode within 30 minutes of maintenance dose, treated with bronchodilators	2 (2.46%) NR	0.03% of doses	NA

Study	Allergen and Asthma Severity	Arms	N	Duration of SCIT Treatment	Time During SCIT When Reaction Occurred	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Tsai, 2010[35]	Dust mite Moderate and Severe asthma	SCIT pharmacotherapy	20 20	3 months	Not specified	Not specified	0 0	NR	0
Adkinson, 1997[32]	Multiple Moderate to severe asthma	SCIT Placebo	61 60	30 months	Not specified	114 total systemic reactions (52 treated with adrenergic drugs and all responded to treatment)	21 (34%) 4 (7%)	2.6/100 injections	0.278

* the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table E7.A – Deaths*

No deaths reported

*Data abstracted ONLY if studies specifically reported on deaths

SECTION B SCIT SAFETY FOR NON RCTs

Table E1.B – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Quiralte,2013[40] Europe	SCIT cluster SCIT conventional	Asthma diagnosis NS Severity NS Control status NS	Not reported	Not reported	Multiple allergens	Clinic
	Rank, 2008[41] US	SCIT Cluster wo comparator	Asthma diagnosis criteria NS Severity NS Control status NS	SPT and IgE wheal >3mm IgE NS	Both mono and polysensitized Not specified	Multiple allergens	Not specified
	Rank, 2014[42] US	SCIT wo comparator	Asthma diagnosis not described Severity NS Asthma control NS	Not reported	Not reported	Multiple allergens	Clinic
	Sana, 2013[43] Europe	SCIT wo comparator	Asthma diagnosis criteria NS Severity Moderate persistent Control status NS	SPT and IgE NS	Not reported	Multiple allergen (Alustal – respiratory allergens)	Not specified AE treated in ICU

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Kim, 2011[44] Asia	SCIT Rush and ultrarush wo comparator	Asthma diagnosis Pulmonary tests (20% decrease in FEV1 following < 8mg ethacholine/mL or reversibility of FEV1 > 15% after bronchodilator + clinical symptoms) Severity NS Control status NS	SPT and IgE Wheal ≥3 mm above negative control; serum-specific IgE antibody tests to HDM (≥ 0.7 kU/L)	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic
	Sanchez-Morillas, 2005[45] Europe	SCIT wo comparator	Asthma diagnosis criteria NS Severity NS Control status NS	SPT and IgE SPT NS IgE: Cupressus arizónica 0.94 KU/l, Cupressus sempervirens 1.26 KU/l	Monosensitized Tree cypress	Single allergen Tree Arizona cypress	Clinic
	Ozden, 2009[46]	SCIT wo comparator	Asthma diagnosis NS Severity NS Control status NS	Not reported	Not reported	Single allergen Timothy Grass	Clinic
Mixed age	Gozde Kanmaz, 2011[47] US	SCIT VS. SCIT	Asthma diagnosis GINA criteria Severity Mild persistent and moderate persistent Control status NS	SPT > 3mm	Monosensitized Dust mite (D pter OR D far)	Single allergen Dust mite (D pter-D far)	Not reported
	Kartal, 2015[48] Europe	SCIT wo comparator	Asthma diagnosis NS Severity NS Asthma control NS	Not described	Polysensitized Dust mites (HDM), Pollen,cat, mold	Single allergen Dust mite (HDM)	Clinic
	Copenhaver, 2011[49] US	SCIT Cluster wo comparator	Asthma diagnosis Physician Severity NS Control status NS	Not reported	Not reported	Multiple allergens Dust mites, grass, trees, cat, dog, mold, cockroach	Clinic
	Confino-Cohen, 2010[50] Asia	SCIT wo comparator	Asthma diagnosis NS Severity NS Control status NS	Not reported	Not reported	Multiple allergens	Clinic
	Smits, 2007[51] US	SCIT Rush wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT NS	Polysensitized grass, dust mites, cats, ragweed	Multiple allergens	Clinic
	Chen, 2014[52] Asia	SCIT adults SCIT children	Asthma diagnosis NS Severity NS Control status NS	SPT and IgE SPT NS IgE Class II	Monosensitized and Polysensitized	Dust mite (D pter)	Clinic
	Cardona, 2014[53] South America	SCIT Ultrarush wo comparator	Asthma diagnosis NS Severity NS Control status NS	Not reported	Monosensitized Dust mite (D pter)	Dust mite (D pter)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Santos, 2015[54] Europe	SCIT wo comparator	Asthma diagnosis not described Severity NS Asthma control NS	Not reported	Not reported	Pollen, dust mites (NS)	Clinic
	Eng, 2006[55] Europe	SCIT wo comparator	Asthma diagnosis criteria NS Severity NS Control status NS	SPT and IgE NS	Monosensitized Grass	Single allergen Grass	Not specified
	Dong, 2017[56] Asia	SCIT wo comparator	Asthma diagnosis per GINA guidelines Severity NS Control status NS	SPT and IgE SPT Wheal size > 3mm IgE >0.35 kUA/L	103 patients were monosensitized to dust mites 18 were polysensitized	Single allergen Dust mite	Clinic
	Lim,2017[57] Asia	SCIT wo comparator	Asthma diagnosis NS Severity NS Control status NS	SPT NS	Polysensitized	Multiple allergens	Not specified

SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified -Not described D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*
* Authors did not report sensitization status

Table E2.B – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (range)	Sex (% male/female)	Patients Enrolled/ Dropouts	Duration of disease (Mean years affected)
Adults	Quiralte,2013[40]	183 169	Cluster-SCIT Short Conventional-SCIT	26.2 (13.3) 26.7 (13.8)	49%/51% 57.4%/42.6%	19/NR 26/NR	NR
	Rank, 2008[41]	NA	Systemic Reaction with SCIT No Systemic Reaction with SCIT	NR	NR	NR	NR
	Rank, 2014[42]	1	Case Report	42 years' old	NA/1	1/NR	NR
	Sana, 2013[43]	1	Case Report	17 years' old	NA/1	1/NR	NR
	Kim, 2011[44]	NR	BA rush IT	25.5 (10.3)	27.8%/NR	18/NR	NR
	Sanchez-Morillas, 2005[45]	1	Case Study	66 years' old	NA/1	1/NR	3 years
	Ozden, 2009[46]	1	Case Study	NR	NR	1/NR	NR
Mixed age	Gozde Kanmaz, 2011[47]	102	SCIT Pharmacotherapy	12.4 (2.3) 12.5 (2.4)	46/54 65/35	50/NR 52/NR	NR
	Kartal, 2015[48]	706	SCIT wo comparator	25.7 (12.2)	54.7%/45.3%	1816/NR	NR
	Copenhaver, 2011[49]	NR	SCIT wo comparator	NR	NR	NR	NR

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (range)	Sex (% male/female)	Patients Enrolled/ Dropouts	Duration of disease (Mean years affected)
	Confino-Cohen, 2010[50]	133	SCIT wo comparator	NR	NR	NR	NR
	Smits, 2007[51]	505	SCIT wo comparator	NR	NR	NR	NR
	Chen, 2014[52]	130	SCIT – Children SCIT - Adults	9.62 (2.71) 28.31 (10.3)	62.45%/NR 47.9%/NR	67/16 63/31	NR
	Cardona, 2014[53]	313	SCIT wo comparator	15 (NR)	NR/51%	313/NR	NR
	Santos, 2015[54]	NR	SCIT wo comparator	NR	NR	NR/NR	NR
	Eng, 2006[55]	NR	SCIT No SCIT	23.8 (NR) 23.4 (NR)	9/3 7/3	NR/NR	NR
	Dong, 2017[56]	68	SCIT wo comparator	24 adults 44 children Age not specified for asthma only patients	NR for asthma only patients	NR	NR
	Lim,2017[57]	144	SCIT wo comparator	69 adults 75 children Age not specified for asthma only patients	NR for asthma only patients	NR	NR

Table E3.B– Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Quiralte,2013[40]	SCIT Cluster SCIT Conventional	NR	NR	Targeted: 14.8 IR Actual: 8 IR Targeted: 16.5 IR Actual: 8 IR	Weekly	NR	4 weeks or 8 weeks
	Rank, 2008[41]	Systemic Reaction with SCIT No Systemic Reaction with SCIT	Conventional therapy and Rescue therapy	NR	NR	NR	NR	NR
	Rank, 2014[42]	Case Study	NR	NR	Targeted: NR Actual: .25	Cluster	NR	NR
	Sana, 2013[43]	Case Study	NR	NR	NR	NR	NR	NA
	Kim, 2011[44]	Rush IT	Conventional therapy and Rescue therapy	Targeted: 0.8 mL of the highest allergen concentration (5000 units/ml) once a month as maintenance therapy Actual: NR	Targeted: 5,000 units/ ml Actual: NR	Monthly	NR	3 days

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Sanchez-Morillas, 2005[45]	Case Study	NR	Targeted: NR Actual: Depot preparation monthly for 2 years	Targeted: NR Actual: 19475 STU accumulated	Monthly	NR	2 years
	Ozden, 2009[46]	Case Study	NR	NR	NR	NR	NR	NR
Mixed age	Gozde Kanmaz, 2011[47]	SCIT Pharmacotherapy	NR	Targeted: NR Actual: 100,000 SQ-U Targeted: NR Actual: 0.00001, 0.0001, 0.001 and 0.01 mg/ml	NR	Weekly	NR	33 months average
	Kartal, 2015[48]	SCIT wo comparator	NR	Targeted: NR Actual: 0.8 ml/5000 TU/ml (NH) and 0.8 ml/10 IR/ml (P)	Targeted: NR Actual: 10 IR/ml	Weekly	NR	30 years
	Copenhaver, 2011[49]	SCIT wo comparator	NR	NR	Targeted: concentration 1:1, 0.5ml Actual: NR	Cluster	NR	8 office visits
	Confino-Cohen, 2010[50]	SCIT wo comparator	Conventional therapy and Rescue therapy	NR	NR	NR	NR	NR
	Smits, 2007[51]	SCIT wo comparator	NR	Targeted: 0.4ml Actual: 0.4ml	NR	Every 4-10 days	NR	3 days
	Chen, 2014[52]	SCIT – Children SCIT - Adults	NR	Targeted: 100,000 SQ-U/mL Actual: NR	NR	Every 6 weeks	NR	NR
	Cardona, 2014[53]	SCIT wo comparator	NR	Targeted: 0.5 ml 50 DPP Actual: 0.5 ml 50 DPP	NR	Monthly	NR	NR
	Santos, 2015[54]	SCIT wo comparator	NR	NR	NR	NR	NR	NR
	Eng, 2006[55]	SCIT No SCIT	Conventional therapy and Rescue therapy	NR	NR	NR	NR	2 years
	Dong, 2017[56]	SCIT wo comparator	NR	Standardized allergens, increased by 10-fold from 100 to 100.000 SQ-U	NR	Weekly	NR	6 weeks
	Lim,2017[57]	SCIT wo comparator	No Beta blockers	NR	NR	NR	NR	NR

Table E4.B – Anaphylaxis

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Comparative Value
Quiralte, 2013[40]	Dust mite, Mold, Animals, Trees and Grass Severity NS	SCIT cluster SCIT conventional	339 (2712 doses) 319 (2552 doses)	No anaphylaxis events were reported	0	0
Confino-Cohen, 2010[50]	Multiple allergens Severity NS	SCIT wo comparator	133 (21,022 injections)	Frequency of anaphylaxis in a case series of SCIT in children and adults. Anaphylaxis was classified as "mild, moderate, or severe" based on symptoms. Reactions were classified as Uniphasic or Biphasic. Uniphasic reactions: 54 out of 101 patients had asthma Biphasic reactions: 9 out of 11 patients had asthma	54/101 (54) 9/11 (82) Incidence 1.3%	*P*=0.07
Rank, 2014[42]	Grass Severity NS	SCIT wo comparator	1	flushing, nasal congestion, nasal itching, and chest tightness with wheezing; treated with epinephrine IM, diphenhydramine IM, prednisone, and albuterol note: patient was receiving cluster SCIT during the pollen season	1	1
Lim,2017[57]	Multiple allergens. Severity NS	SCIT wo comparator	144	1 adult, male, with intermittent asthma at baseline, during the build-up phase presented shortness of breath and hypotension (WAO-Grade 4)	1	1

Table E5.B – Local Reactions

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Quiralte,2013[40]	Dust mite, Mold, Animals, Trees and Grass Severity NS	SCIT cluster SCIT conventional	339 (2712 doses) 319 (2552 doses)	Local urticarial plaques at their injection sites	85 (25.1%) 87 (27.3%)	177 (6.5% of doses) 274 (10.7% of doses)
Kartal, 2015[48]	Dust mite Severity NS	SCIT W/O COMP	1816	Large local reaction	93	NR
				Small local reaction	71	NR
Ozden, 2009[46]	Timothy Grass Severity NS	SCIT W/O COMP	1	multiple subcutaneous itchy nodules on the lateral aspects of both arms, at the site of previous immunotherapy injections	1	Case report

Table E6.B – Systemic Reactions

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Gozde Kanmaz, 2011[47]	Grass and Dust mite Mild and Moderate asthma	SCIT Pharmacotherapy	50 52	Worsening of condition attributed to mild systemic reaction	1 0	NR
				Undercurrent illnesses, or worsening of condition	5 0	NR
Quiralte,2013[40]	Dust mite, Mold, Animals, Trees and Grass Severity NS	SCIT cluster SCIT conventional	339 (2712 doses) 319 (2552 doses)	Total Systemic reactions	5 (1.5 %) 14 (4.4 %)	5 (0.2% of doses) 24 (0.9 %of doses)
				Systemic reactions Grade 0 = “Non-specific systemic symptoms”	1 (0.3 %) 8 (2.5 %)	1 13
				Systemic reactions Grade 1 = localized yrticaria, rhinitis or mild asthma; peak flow [PEF] <20% decrease from baseline)	3 (0.9 %) 4 (1.2 %)	3 8
				Systemic reactions Grade 2 = generalized urticaria, moderate asthma or both; PEF <40% decrease from baseline	1 (0.3 %) 2 (0.6 %)	1 3
Rank, 2014[42]	Grass Severity NS	SCIT wo comparator	1	flushing, nasal congestion, nasal itching, and chest tightness with wheezing; treated with epinephrine IM, diphenhydramine IM, prednisone, and albuterol note: patient was receiving cluster SCIT during the pollen season	1	1
				Odds of an SR to SCIT for a patient with asthma were lower than those without. Patients with asthma with SR 1 (3%) Patients with asthma without SR 1144 (11%) OR 0.29 (0.04–2.14)	NR	NR
Kim, 2011[44]	Dust mite Severity NS	SCIT wo comparator	18	1 participant had moderate bronchospasm (grade 2). Occurred at therapeutic dose 4000 (planned max therapeutic dose = 4000). Onset time 160 min. Treatment: Inhalation of 200 µg of salbutamol.	1	NR
				1 participant had localized urticaria grade 1 systemic reaction. Planned max therapeutic dose = 4000units. Allergen dose that induced SR = 4000 TU Onset time = 30 min	1	NR
				2 had generalized urticaria(grade 2). Occurred at therapeutic dose 4000 (planned max therapeutic dose = 4000). Onset time 160 min. Treatment: Inhalation of 200 µg of salbutamol.	2	NR

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Kartal, 2015[48]	Dust mite Severity NS	SCIT wo comparator	702	Only results available regarding asthma patients: The rate of systemic reactions in asthma plus AR patients (11%) was higher than asthma alone (1.5%) and AR alone patients (9.5%). The risk of SR was lowest for asthmatic patients than in patients with asthma plus rhinitis (OR, 0.13; 95% CI, 0.04-0.41; p50.001), or (OR, 0.15; 95% CI, 0.05-0.48; p50.001)		NR
Sanchez-Morillas, 2005[45]	Trees Severity NS	SCIT wo comparator	1	Leukocytoclastic Vasculitis on both legs, diagnosed by skin biopsy, after being on depot SCIT for 2 years, the same episodes occurred with the next 2 doses of SCIT	1	1
Copenhaver, 2011[49]	Dust mites, Grass, Trees, Cat, Dog, Mold, Cockroach Severity NS	SCIT wo comparator	127	Not specified Significantly higher than patients without asthma (19.7% vs 7.3%, P = .0005)	19.7%	25
Smits, 2007[51]	Grass, Dust mite, Animals, and Weeds Severity NS	SCIT wo comparator	505	Study included patients with asthma and rhinitis. 14 of the 18 SRs were in patients with asthma (79%)	14	NR
Chen, 2014[52]	Dust mite Severity NS	SCIT children SCIT adults	67 63	Total non-fatal systemic reactions	16 (23.88%) 8 (12.7%)	NR
Cardona, 2014[53]	Dust mite Severity NS	Ultra-rush SCIT wo comparator	313	4 patients had hives and/or wheezing 2 patients had rhinorrhea ocular itching 6 out of 8 patients who had systemic reactions had asthma	6	NR
Santos, 2015[54]	Pollen and Dust mites Severity NS	SCIT wo comparator	3732 (22332 injections both asthma and rhinitis)	3 year retrospective study; there were 26 reactions (0.1% of administrations) in 16 (0.6%) of the patients) 9 subjects with asthma had systemic effects (not clear what number of subjects had asthma Most of the grade 2 reactions occurred in individuals with asthma and presented as cough and/or dyspnea and/or asthma exacerbation (79%)	NR	NR
Dong, 2017[56]	Dust mite Severity NS	SCIT wo comparator	63	Systemic reactions were classified per WAO criteria, and ranged from 1 to 3. However the severity of systemic reactions was not broken down in patients with asthma 27 patients presented unspecified systematic reactions 17 of which had asthma. Some patients responded to epinephrine but numbers not reported and also not how many of those had asthma.	17 (25) OR 4.102	NR

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Lim,2017[57]	Multiple allergens. Severity NS	SCIT wo comparator	144	Grade 3 WAO reactions – 12 total; 7 adults and 5 in children (9-13 years old), 10 during build up phase	12	NR

Table E7.B – Deaths*

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Rank, 2008[41]	Dust mite and Animals Severity NS	SCIT wo comparator	338	There were no fatalities reported	0	0
Kartal, 2015[48]	Dust mite Severity NS	SCIT wo comparator	1816	There were no fatalities reported	0	0
Sana, 2013[43]	Alustal – respiratory allergens Moderate asthma	SCIT wo COMP	1	12 hours after initiation of treatment, she complained of abdominal pain, vomiting and diarrhea without fever Two days later, she developed an acute respiratory failure and was referred to the intensive care unit on day 4 she developed hypoxic coma leading to intubation and mechanical ventilation. Rapidly, she experienced intractable shock and acute renal impairment. By day 5 she developed multiorgan failure and died	1	1
Dong, 2017[56]	Dust mite Severity NS	SCIT wo comparator	68	There were no fatal reactions	0	0
Lim,2017[57]	Multiple allergens. Severity NS	SCIT wo comparator	144	There were deaths (Grade 5 reactions)	0	0

*Data abstracted ONLY if studies specifically reported on deaths

Appendix F. KQ3- What is the evidence for the efficacy of sublingual immunotherapy (SLIT) in tablet and aqueous form, in the treatment of asthma?

(Organization in tables first by population; adults-mixed population- children. Within each category by comparator SCIT vs placebo- SCIT vs pharmacotherapy- SCIT vs SCIT. Within each subcategory by allergen; HDM-grass- weed- tress- animal-multiple allergen)

Table F1 – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Virchow, 2016[58] Europe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Pulmonary tests (PFT reversibility) Moderate to severe Asthma Poorly Controlled	SPT and IgE SPT ≥ 3 mm SIgE≥ 0.70 ku/L	Both mono and polysensitized "Patients could have multiple sensitization but no perennial asthma caused by other allergens"	Single allergen Dust mite (D pter-D far)	Home
	de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61] Europe	SLIT(T) 6 SQ-HDM SLIT(T) 3 SQ-HDM SLIT(T) 1 SQ-HDM Placebo	Asthma diagnosis GINA criteria (steps 2 and 3) Pulmonary tests (documented history of reversible airway obstruction) Mild persistent and moderate persistent Controlled (ACQ scores and ICS dose of 100 to 800 mg/d)	SPT and IgE wheal size >3mm to D farinae, D pteronyssinus, or both IgE NS	Both mono and polysensitized	Single allergen Dust mite (D pter-D far)	Not specified
	Maloney, 2016[62] US	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Severity not specified Controlled (FEV1 ≥70% predicted, no more than 2 symptoms per week, no more than 2 days of SABA use per week, no more than 2 awakenings per month due to asthma)	SPT and IgE wheal diameter ≥5mm larger than saline control; serum-specific IgE≥ 0.7 kU/L or at least class II (all against D pter or D far)	Both mono and polysensitized Dust mite (D pter-D far) grass, cat, dog, mold, birch,mugwort	Single allergen Dust mite (D pter-D far)	Home
	Devillier, 2016[63] Wang, 2014[64] Multisite	SLIT (A) Placebo	Asthma diagnosis pulmonary tests (bronchial reversibility test and methacoline challenge) Mild persistent and moderate persistent	SPT and IgE wheal diameter ≥ 4 mm in an SPT after washout of antihistamines, specific IgE ≥ 0.70 kU/ l	Monosensitized Dust mites (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic
	Gomez, 2004[65] Mexico	SLIT (A) Placebo	Asthma diagnosis GINA criteria Pulmonary tests (FEV change >14% after salbutamol) Mild persistent and moderate persistent Control status NS	SPT and IgE SPT NS Specific IgE ≥ 200UI	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D pter)	Single allergen Dust mite (D pter)	Not specified
	Dahl, 2006[66] Europe	SLIT (T) Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate	SPT and IgE wheal >3mm	Monosensitized Grass mix	Single allergen	Home

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
			Controlled asthma	IgE NS		Grass mix	
	Calderon, 2006[67] Europe	SLIT (A) Placebo	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Controlled asthma	SPT and IgE wheal >3mm IgE > class 2	Monosensitized Grass (Phleum pratense)	Single allergen Grass (Phleum pratense)	Not specified
	Marogna, 2013[68] Europe	SLIT (T) Pharmacotherapy	Asthma diagnosis GINA criteria Pulmonary tests (Positive methacholine challenge -PD20 FEV1 <800g) Severity Mild persistent Control status Poorly controlled	SPT and IgE Skin test >5mm (does not specify if wheal or flare); and class II positivity to birch assessed with ImmunoCAP (Unicap)	Monosensitized Trees (Birch)	Single allergen Birch	Home
	Voltolini 2010[69] Europe	SLIT (A) Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate Control status NR	SPT and IgE NS	Monosensitized White birch	Single allergen Birch	NS
	Marogna, 2009[70] Europe	SLIT (A) Pharmacotherapy	Asthma diagnosis GINA criteria – FEV 60-80%) Severity Moderate Control status controlled	SPT Wheal >5mm	Monosensitized White birch	Single allergen Birch	NS
	Marogna, 2010[71] Europe	SLIT (A) Pharmacotherapy	Asthma diagnosis GINA criteria – FEV>79%) Severity Mild Control status controlled	SPT and IgE Wheal >5mm IgE class 2	Monosensitized Grass mix	Single allergen Grass mix	NS
Mixed age	Pham-Thi, 2007[72] Europe	SLIT (T) Placebo	Asthma diagnosis pulmonary tests (reversible bronchial obstruction – salbutamol inhalation) Severity Mild persistent and moderate persistent Control status NS	SPT and IgE SPT NS IgE level ≥ 2 CAP RAST	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified
	Bahceciler, 2001[73] Asia	SLIT (A) Placebo	Asthma diagnosis criteria NS Severity Persistent (NS) Control status – ongoing respiratory symptoms despite HDM avoidance and ICS	SPT and IgE Wheal >5mm IgE class 2	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified
	La Grutta, 2007[74]	SLIT (T) Pharmacotherapy	Asthma diagnosis criteria NS Severity Mild persistent (NS) Controlled asthma	SPT >3mm	Both mono and polysensitized Dust mite and parietaria	Single allergen Dust mite (NS)	Home
	Stelmach, 2009[75]	SLIT (A) Placebo	Asthma diagnosis pulmonary tests (reversible bronchial obstruction – salbutamol inhalation ≥12%) Severity Excluded severe asthma	SPT and IgE SPT NS IgE NS	Monosensitized Grass	Single allergen Grass mix	Not specified

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
			Control status NS				
Children	Lue, 2006[76] Asia	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE > 3	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified
	Niu, 2006[77] Asia	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE > 3	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified
	Ippoliti, 2003[78] Europe	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE class 3	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified

T: Tablet A: Aqueous SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*
***** Authors did not report sensitization status

Table F2 – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Adults	Virchow, 2016[58]	834	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	34 +/- 12 (Range 18-75) 34 +/- 12 (Range 17-74) 33 +/- 12 (Range 17-74)	48/52 52/48 55/45	257/34 282/43 277/48	NR
	de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	604	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	NR	NR	156/16 159/25 146/14 143/17	12 weeks
	Maloney, 2016[62]	68	SLIT (T) 6 SQ HDM SLIT (T) 12 SQ HDM Placebo	Range (12-17)	NR	NR	6 months
	Devillier, 2016[63] Wang, 2014[64]	484	SLIT (A) Placebo	31 +/- 9 (Range 14-50) 31 +/- 8 (Range 16-49)	27/73 42/58	322/14 162/4	1 year
	Gomez, 2004[65]	60	SLIT (A) Placebo	22.8 20.6	53/47 33/67	30/NR 30/NR	3.8
	Dahl, 2006[66]	114	SLIT (T) Placebo	36 (11) 34 (10)	71/29 60/40	74/13 40/8	14 12
	Calderon, 2006[67]	43	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	22 (3) 23 (3) 28 (9) 26 (5) 24 (5)	67/33 67/33 67/33 60/40 55/45	9/0 9/0 9/0 5/0 11/0	12.9 years 15.7 years 22.2 years 19.4 years 15.4 years

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
	Marogna, 2013[68]	84	SLIT (T)+ Budesonide 400 µg Budesonide 800 µg Budesonide 1600 µg Budesonide 400 µg + ALKT	NR	NR	21/2 21/3 21/1 21/2	2 years
	Voltolini, 2010[69]	24	SLIT (A) Placebo	44 +/- 9 40 +/- 7	50/50 30/70	14/1 10/1	NR
	Marogna, 2009[70]	51	SLIT (A) Pharmacotherapy	27 +/- 1 (Range 17-41) 27 +/- 1 (Range 19-41)	44/56 46/54	25/2 26/3	8 7
	Marogna, 2010[71]	33	SLIT (A) Pharmacotherapy	NR	NR	17/1 16/3	2 years
Mixed age	Pham-Thi, 2007[72]	111	SLIT (T) Placebo	9.6 (Range 5-14) 9.5 (Range 5-16)	72/28 72/28	54/11 54/8	5
	Bahceciler, 2001[73]	15	SLIT (A) Placebo	Median 12 (Range 8-18) Median 12 (Range 7-15)	50/50 58/43	8/0 7/0	Median 1.5 Median 3
	La Grutta, 2007[74]	56	SLIT (T) Pharmacotherapy	15 +/- 9 (Range 8-44) 22 +/- 15 (Range 7-68)	67/33 56/44	33/0 23/0	NR
	Stelmach, 2009[75]	50	SLIT (A) Placebo	9.1 +/-2.4 8.5 +/- 2.8	60/40 66/33	25/5 25/10	NR
Children	Lue, 2006[76]	20	SLIT (A) Placebo	7.7 +/- 1.8 8.6 +/- 1.8	40/60 40/60	10/0 10/0	1
	Niu, 2006[77]	110	SLIT (A) Placebo	7.9 +/- 1.6 (Range 5-11) 8.2+/- 1.7 (Range 5-12)	61/39 58/42	56/7 54/6	1
	Ippoliti, 2003[78]	86	SLIT (A) Placebo	Median;9 (Range 5-12) Median;9 (Range 7-11)	60/41 56/44	47/0 39/0	2 2

T: Tablet A: Aqueous NR: Not reported

Table F3 – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Virchow, 2016[58]	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Only rescue (ICS)	6 SQ-HDM 12 SQ-HDM	360 SQ/ month 720 SQ /month	Daily	NR	7-12 months
	de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	Only rescue (ICS and B2)	6 SQ-HDM 3 SQ-HDM 1 SQ-HDM	NR	Daily	NR	1 year
	Maloney, 2016[62]	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Only rescue (ICS)	6 SQ-HDM 12 SQ-HDM	168 SQ 336 SQ	Daily	NR	28 days
	Devillier, 2016[63] Wang, 2014[64]	SLIT (A) Placebo	Both (Budesonide, Salbutamol, Prednisone)	300 IR	NR	Daily	28ug Der p 1 and 50 ug Der f 1	52 weeks

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Gomez, 2004[65]	SLIT (A) Placebo	Both BUT excluded systemic corticosteroids	710 UBE/ml	10469 UBE	3 times a week	NR	6 months
	Dahl, 2006[66]	SLIT (T) Placebo	Both (NS)	7500 SQT	NR	Daily	15 phl p5	137 days (Ultrarush)
	Calderon, 2006[67]	SLIT 75000 (T) SLIT 150000 (T) SLIT 300000 (T) SLIT 500000 (T) Placebo	NR	75000 SQT 150000 SQT 300000 SQT 500000 SQT	NR	Daily	15 ug /dose 30 ug /dose 60 ug /dose 100 ug /dose	28 days
	Marogna, 2013[68]	SLIT (T)+Budesonide 400µg Budesonide 800 µg Budesonide 1600 µg Budesonide 400 µg + LTRA	ICS BID Montelukast only for arm 4 No other treatment allowed	Pre-coseasonal	60,000 AU	1000 AU day/ 5 days a week for 12 weeks/ season for 3 years	60,000 AU (214,200µg of modified major allergen)	3 years
	Voltolini 2010[69]	SLIT (A) Placebo	Conventional therapy	300 IR	13.8 IR per season	Daily	13.8 IR (6.9 µgBet v1 per season)	4 months
	Marogna, 2009[70]	SLIT (A) Pharmacotherapy	Conventional therapy	5 drops of 10,000 RU/ml	70 µg (yearly)	3 times a week	70 Phl p1 (per year)	5 years
	Marogna, 2010[71]	SLIT (A) Pharmacotherapy	Conventional therapy (Formoterol/ Fluticasone)	5 drops of 10,000 RU/ml	NR	3 times a week	100 µg Bet v 1 per year	5 years
Mixed age	Pham-Thi, 2007[72]	SLIT (T) Placebo	Both (ICS and B2)	300 IR	155,000 IR	Daily	6.9mg Der p 1 and 14.7mg Der f 1	18 months
	Bahceciler, 2001[73]	SLIT (A) Placebo	Conventional therapy	20 drops of 100 IR/mL	7000 IR	daily 4 weeks, then 2 times a week for 4 months	560 Der P, 980 Der F (cumulative)	6 months
	La Grutta, 2007[74]	SLIT (T) Pharmacotherapy	Only rescue (ICS)	Rush 1000 AU	NR	Biweekly	NR	1 year
	Stelmach, 2009[75]	SLIT (A) Ultrarush Placebo	Conventional therapy BUT excluded systemic corticosteroids	120IR	43800 IR	3 times a week	3.65 mg of major allergens (5 grasses)	6 months
Children	Lue, 2006[76]	SLIT (A) Placebo	Conventional and rescue as needed	20 drops of 300 IR/mL	41824 IR	Daily	3 mg Der F 1.7 mg Der P (Cumulative)	24 weeks
	Niu, 2006[77]	SLIT (A) Placebo	Conventional and rescue as needed	20 drops of 300 IR/ml	41824 IR	Daily	3 mg Der F, 1.7 mg Der P (Cumulative)	24 weeks

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Ippoliti, 2003[78]	SLIT (A) Placebo	Conventional therapy	5 drops of 10 BU/mL	NR	3 times a week	2.4 Der p1 1.2 Der p2 (per week)	6 months

T: Tablet A: Aqueous BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg: microgram Ag/ml: major protein unit
TU: Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR; Index of reactivity unit LTRA: Leukotriene receptor antagonist

Table F4 – Asthma Control

Study	Allergen and Asthma Severity	Arms	N	Outcome Description	Time of Measure	Value Pre	Value post	Comparative Values
Virchow, 2016[58]	Dust mite Moderate to severe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	275 282 277	ACQ	12 months	Mean (SD) [IQR] 1.24 (0.17) [0.86-1.71] 1.23 (0.17) [0.71-1.57] 1.22 (0.18) [0.86-2.00]	Improvement 218 (78.88%) 221 (80.63% 232 (83.02%)	OR (95% CI): 6SQ-HDM vs placebo 1.12 (0.73 to 1.70) 12SQ-HDM vs placebo 1.31 (0.85 to 2.01) *P* = 0.22
de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	29 27 25 27	ACQ	12 months	Mean score 1.15 1.16 1.21 1.20	Change within group -0.41 -0.22 -0.16 0	SLIT 6SQ-HDM pre vs post *P*=0.0002
Devillier, 2016[63] Wang, 2014[64]	Dust mite Mild and moderate	SLIT (A) Placebo	113 62	ACQ	52 weeks	1.81 +/- 0.88 1.78 +/- 0.90	Percentage improvement 56.6% 40%	SLIT vs Placebo *P*<0.039
Marogna, 2013[68]	Birch Mild asthma	SLIT(T)+Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	19 19 20 18	ACT	3 years	Mean 14.1 16.1 15.3 13.4	Mean 24 17.2 19.1 18.4	SLIT vs all other arms *P*<0.05

ACT: Asthma control test ACQ: Asthma control questionnaire SQ-HDM: standard quality house dut mite tablet LTRA: Leukotriene receptor antagonist

Table F5 – Quality of Life
Asthma Specific Quality of Life – Asthma Quality of Life Questionnaire (AQLQ)
No study reported on Asthma QOL using Pediatric Asthma Specific Quality of Life – Asthma Quality of Life Questionnaire (PAQLQ)- School/Work Absences

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post
Virchow, 2016[58]	Dust mite Moderate to severe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	275 285 277	12 months	Mean +/- SD 5.46 +/- 0.88 5.49 +/- 0.78 5.54 +/-0.78	Improvement 231 (84.98%) 236 (84.39% 233 (84.80%)	6SQ-HDM vs placebo post OR (95% CI); 1.01 (0.63- 1.62) 12SQ-HDM vs placebo post OR (95% CI): 0.97 (0.61- 1.53) *P* = 0.89
de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	29 27 25 27	12 months	5.62 5.58 5.75 5.52	Change within group + 0.52 + 0.32 + 0.30 0	SLIT 6SQ-HDM pre vs post *P*=0.01 Other arms NR Between arms comparisons NR

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post
Devillier, 2016[63] Wang, 2014[64]	Dust mite Mild and moderate	SLIT (A) Placebo	13 62	52 weeks	Mean +/- SD 4.6 +/-1.0 4.5 +/- 1.1	Mean +/- SD 6.0 +/-0.9 5.9 +/- 0.9	NR

T: Tablet A: Aqueous SQ-HDM: standard quality house dust mite tablet NR: Not reported

Table F6 – Medication Use

A. Quick Relief Medication

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Marogna, 2009[70]	Birch Moderate asthma	SLIT (A) Pharmacotherapy (montelukast)	5 6	5 years	SABA, (Doses used over 3 month period)	20.1 +/- 0.7 19.4 +/- 0.9	4.0 +/- 0.9 15.8 +/- 1.0	SLIT pre vs post P<0.01, pharm pre vs post *P* =0.019 SLIT vs pharm *P*<0.001
Marogna, 2013[68]	Birch Mild asthma	SLIT (T) + Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	21 21 21 21	3 years	SABAS (doses used over 3 month period)	Mean +/- SE 11.1 +/- 0.6 11.1 +/- 0.6 11.2 +/- 0.6 11.9 +/- 0.9	Mean +/- SE 1 +/- 0.2 10.4 +/- 1.2 8.3 +/- 1.3 7.4 +/- 1.1	SLIT vs all budesonide control groups *P* <0.001
Marogna, 2010[71]	Grass mix Mild asthma	SLIT (A) Pharmacotherapy (budesonide)	17 16	5 years	SABA (doses over 3 month period)	23.0 +/- 1.5 22.4 +/- 0.9	5.1 +/- 1.4 13.0 +/- 1.2	SLIT vs budesonide *P*<0.001
Gomez, 2004[65]	Dust mite Mild-moderate asthma	SLIT (A) Placebo	30 30	6 months	SABA; Inhaled B agonist use reduction (Salbutamol)	NA	50% 21%	SLIT vs. placebo z-1.44 *P*<0.03
Niu, 2006[77]	Dust mite Mild-moderate asthma	SLIT (A) Placebo	56 54	24 weeks	Inhaled B agonist (puff/ day)	Mean (SD) SLIT: 0.06 (0.09) Placebo: 0.03 (0.01)	Mean (SD) SLIT: 0.02 (0.31) Placebo:0.05 (0.27)	SLIT pre vs. post *P*= 0.371 Placebo pre vs. post *P*= 0.185 SLIT vs. placebo change from baseline *P*= 0.951

T: Tablet A: Aqueous SQ-HDM: standard quality house dut mite tablet SABA; Short acting Beta Agonist LTRA: Leukotriene receptor antagonist NR: Not reported

B. Long Term Control Medication

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Devillier, 2016[63] Wang, 2014[64]	Dust mite Mild and moderate	SLIT (A) Placebo	322 164	52 weeks	Inhaled corticosteroid (ICS) Absolute decrease in budesonide dose	NR NR	218.5 126.5	SLIT vs placebo post *P* = 0.004
de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	156 159 146 143	6 months	Inhaled corticosteroid (ICS) Average daily use (µg)	541 648 636 641	-327 -75 -103 -50	SLIT 6HQ-HDM pre vs post *P*< 0.05

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Pham-Thi, 2007[72]	Dust mite Mild and moderate	SLIT (T) Placebo	54 54	18 months	Use of inhaled steroids (ICS) (Budesonide) µg/day	Mean +/- SD 548 +/- 220 534 +/-237	Mean +/- SD 257 +/- 232 223 +/-270	NR
Niu, 2006[77]	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	ICS (puff/ day)	Mean (SD) SLIT: 0.6 (1.14) Placebo: 0.47 (0.84)	Mean (SD) SLIT: 0.43 (1.09) Placebo: 0.37 (0.86)	change from baseline SLIT pre vs. post *P*= 0.782 Placebo pre vs. post *P*= 0.522 SLIT vs. placebo *P*= 0.215

T: Tablet A: Aqueous SQ-HDM: standard quality house dut mite tablet LTRA: Leukotriene receptor antagonist NR: Not reported

C. Systemic Corticosteroids

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Niu, 2006[77]	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	Oral steroids (tablet/ day)	Mean (SD) SLIT: 0.11(0.35) Placebo: 0.04(0.15)	Mean (SD) SLIT: 0.03(0.22) Placebo: 0.04(0.22)	Change from baseline SLIT pre vs post *P*= 0.183 Placebo pre vs. post P= 1.000 SLIT vs. placebo *P*= 0.195

SLIT vs comparator post data unless otherwise noted

Table F7 – Asthma Exacerbations

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Virchow, 2016[58]	Dust mite Moderate to severe	SLIT 6 SQ-HDM SLIT12 SQ-HDM Placebo	275 285 277	6 months	Time to asthma exacerbation	NR	HR (95% CI) 0.72 (0.52-0.99) 0.69 (0.50- 0.96)	SLIT(T) 6 SQ-HDM vs placebo *P*=0.045 SLIT(T) 12 SQ-HDM vs placebo *P*=0.03
					Time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings	NR	HR (95% CI) 0.72 (0.49-1.07) 0.64 (0.42- 0.96)	SLIT(T) 6 SQ-HDM vs placebo *P*= 0.17 SLIT(T) 12 SQ-HDM vs placebo *P*=0.03
					Time to first asthma exacerbation with deterioration in lung function	NR	HR (95% CI) 0.60 (0.38- 0.95) 0.52 (0.29- 0.94)	SLIT(T) 6 SQ-HDM vs placebo *P*= 0.03 SLIT(T) 12 SQ-HDM vs placebo *P*=0.02
					Time to first asthma exacerbation with increased use of SABA	NR	HR (95% CI) 0.62 (0.36- 1.07) 0.52 (0.29- 0.94)	SLIT(T) 6 SQ-HDM vs placebo *P*= 0.09 SLIT(T) 12 SQ-HDM vs placebo *P*=0.03
					Time to first severe asthma exacerbation	NR	HR (95% CI) 0.72 (0.52- 0.99) 0.69 (0.50- 0.96)	SLIT(T) 6 SQ-HDM vs placebo*P*= 0.03 SLIT(T) 12 SQ-HDM vs placebo *P*=0.02

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	Dust mite Mild and moderate	SLIT 6 SQ-HDM (T) SLIT 3 SQ-HDM (T) SLIT 1 SQ-HDM (T) Placebo	156 159 146 143	1 year	Number of asthma exacerbations	NR	NR	Not a statistical significance for either of the treatment groups or the placebo groups
Gomez, 2004[65]	Dust mite Mild- moderate asthma	SLIT (A) Placebo	30 30	6 months	Total Number of asthma exacerbations at the end of study	NR	71 123	SLIT vs Placebo T 2.6 *P*<0.001

T: Tablet A: Aqueous SQ-HDM: standard quality house dut mite tablet LTRA: Leukotriene receptor antagonist NR: Not reported
SLIT vs comparator post data unless otherwise noted

Table F8 – Healthcare Utilization

No study reported on Healthcare Utilization; Asthma Specific Hospitalizations, Emergency Department (ED) or Outpatient visits, Asthma Specific ICU admissions or intubations.

Table F9 – Pulmonary Physiology

A. PEF

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Calderon, 2006[67]	Phleum pratense Mild and moderate	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	32 11	NR	PEF	NR	NR	No clinically significant changes were observed
Pham-Thi, 2007[72]	Dust mite Mild and moderate	SLIT (T) Placebo	54 54	18 months	PEF	Mean +/- SD 8.03 +/- 7.21) 7.48 +/- 6.14)	Mean +/- SD 6.06 +/- 5.45 6.36 +/-5.65	NR
Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	20 15	2 years	PEF Mean % predicted	81.4 78.7	Mean (95% CI) 92.9 (84- 101.4) 84.0 (75 – 92)	SLIT vs Placebo pre *P*=0.777 SLIT vs Placebo post *P*=0.949
Lue, 2006[76]	Dust mite Mild asthma	SLIT (A) Placebo	10 10	6 months	PEF	NR	NR	SLIT pre vs post improved *P*=0.0088, in the evening but not in am. Placebo pre vs post *P* NS SLIT vs Placebo post *P* NS
Niu, 2006[77]	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	PEF	NR	NR	SLIT pre vs. post *P*= 0.001 Placebo pre vs. post NS SLIT vs placebo NS

T: Tablet A: Aqueous SQ-T: standard quality tablet PEF: Peak expiratory flow NR: Not reported NS: Not significant

B. FEV_1

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Devillier, 2016[63] Wang, 2014[64]	Dust mite Mild and moderate	SLIT (A) Placebo	322 164	52 weeks	FEV1	NR	NR	The mean FEV1% predicted remained above 80% during the treatment period in both SLIT and placebo groups. No significant difference
de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	Dust mite Mild and moderate	SLIT(T) 6 SQ-HDM SLIT(T) 3 SQ-HDM SLIT(T) 1 SQ-HDM Placebo	156 159 146 143	1 year	FEV1	NR	NR	SLIT versus placebo post NS
Gomez, 2004[65]	Dust mite Mild- moderate asthma	SLIT (A) Placebo	30 30	6 months	FEV1 Median percentage increase after salbutamol	Median 2.16 2.58	Median 2.86 2.81	SLIT versus placebo post Z=0.66 P<0.03
Marogna, 2010[71]	Grass mix Mild asthma	SLIT (A) Pharmacotherapy (Montelukast)	17 16	5 years	FEV1	78.5(1.0) 76.4 (1.3)	96.2(1.2) 81.2(1.4)	SLIT vs Pharm *P*<0.0001
Calderon, 2006[67]	Phleum pratense Mild and moderate	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	32 11	NR	FEV1	NR	NR	No clinically significant changes were observed
Marogna, 2013[68]	Birch Mild asthma	SLIT (T) + Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	21 21 21 21	3 years	FEV1	Mean +/-SE 85.2 +/- 0.6 88.3 +/- 0.8 87 +/- 0.8 86.2 +/- 0.6	Mean +/- SE 103.3 +/- 1.5 90.3 +/ -2.1 92.4 +/- 2.0 96.5 +/- 2.9	SLIT vs all other arms *P*<0.05
Pham-Thi, 2007[72]	Dust mite Mild and moderate	SLIT (T) Placebo	54 54	18 months	FEV1	Mean +/- SD 91.9 +/- 3.4 95.1 +/-15.1	Mean +/- SD 88.5 +/- 13.4 94.5 +/- 14.6	SLIT vs placebo post NS
Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	20 15	2 years	FEV1 Mean % predicted	92.9 87.9	Mean (95% CI) 100.4 (95- 105) 88.2 (81 – 94)	SLIT vs Placebo pre *P*=0.649 SLIT vs Placebo post *P*=0.005
Niu, 2006[77]	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	FEV1	85 90	95 90	SLIT pre vs post *P*=0.048 Placebo pre vs post NS SLIT vs Placebo NS
Ippoliti, 2003[78]	Dust mite Mild- moderate asthma	SLIT (A) Placebo	47 39	6 months	FEV1	83.4 80.7	92.6 81.2	SLIT pre vs post *P*< 0.001 Placebo pre vs post *P* NS SLIT vs Placebo NR

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Lue, 2006[76]	Dust mite Mild- moderate asthma	SLIT (A) Placebo	10 10	6 months	FEV1	NR	NR	SLIT pre vs post improved *P*=0.01 Placebo *P* =0.48 SLIT vs Placebo = 0.929

T: Tablet A: Aqueous SQ-T: standard quality tablet FEV: Flow expiratory volume NR: Not reported NS: Not significant

C. FVC

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Gomez, 2004[65]	Dust mite Mild- moderate asthma	SLIT (A) Placebo	30 30	6 months	FVC	NR	Percentage increase in FVC 15% 14.7%	SLIT versus placebo post P>0.07
Niu, 2006[77]	Dust mite Mild – moderate asthma	SLIT (A) Placebo	56 54	24 weeks	FVC	NR	NR	SLIT pre vs post *P*=0.042 Placebo pre vs. post- NS SLIT vs placebo post NS

A: Aqueous NR: Not reported NS: Not significant SLIT vs comparator post data unless otherwise noted

Table F10 – Airway Hyperresponsiveness AHR

A. Methacholine Challenge

Study	Allergen and Asthma Severity	Arms	Time of measure	N	Outcome Description	Units Value Pre	Value post	Comparative Values
La Grutta, 2007[74]	Dust mite Severity NS	SLIT (A) pharmacotherapy	1 year	33 23	AHR- PD20 FEV1	µg of methacholine Mean +/- SD 626.4 +/- 526.19 616.1+/- 578.08	µg of methacholine Mean +/- SD 1277.7 +/-963.51 860.3 +/- 732.39	SLIT pre vs post *P* = 0.001 Pharm pre vs post P = 0.08 SLIT vs pharm not reported
Marogna, 2010[71]	Birch Mild asthma	SLIT (A) Pharmacotherapy (Montelukast)	5 years	17 16	AHR- PD20 FEV1	µg of methacholine Mean +/- SD 326.4(50.1) 288.6(44.9)	µg of methacholine Mean +/- SD 919.3(85.7) 478.7 (76.2)	SLIT pre vs post *P*<0.001; Mont pre vs post *P*=0.019 SLIT vs Mont *P*=0.001
Marogna, 2013[68]	Birch Mild asthma	SLIT + Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + ALKT	3 years	21 21 21 21	AHR- PD20 FEV1	µg of methacholine Mean +/- SE 166.8(18.3) 199.8(24.7) 226.9(22.6) 165.7(17.0)	µg of methacholine Mean +/- SE 997.1(39.7) 644.9(89.3) 520.0(64.7) 728.7(76.0)	SLIT vs all other arms *P*<0.05
Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	6 months	20 15	AHR- PD20 FEV1	Mg/ml methacholine 3.51 4.35	Mg/ml methacholine 4.05 4.00	SLIT vs placebo post P=0.058

T: Tablet A: Aqueous µg:micrograms D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina* PD20: Concentration of allergen causing a fall of 20% in FEV1

B. Allergen Challenge

No study measured allergen challenges

C. Exercise Challenge

No study measured exercise challenges

Table F11 – Immunologic Parameters
A. IgE

Study	Allergen	Arms	Time of Measure	Outcome/ Units	Baseline Values	Final Values	Comparative Values
Devillier, 2016[63]	Dust mite (D pter-D far)	SLIT (T) Placebo	52 weeks	Specific IgE to D pter kU/L	Mean – [IQR] D pter 28.7 [24.7-33.4] 30.3 [24.7-37.3] D far 26.4 [22.7-30.6] 26.3 [21.3-32.4]	geometric mean fold-change D pter 1.58 D far NR	SLIT pre vs post 95%CI [1.44-1.74] Placebo pre vs post NS changes
Lue, 2006[76]	Dust mite (D pter-D far)	SLIT (A) Placebo	6 months	Specific IgE to D pter IU/L	Mean 500 400	Increased Did not chnge	No significant change
Niu, 2006[77]	Dust mite (D pter-D far)	SLIT (A) Placebo	24 weeks	Specific IgE to D pter kU/L	Mean 829.8 780.6	Change 129 +/- 460 -85.+/-59.8	SLIT vs placebo post *P*=0.063
Bahceciler, 2001[73]	Dust mite (D pter-D far)	SLIT (A) Placebo	6 months	Specific IgE to D pter kU/L	Median (range) 420 (42-2751) 405 (197-5967)	Median (range) 295 (40-1701) 536 (166-3948)	No significant difference
Pham-Thi, 2007[72]	Dust mite (D pter-D far)	SLIT (T) Placebo	18 months	Specific IgE to D pter kU/L	Mean (SD) 208 (38) 197 (30)	Mean (SD) 250 (36) 135 (21)	NR

Study	Allergen	Arms	Time of Measure	Outcome/ Units	Baseline Values	Final Values	Comparative Values
Tian, 2014[79]	Dust mite (D far)	SLIT (A) Placebo	48 weeks	Specific IgE to D pter kU/L	Specific IgE Grading n(%) Grade II 4 (13.3) 5 (16.7) Grade III 14 (46.7) 13 (43.3) P = 0.95	No changes	NS changes
Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	2 years	Total IgE kU/L geometric mean	549.3 424.6	Mean (95% CI) 496 (328-750) 503 (268-942)	SLIT vs Placebo pre *P*=0.668 SLIT vs Placebo post *P*=0.163
				Specific IgE kU/L geometric mean	46.8 73.8	Mean (95% CI) 53.1 (33-84) 76.8 (48-121)	SLIT vs Placebo pre *P*=0.359 SLIT vs Placebo post *P*=0.633

T: Tablet A: Aqueous µ:micrograms D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*

B. IgG4

Study	Allergen	Arms	Outcome Description	Time of Measure	Baseline Values	Final values	Comparative values
Virchow, 2016[58]	Dust mite (D pter-D far)	SLIT 6 SQ HDM SLIT 12 SQ HDM Placebo	D pter 1 specific IgG4 (mgA/L)	NR	Mean (SD) [range] 0.4 (0.4) [0.0-3.3] 0.4 (0.6) [0.0-6.4] 0.5 (0.5) [0.0-3.4]	0.425 (0.022) 0.558 (0.024) -0.037 (0.014)	SLIT 6 vs Placebo post *P* < 0.001 SLIT 12 vs Placebo post *P* < 0.001
			D far specific IgG4 (mgA/L)	NR	Mean (SD) [range] 0.4 (0.3) [0.0-2.7] 0.5 (0.9) [0.0-9.8] 0.4 (0.5) [0.0-3.7]	0.404 (0.022) 0.540 (0.026) -0.054 (0.015)	SLIT 6 vs Placebo post *P* < 0.001 SLIT 12 vs Placebo post *P* < 0.001
Devillier, 2016[63]	Dust mite (D pter-D far)	SLIT - Dpt-D far Placebo	D pter p 1 specific IgG4	NR	NR	geometric mean fold-change D pter 1.99 D far NR	SLIT pre vs post 95%CI [1.81-2.18] Placebo pre vs post NS changes SLIT vs placebo NR
Pham-Thi, 2007[72]	Dust mite (D pter-D far)	SLIT tablet Placebo	IgG4 antibody assay, (µg/l)	18 months	Mean (SD) (ug/ml 1166 (188) 761 (73)	Mean (SD) (ug/ml) 4462 (860) 650 (51)	SLIT pre vs post P < 0.001 Placebo pre vs post NS SLIT vs placebo post NR
Lue, 2006[76]	Dust mite (D pter-D far)	SLIT aqueous Placebo	NR	Specific IgE to D pter IU/L	NR	NR	Statistically significant increase within group and when compared to placebo *P*=0.026
Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	Total IgG4 µg/l geometric mean	2 years	0.9 0.58	Mean (95% CI) 0.31 (0.19-0.51) 0.25 (0.18-0.33)	SLIT vs Placebo pre *P*=0.469 SLIT vs Placebo post *P*=0.607

T: Tablet A: Aqueous µ:micrograms D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*

C. Allergy Skin Testing

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final values	Comparative values
Devillier, 2016[63]	Dust mite (Ppter-D far)	SLIT tablet Placebo	50 weeks	Wheal size mm	mean (SD) D pter 8.9 (5.4) D far 8.5 (4.9) D pter 9.1 (5.5) D far 9.0 (5.9)	change mean (SD) D pter -2.8 (5.4) D far -2.9 (4.7) D pter -1.4 (5.4) D far -1.8 (6.3)	SLIT pre vs post *P* < 0.0001 Placebo pre vs post NR
Pham-Thi, 2007[72]	Dust mite (D pter-D far)	SLIT tablet Placebo	18 months	Skin wheal diameter	Mean 5.31 5.81	Mean 2.9 5.3	SLIT pre vs post difference -2.15 Placebo pre vs post difference -0.46 SLIT vs placebo *P* <0.001
Tian, 2014[79]	Dust mite (D far)	SLIT aqueous Placebo	48 weeks	Specific Skin prick test	n(%) 2+ 16 (53.3) 15 (50.0) 3+ 14 (46.7) 15 (50.0) *P* = 0.79	No changes	NS changes

T: Tablet A: Aqueous NS: Not significant D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*

Table F12 – Other Outcomes - Compliance

Study	Allergen	Arms	N	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Maloney, 2016[62]	Dust mite (D pter-D far)	SLIT - 6 SQ-HDM (T) SLIT - 12 SQ-HDM (T) Placebo	22 24 22	14 days	mean compliance with study drug	NR	97 99 98	NR
de Blay, 2014[59]	Dust mite (D pter-D far)	SLIT 6-HQ HDM (T) SLIT 3-HQ HDM (T) SLIT 1-HQ HDM (T) Placebo	134 131 117 107	1 year	Number of non-compliant subjects	NR	4 (3%) 2 (2%) 3 (3%) 1 (1%)	NR
Devillier, 2016[63]	Dust mite (D pter-D far)	SLIT (T) Placebo	308 157	52 weeks	Number of unused SLIT packs	NR	90.9% 93%	NR

T: Tablet A: Aqueous NR: Not reported D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*

Appendix G. KQ4- What is the evidence for the safety of sublingual immunotherapy (SLIT) in tablet and aqueous form, in the treatment of asthma?

(Organization in tables first by population; adults-mixed population- children. Within each category by comparator SCIT vs placebo- SCIT vs pharmacotherapy- SCIT vs SCIT. Within each subcategory by allergen; HDM-grass- weed- trees- animal-multiple allergen)

SECTION A SLIT SAFETY FOR RCTS

Table G1.A – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Virchow, 2016[58] Europe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Moderate to severe Asthma Pulmonary tests (PFT reversibility) Poorly Controlled	SPT and IgE SPT ≥ 3 mm SIgE≥ 0.70 ku/L	Both Mono and Polysensitized "Patients could have multiple sensitization but no perennial asthma caused by other allergens"	Single allergen Dust mite (D pter-D far)	Home
	de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61] Europe	SLIT(T) 6 SQ-HDM SLIT(T) 3 SQ-HDM SLIT(T) 1 SQ-HDM Placebo	Asthma diagnosis GINA criteria (steps 2 and 3) Pulmonary tests (documented history of reversible airway obstruction) Mild persistent and moderate persistent Controlled (ACQ scores and ICS dose of 100 to 800 mg/d)	SPT and IgE wheal size >3mm to D farinae, D pteronyssinus, or both IgE NS	Both Mono (17%) and Polysensitized (83%)	Single allergen Dust mite (D pter-D far)	Not specified
	Maloney, 2016[62] US	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Severity not specified Controlled (FEV1 ≥70% predicted, no more than 2 symptoms per week, no more than 2 days of SABA use per week, no more than 2 awakenings per month due to asthma)	SPT and IgE wheal diameter ≥5mm larger than saline control; serum-specific IgE≥ 0.7 kU/L or at least class II (all against D pter or D far)	Both Mono and Polysensitized Dust mite (D pter-D far) Grass, cat, dog, mold, birch,mugwort	Single allergen Dust mite (D pter-D far)	Home
	Devillier, 2016[63] Wang, 2014[64] Multisite	SLIT (A) Placebo	Pulmonary tests (bronchial reversibility test and methacholine challenge) Mild persistent and moderate persistent	SPT and IgE wheal diameter ≥ 4 mm in an SPT after washout of antihistamines, specific IgE ≥ 0.70 kU/ l	Monosensitized Dust mites (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Gomez, 2004[65] Mexico	SLIT (A) Placebo	Asthma diagnosis GINA criteria Pulmonary tests (FEV change >14% after salbutamol) Mild persistent and moderate persistent Control status NS	SPT and IgE specific IgE ≥ 200IU	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Ppter)	Single allergen Dust mite (D pter)	Not specified
	Dahl, 2006[66] Europe	SLIT (T) Placebo	Asthma diagnosis GINA critera Severity Mild to moderate Controlled asthma	SPT and IgE wheal >3mm IgE NS	Monosensitized Grass (Phleum pratense)	Single allergen Grass (Phleum pratense)	Home
	Calderon, 2006[67] Europe	SLIT (A) Placebo	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Controlled asthma	SPT and IgE wheal >3mm IgE > class 2	Monosensitized Grass (Phleum pratense)	Single allergen Grass (Phleum pratense)	Not specified
	Marogna, 2013[68] Europe	SLIT Pharmacotherapy	Asthma diagnosis GINA criteria Pulmonary tests (Positive methacholine challenge -PD20 FEV1 <800g) Severity Mild persistent Control status Poorly controlled	SPT and IgE Skin test >5mm (does not specify if wheal or flare); and class II positivity to birch assessed with ImmunoCAP (Unicap)	Monosensitized Trees (Birch)	Single allergen Birch	Home
	Voltolini 2010[69] Europe	SLIT (A) Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate Control status NS	SPT and IgE NS	Monosensitized Pollen (White birch)	Single allergen Birch	Not specified
	Shao, 2014[80] Asia	SLIT (A) Pharmacotherapy	Asthma diagnosis Global Initiative for Asthma Excluded severe asthma Controlled Asthma	SPT and IgE wheal size ≥3mm IgE ≥ 0.7	Polysensitized (D pter-D far), cat, dog, german cockroach, artemisia pollen, humulus pollen, and plantain pollen)	Single allergen Dust mite (D far)	Clinic
Mixed age	Corzo, 2014[81] Europe	SLIT (T) SLIT	WHO/GINA criteria Mild persistent and moderate persistent Controlled	SPT and IgE wheal ≥3mm IgE ≥ class2	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic
	La Grutta, 2007[74] Europe	SLIT (T) Pharmacotherapy	Asthma diagnosis criteria NS Severity NS Control status NS	SPT >3mm	Both mono and polysensitized Dust mite and Parietaria	Single allergen Dust mite (NS)	Home
	Pham-Thi, 2007[72] Europe	SLIT (T) Control	Asthma diagnosis pulmonary tests (reversible bronchial obstruction – salbutamol inhalation) Severity Mild persistent and moderate persistent Control status NS	SPT and IgE SPT NS IgE level ≥ 2 CAP RAST	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Bahceciler, 2001[73] Asia	SLIT (A) Placebo	Asthma diagnosis criteria NS Severity Persistent (NS) Control status – ongoing respiratory symptoms despite HDM avoidance and ICS	SPT and IgE Wheal >5mm IgE class 2	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified
	Bufe, 2009[82] Europe	SLIT (T) placebo	Asthma diagnosis criteria GINA and FEV1<80% expected after treatment with ICS and SABA) Severity Mild persistent Control status NS	SPT and IgE wheal >3mm, serum specific IgE class 2	Monosensitized Timothy grass	Single allergen Timothy grass	NR
	Stelmach, 2009[75]	SLIT (A) Placebo	Asthma diagnosis pulmonary tests (reversible bronchial obstruction – salbutamol inhalation ≥12%) Severity Excluded severe asthma Control status NS	SPT and IgE SPT NS IgE NS	Monosensitized Grass	Single allergen Grass mix	Not specified
Children	Lue, 2006[76] Asia	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE > 3	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified
	Niu, 2006[77] Asia	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE > 3	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified
	Ippoliti, 2003[78] Europe	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE class 3	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified
	Mosges, 2010[83] Europe	SLIT(A) OTHER	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Control status NS	SPT and IgE SPT NS IgE ≥0.7 kU/L	Polysensitized tree pollens (birch alder and/or hazel)	Single allergen Birch	Not specified

T: Tablet A: Aqueous SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*

***** Authors did not report sensitization status

Table G2.A – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Adults	Virchow, 2016[58]	834	SLIT 6 SQ HDM SLIT 12 SQ HDM Placebo	33.6 (12.2) 33.7 (11.6) 33 (12.2)	48/52 52/48 55/45	275/34 282/43 277/48	NR
	de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	604	SLIT 6 SQ-HQM SLIT 3 SQ-HQM SLIT 1 SQ-HQM Placebo	32 (NR) 32 (NR) 32 (NR) 32 (NR)	NR	156/16 159/25 146/14 143/17	NR
	Maloney, 2016[62]	68	HDM SLIT 6 SQ-HDM HDM SLIT 12 SQ-HDM Placebo	Range (12-17)	NR	NR	6 months
	Devillier, 2016[63] Wang, 2014[64]	484	SLIT Placebo	31.2 (9) 31.3 (8.2)	46.8/53.2 41.4/58.6	308/23 157/8	12.8 years 13.7 years
	Gomez, 2004[65]	60	SLIT (A) Placebo	22.8 20.6	53/47 33/67	30/NR 30/NR	3.8
	Dahl, 2006[66]	114	SLIT (T) Placebo	36.5 (11) 34.1 (10)	71/29 60/40	74/13 40/8	14 years 12 years
	Calderon, 2006[67]	43	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	22.1 (3.2) 23.2 (2.8) 28 (9.5) 25.8 (5.5) 24.5 (5.5)	67/33 67/33 67/33 60/40 55/45	9/0 9/0 9/0 5/0 11/0	12.9 years 15.7 years 22.2 years 19.4 years 15.4 years
	Marogna, 2013[68]	84	SLIT+ BUD 400 µg/day BUD 800 µg/day BUD 1600 µg/day BUD 400 µg/day + LTRA	NR	NR	21/NR 21/NR 21/NR 21/NR	NR
	Voltolini, 2010[69]	24	SLIT (A) Placebo	44+/- 9 40 +/- 7	50/50 30/70	14/1 10/1	NR
	Shao, 2014[80]	218	SLIT Pharmacotherapy	NR	NR	NR	NR
Mixed age	Corzo, 2014[81] adults Corzo, 2014[81] Peds	71	SLIT 1 DU SLIT 2 DU SLIT 4 DU SLIT 8 DU SLIT 16 DU SLIT 16 DU Placebo	30.7(10.4) 32.4 (14.1) 25.9 (5.3) 30 (11.2) 27.9 (6) 25.2 (7.6) 29 (9.7)	33/67 22/78 33/67 56/44 44/56 22/78 47/53	54/NR 17/NR	Range: 13.8 years 14.8 years 13 years 17.1 years 16.1 years 15.8 years 0.2 years
	La Grutta, 2007[74]	56	SLIT Pharmacotherapy	15.4 (9) 21.8 (15)	22/11 13/10	33/0 23/0	NR

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
	Pham-Thi, 2007[72]	111	SLIT Placebo	9.6 (5-14) 9.5 (5-16)	72/28 71/29	55/11 56/8	6.1 years 5.7 years
	Bahceciler, 2001	15	SLIT (A) Placebo	Median 12.4 (range 8-18) Median 12 (range 7- 15)	50/50 43/57	8/0 7/0	NR
	Bufe, 2009[82]	105	SLIT Placebo	Range: 5-16	NR	253/19	NR
	Stelmach, 2009[75]	50	SLIT (A) Placebo	9.1 +/-2.4 8.5 +/- 2.8	60/40 66/33	25/5 25/10	NR
Children	Lue, 2006[76]	20	SLIT (A) Placebo	7.7 +/- 1.8 8.6 +/- 1.8	40/60 40/60	10/0 10/0	1
	Niu, 2006[77]	110	SLIT (A) Placebo	7.9 +/- 1.6 (Range 5-11) 8.2+/- 1.7 (Range 5-12)	61/39 58/42	56/7 54/6	1
	Ippoliti, 2003[78]	86	SLIT (A) Placebo	Median;9 (Range 5-12) Median;9 (Range 7-11)	60/41 56/44	47/0 39/0	2 2
	Mosges, 2010[83]	116	SLIT Placebo	10.2 (2.64) 10.5 (2.55)	37/63 67/33	27/NR 27/NR	NR

T: Tablet A: Aqueous NR: Not reported SQU: standard quality tablet SQ-HDM-T standard quality House dust mite tablet

Table G3.A – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Virchow, 2016[58]	SLIT 6 SQ HDM T SLIT 12 SQ HDMT Placebo	Both	Targeted: 6 SQ Actual: 6 SQ Targeted: 12 SQ Actual: 12 SQ	Targeted: 360 SQ/month Actual: 360 SQ/month Targeted: 720 SQ/month Actual: 720 SQ/month	Daily	NR	7-12 months
	de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	SLIT 6 SQ-HQM SLIT 3 SQ-HQM SLIT 1 SQ-HQM Placebo	Rescue therapy	Targeted:6SQ Actual 6 SQ Targeted:3SQ Actual: 3 SQ Targeted:1SQ Actual: 1 SQ Targeted: NR Actual: NR	NR	Daily	NR	1 year
	Maloney, 2016[62]	SLIT T 6 SQ-HDM SLIT T 12 SQ-HDM Placebo	Both	Targeted: 6 SQ-HDM Actual: 6 SQ-HDM Targeted: 12 SQ-HDM Actual: 12 SQ-HDM Targeted: NA Actual: NA	Targeted: 168 SQ Actual: 168 SQ Targeted: 336 SQ Actual:336 SQ Targeted: NR Actual: NR	Daily	NR	28 days

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Devillier, 2016[63] Wang, 2014[64]	SLIT Placebo	Both	Targeted: 300 IR Actual: 300 IR	NR	Daily	28ug Der p 1 and 50 ug Der f 1 NR	52 weeks: 24 w active treatment, 16 w step- down, 20 w efficacy measurement phase (8 w' overlap (between w 32 and 40)
	Gomez, 2004[65]	SLIT (A) Placebo	Both BUT excluded systemic corticosteroid s	710 UBE/ml	10469 UBE	3 times a week	NR	6 months
	Dahl, 2006[66]	SLIT (T) Placebo	Both (NS)	7500 SQT	NR	Daily	15 phl p5	137 days (Ultrarush)
	Calderon, 2006[67]	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	NR	Targeted: 75000 SQ-T Actual: 75000 SQ-T Targeted: 150000 SQ-T Actual: 150000 SQ-T Targeted: 300000 SQ-T Actual: 300000 SQ-T Targeted:500000 SQ-T Actual: 500000 SQ-T Targeted: NR Actual: NR	NR	Daily	15 µg/dose 30 µg /dose 60 µg /dose 100 µg /dose NR	28 days
	Marogna, 2013[68]	SLIT + BUD 400 µg/day BUD 800 µg/day BUD 1600 µg/day BUD 400 µg/day + LTRA	Both	Targeted: 1000 AU once a day for five days/week Actual: 1000 AU once a day for five days/week	Targeted: Annual average dose approximately 60,000 AU Actual: Annual average dose approximately 60,000 AU Targeted: NR Actual: NR Targeted: NR Actual: NR	Daily	214,200 µg of protein (Annual cumulative) NR NR NR	12 weeks
	Voltolini 2010[69]	SLIT (A) Placebo	Conventional therapy	Targeted 300 IR Actual 300IR	13.8 IR per season	Daily	13.8 IR (6.9 µgBet v1 per season)	4 months
	Shao, 2014[80]	SLIT aqueous Pharmacotherapy	NR	NR	Targeted: 0.15 ml Actual: 0.15 ml Targeted: NR Actual: NR	Weekly	49.95 µg/dose	12 months

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Mixed age	Corzo, 2014[81] adults Corzo, 2014[81] Peds	SLIT 1 DU SLIT 2 DU SLIT 4 DU SLIT 8 DU SLIT 16 DU SLIT 16 DU Placebo	Both	Targeted: 1 to 32 DU Actual: NR Targeted: NR Actual: NR	NR	Daily	NR	28 days
	La Grutta, 2007[74]	SLIT Pharmacotherapy	Conventional therapy	Targeted: 1,000 AU Actual: 1,000 AU	NR	Biweekly NR	NR	1 year
	Pham-Thi, 2007[72]	SLIT Placebo	Both	Targeted: 300 IR Actual: 300 IR Targeted: NR Actual: NR	Targeted: NR Actual: 155,000 IR, corresponding to 6.9mg Der p 1 and 14.7mg Der f 1 Targeted: NR Actual: NR	Daily NR	Daily dose: DerP1 27µg, Der f1 57µg	18 months
	Bahceciler, 2001	SLIT (A) Placebo	Both	20 drops of 100 IR/mL	Average 7,000 IR	Twice a week	Average cumulative dose of 0.56 mg Der P and 0.98 mg Der F)	24 weeks
	Bufe, 2009[82]	SLIT Placebo	Both	NR	NR	NR	NR	NA
	Stelmach, 2009[75]	SLIT (A) Ultrarush Placebo	Conventional therapy BUT excluded systemic corticosteroids	120IR	43800 IR	3 times a week	3.65 mg of major allergens (5 grasses)	6 months
Children	Lue, 2006[76]	SLIT (A) Placebo	Conventional and rescue as needed	20 drops of 300 IR/mL	41824 IR	Daily	3 mg Der F 1.7 mg Der P (Cumulative)	24 weeks
	Niu, 2006[77]	SLIT (A) Placebo	Conventional and rescue as needed	20 drops of 300 IR/ml	41824 IR	Daily	3 mg Der F, 1.7 mg Der P (Cumulative)	24 weeks
	Ippoliti, 2003[78]	SLIT (A) Placebo	Conventional therapy	5 drops of 10 BU/mL	NR	3 times a week	2.4 Der p1 1.2 Der p2 (per week)	6 months

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Mosges, 2010[83]	SLIT Placebo	Both	Targeted: 300 IR within 90 minutes Targeted: NR Actual: NR	NR	NR	NR	6 months

T: Tablet A: Aqueous BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg: microgram Ag/ml: major protein unit
TU: Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: Index of reactivity unit NR: Not reported DU dosing unit

Table G4.A – Local Reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
Pruritis/swelling of mouth, tongue or lip	Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	Oral pruritus Treatment related	37 (13) 55 (20) 8 (3)	45 78 8	-0.029
					Edema mouth Treatment related	24 (9) 28 (10) 0 (0)	26 35 0	0.0
					Tongue pruritus Treatment related	12 (4) 13 (5) 1 (1)	13 15 1	-0.004
					Lip edema Treatment related	3 (1) 9 (3) 0 (0)	3 10 0	0.02
					Lip pruritus Treatment related	0 (0) 7 (2) 0 (0)	0 8 0	0.01
					Lip swelling Treatment related	4 (1) 6 (2) 0 (0)	4 7 0	0.01
					Swollen tongue Treatment related	1 (1) 5 (2) 0 (0)	1 6 0	0.0
					Laryngeal edema [moderate, no airway obstruction or dyspnea]	0 1 0	NR	0.0
	Devillier, 2016[63]	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	322 162	Swollen tongue	85 (26.4%) 2 (1.2%)	NR NR	0.252
					Oral pruritus	75 (23.3%) 23 (14.2%)	NR NR	0.091
					Glossitis	64 (19.9%) 17 (10.5%)	NR NR	0.094
					Mouth Edema	26 (8.1%) 0 (0)	NR NR	0.081

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
	de Blay, 2014[59]	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM SLIT 3-HQ HDM SLIT 1-HQ HDM Placebo	29 27 25 27	Mouth edema	8% 3% 2% 0%	NR NR NR NR	-0.001
					oral pruritus	19% 19% 12% 3%	NR NR NR NR	-0.001
	Pham-Thi, 2007[72]	Dust mite Mild and Moderate asthma	SLIT tablet Placebo	54 55	mouth itching/lip swelling	NR NR	10 5	NA
	Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	20 15	Sublingual itching	35% 20%	NR	0.15
	Calderon, 2006[67]	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Mouth edema	3 (33) 1 (11) 2 (22) 0 0	3 1 4 NR NR	0.006
					Oral pruritus	6 (67) 9 (100) 8 (89) 5 (100) 4 (36)	13 49 96 77 5	-0.336
					Swollen tongue	1 (11) 0 1 (11) 1 (20) 0	1 NR 1 1 NR	0.003
	Dahl, 2006[66]	Timothy Grass Mild and Moderate asthma	SLIT (T) Placebo	61 32	Oral pruritus	53% 5%	NR NR	0.007
	Corzo, 2014[81] (adults) Trial 1	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 17	Oral pruritis	NR NR	277 0	NA
					Mouth edema	NR NR	90 0	NA
	Corzo, 2014[81] (peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 18	Oral pruritis	NR NR	263 5	NA
					Mouth edema	NR NR	96 0	NA
	Niu, 2006[77]	Dust mite Mild and Moderate asthma	SLIT (A) Placebo	56 54	Tongue disorder and circumoral paresthesia	5 0	10 0	NA
	Ippoliti, 2003[78]	Dust mite	SLIT (A)	47	No local side effects in 86	0	0	0.0

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
		Mild and Moderate asthma	Placebo	39	children			
	Voltolini 2010[69]	Birch Mild and Moderate asthma	SLIT (A) Placebo	14 10	at least one adverse event was reported by 75% of actively trea-ted and 44.4% of placebo treated patients, most defined slight/moderate and consisting of local reaction in the mouth.	NA	NA	NA
Throat Irritation	de Blay, 2014[59]	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM SLIT 3-HQ HDM SLIT 1-HQ HDM Placebo	29 27 25 27	throat irritation	6% 4% 2% 1%	NR NR NR NR	0.0
					oral paresthesia	6% 3% 1% 0.5%	NR NR NR NR	0.0
	Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	Throat irritation Treatment related	21 (8) 27 (10) 4 (1)	26 32 4	-0.014
					Pharyngeal edema Treatment related	0 (0) 5 (2) 0 (0)	1 6 0	0.008
	Calderon, 2006[67]	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Throat irritation	0 0 1 1 1	NR NR NR NR NR	-0.089
					Dry throat	2 (22) 0 0 1 (20) 0	4 NR NR 1 NR	0.003
					Oral Hypoesthesia	0 0 1 (11) 3 (60) 0	NR NR 4 11 NR	0.004
	Calderon, 2006[67]	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Odynophagia	0 0 1 (11) 0 0	NR NR 1 NR NR	0.001

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
					Dysphagia	0 0 1 (11) 0 0	NR NR 2 NR NR	0.001
					Pharyngitis	3 (33) 0 4 (44) 0 1 (9)	3 NR 9 NR 1	-0.084
	Dahl, 2006[66]	Timothy Grass Mild and Moderate asthma	SLIT (T) Placebo	61 32	nasopharyngitis	36% 25%	NR NR	-0.02
					throat irritation	32% 25%	NR NR	-0.03
	Corzo, 2014[81] (adults) Trial 1	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 17	Stomatitis	NR NR	8 0	NA
					Throat irritation	NR NR	151 0	NA
					Oral paresthesia	NR NR	0 0	NA
	Corzo, 2014[81] (peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 18	Stomatitis	NR NR	195 0	NA
					Throat irritation	NR NR	234 1	NA
					Oral paresthesia	NR NR	105 2	NA
Abdominal pain, nausea, vomiting/ gastrointestinal complaints	Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	Nausea Treatment related	0 (0) 8 (3) 0 (0)	0 8 0	0.0
	Devillier, 2016[63]	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Abdominal pain	81 (25.2%) 17 (10.5%)	NR	0.147
					Gastrointestinal disorders	239 (74.2%) 58 (35.8%)	NR	0.384
	Pham-Thi, 2007[72]	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 55	Gastrointestinal complaint	NR NR	19 2	NA
	Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	20 15	Stomach ache	5% 6.6%	NR	-0.0016
	Shao, 2014[80]	Dust mite Mild asthma	SLIT (A) Pharmacotherapy	141 (54 AEs) 77 (11 AEs)	gastrointestinal intolerance	NR NR	2 (3.7%) 2 (18.18%)	NA
					Oral intolerance	NR NR	1 (1.85%) 0 (0)	NA

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
	Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 12 SQ HDM (T) SLIT 6 SQ HDM (T) Placebo	282 275 277	erosive esophagitis	0 0 1	NR	-0.004
	Corzo, 2014[81] (adults) Trial 1	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 17	vomiting	0	1 0	NA
Local rashes	Devillier, 2016[63]	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Chelitis	36 (11.2%) 8 (4.9%)	NR NR	0.62
	Shao, 2014[80]	Dust mite Intermittent and Mild asthma	SLIT (A) Pharmacotherapy	141 77	Local rashes	NR	5 (9.2%) 0 (0)	NA
	Mosges, 2010[83]	Tree Pollen Mild and Moderate asthma	SLIT Placebo	27 27	Most frequent symptoms were application site itching and application site paresthesia	NR	NR	NA

T: Tablet A: Aqueous NR: Not reported NA: Not applicable

Table G5.A – Systemic Reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
Lower Respiratory	Shao, 2014[80]	Dust mite Mild asthma	SLIT (A) Pharmacotherapy	139 (54 AEs) 79 (11 AEs)	Aggravating asthma	NR NR	8 (14.82%) 0 (0)	NA
	Pham-Thi, 2007[72]	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 55	Asthma exacerbations	NR NR	64 67	NA
	Calderon, 2006[67]	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Chest tightness/chest discomfort	0 0 2 (22) 0 0	NR NR 4 NR NR	0.002
					Asthma aggravated	1 (11) 0 1 (11) 0 0	1 NR 1 NR NR	0.002

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
					Wheezing	0 1 (11) 1 (11) 0 1 (9)	0 1 2 0 1	-0.089
					Cough	0 0 1 (11) 0 0	NR NR 1 NR NR	0.001
					Dyspnea NOS	0 1 (11) 1 (11) 0 1 (9)	NR 1 2 NR 1	-0.089
	Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 12 SQ HDM (T) SLIT 6 SQ HDM (T)t Placebo	282 275 277	asthma [moderate, alternative etiology was "recently viral infection"	1 0 0	NR	0.0
	de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM SLIT 3-HQ HDM SLIT 1-HQ HDM Placebo	156 159 146 143	Bronchitis	1/134 (<1) 6/131 (5) 4/117 (3) 3/107 (3)	1 8 7 6	0.0
					Asthma	12/134 (9) 12/131 (9) 6/117 (5) 5/107 (5)	19 17 7 6	0.03
	Maloney, 2016[62]	Dust mite Severity NS	SLIT - 6 SQ-HDM (T) SLIT - 12 SQ-HDM (T) Placebo	22 24 33	Asthma worsening	1 0 1	1 0 1	-0.31
	Bufe, 2009[82]	Timothy Grass Mild, Moderate and Severe asthma	SLIT (T) Placebo	55 50	Asthma, asthma exacerbation	2 (4) 1 (2)	3 1	0.01
	Corzo, 2014[81] (adults) Trial 1 (peds)Trial 2	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 17	Asthma worsening or asthma exacerbations	7 total	9 total	NA
				54 18	Asthma worsening or asthma exacerbations	12 total	7 6	NA
Mucosal irritation (other than mouth or GI tract)	Devillier, 2016[63]	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Rhinitis	67 (20.8%) 28 (17.3%)	NR	0.035
	Shao, 2014[80]	Dust mite Intermittent and Mild asthma	SLIT aqueous Pharmacotherapy	141 77	Eye itching	NR NR	1 (1.85%) 0 (0)	NA

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
	Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 12 SQ HDM (T) SLIT 6 SQ HDM (T) Placebo	282 275 277	Ear pruritus Treatment related	11 (4) 7 (3) 2 (1)	11 7 2	-0.07
	de Blay, 2014[59]	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM (T) SLIT 3-HQ HDM (T) SLIT 1-HQ HDM (T) Placebo	29 27 25 27	Ear pruritus	5% 3% 3% 0%	NR NR NR NR	0.0
	Corzo, 2014[81] (adults) Trial 1 peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 17	Ear pruritis	NR NR	150 0	NA
				54 18	Ear pruritis	NR NR	33 0	NA
Cutaneous	Marogna, 2013[68]	Trees Mild asthma	BUD 400 µg/day + SLIT BUD 800 µg/day BUD 1600 BUD 400 µg/day + LTRA (Montelukast)	19 19 20 18	Generalized itching	0 0 2 0	NR NR NR NR	0.001

T: Tablet A: Aqueous NR: Not reported NA: Not applicable

Table G6.A– Anaphylaxis

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	There were no anaphylactic reactions	0 0 0	0 0 0	0
Pham-Thi, 2007[72]	Dust mite Intermittent, Mild and Moderate asthma	SLIT (T) Placebo	54 55	There were no anaphylactic reactions	0 0	0 0	0
Maloney, 2016[62]	Dust mite Severity NS	SLIT - 6 SQ-HDM (T) SLIT - 12 SQ-HDM (T) Placebo	22 24 22	There were no anaphylactic reactions	0 0 0	0 0 0	0
de Blay, 2014[59] Mosbech, 2014[60] Mosbech, 2015[61]	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM (T) SLIT 3-HQ HDM (T) SLIT 1-HQ HDM (T) Placebo	134 131 117 107	No systemic allergic reactions/requirement for epinephrine.	0 0 0 0	0 0 0 0	0
Shao, 2014[80]	Dust mite Intermittent and Mild asthma	SLIT (A) Pharmacotherapy	141 77	There were no anaphylactic reactions	0 0	0 0	0
Mosges, 2010[83]	Tree Pollen Mild and Moderate asthma	SLIT (A) (ultra-rush) Placebo	27 27	There were no anaphylactic reactions	0 0	0 0	0

T: Tablet A: Aqueous

Table G7.A– Deaths*

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	There were no deaths reported	0	0
Devillier, 2016[63]	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	322 162	There were no deaths reported	0	0
Bufe, 2009[82]	Timothy Grass Mild, Moderate ad Severe asthma	SLIT (T) Placebo	126 127	There were no deaths reported	0	0

T: Tablet A: Aqueous
*Data abstracted ONLY if studies specifically reported on deaths

Table G8.A – Other reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
No reactions reported	La Grutta, 2007[74]	Dust mite Severity NS	SLIT Concomitant pharmacotherapy	33 23	No local or systemic relevant adverse events were observed	NR NR	0 0	NA
	Bahceciler, 2001[73]	Dust mite Mild asthma	SLIT (A) Placebo	8 7	No local or systemic side effects reported	0 0	0 0	NA
	Lue, 2006[76]	Dust mite Mild and Moderate asthma	SLIT (A) Placebo	10 10	No severe drug-related adverse event was reported	0 0	0 0	NA
	Ippoliti, 2003[78]	Dust mite Mild and Moderate asthma	SLIT (A) Placebo	47 39	No systemic side effects in 86 children	0	0	0.0
	Mosges, 2010[83]	Tree Pollen Mild and Moderate asthma	SLIT aqueous (ultra-rush) Placebo	27 27	No serious systemic effects were observed	0 0	NR	NA
	Devillier, 2016[63]	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	AEs or Adverse Drug Reactions life-threatening or disabling	0 0	0 0	0
	Corzo, 2014[81] (adults) Trial 1	Dust mite Mild and Moderate asthma	SLIT tablet Placebo	54 17	There were no serious adverse events	0 0	0 0	0
	Corzo, 2014[81] (peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT tablet Placebo	54 18	There were no serious adverse events	0 0	0 0	0
	Pham-Thi, 2007[72]	Dust mite Intermittent, Mild	SLIT tablet Placebo	54 55	There were no multiple-organ life-threatening events	0 0	0 0	0

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
		and Moderate asthma						
	Gomez, 2004[65]	Dust mite Mild and Moderate asthma	SLIT (A) Placebo	30 30	No adverse events were observed	0 0	0 0	0
Reactions not specified	Calderon, 2006[67]	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Not specified	0 0 0 0 1 (9%)	NR NR NR NR NR	-0.091
	Pham-Thi, 2007[72]	Dust mite Intermittent, Mild and Moderate asthma	SLIT T Placebo	54 55	total number of adverse events, local and systemic	0 4 (10%)	NR	-0.073
	Bufe, 2009[82]	Timothy Grass Mild, Moderate and Severe asthma	SLIT (T) Placebo	126 127	the pattern of adverse events was similar for subjects with and without asthma symptoms.	109 (87%) 106 (83%)	426 278	0.030
	Maloney, 2016[62]	Grass, Cat, Dog, Mold, Birch, Mugwort Severity NS	SLIT - 6 SQ-HDM T SLIT - 12 SQ-HDM T Placebo	22 24 22	Adverse events not specified (TEAEs)	68% 50% 46%	NR	0.013
					Adverse events not specified (TRAEs)	55% 50% 32%	NR	0.009
	Devillier, 2016[63]	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Severe Adverse Drug Reaction SLIT vs placebo P NS	10 (3.1%) 3 (1.9%)	NR	0.013
					Moderate Adverse Drug Reaction SLIT vs placebo P =0.0003	96 (29.8%) 24 (14.8%)	NR	0.150
					Mild Adverse Drug Reaction SLIT vs placebo P<0.0001	228 (70.8%) 70 (43.3%)	NR	0.276
					Severe AE SLIT vs placebo P NS	17 (5.3%) 10 (6.2%)	NR	-0.009
					Moderate AEs SLIT vs placebo P NS	149 (46.3%) 63 (38.9%)	NR	0.074
					Mild AEs SLIT vs placebo P NS	259 (80.4%) 101 (62.3%)	NR	0.181
	Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 12 SQ HDM T SLIT 6 SQ HDM T Placebo	282 275 277	Serious AE	7 (2%) 10 (4%) 11 (4%)	10 (1%) 10 (1%) 12 (2%)	-0.40
					AEs leading to discontinuation	25 (9%) 12 (4%) 8 (3%)	46 (6%) 23 (3%) 10 (2%)	-0.29

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
	Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	20 15	AEs leading to discontinuation	0 0	NR	0
	de Blay, 2014[59]	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM T SLIT 3-HQ HDM T SLIT 1-HQ HDM T Placebo	134 131 117 107	Serious adverse events	6 3 6 4	7 3 7 5	-0.37
Infection	Devillier, 2016[63]	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Infections and infestations	67 (20.8%) 10 (18.5%)	NR	0.146
	Shao, 2014[80]	Dust mite Mild asthma	SLIT (A) Pharmacotherapy	141 (54 AEs) 77 (11 AEs)	Upper respiratory tract infection	NR	23 (42.5%) 7 (63.6%)	NA
Unable to categorize					Nosebleed	NR	1 (1.85%) 1 (9.09%)	NA
					Headache	NR	0 (0) 1 (9.09%)	NA
	Stelmach, 2009[75]	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	20 15	Headache	0% 6.6%	NR	-0.066
	de Blay, 2014[59]	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM SLIT 3-HQ HDM SLIT 1-HQ HDM Placebo	134 131 117 107	dizziness	0 1 0 0	NR	0.002
					migraine	0 0 1 0	NR	0.002
	Virchow, 2016[58]	Dust mite Moderate to severe Asthma	SLIT 6 SQ HDM tablet SLIT 12 SQ HDM tablet Placebo	275 282 277	Accidental overdose Treatment related	4 (1) 15 (5) 9 (3)	5 16 12	-0.032
					Arthralgia	0 1 0	NR	0.001
					hepatocellular injury	0 0 1	NR	-0.004

T: Tablet A: Aqueous TRAE: Treatment related adverse event TEAE: Treatment emergent adverse event

SECTION B SLIT Safety for NON RCTs

Table G1.B– Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Dunsky, 2006[84] US	SLIT wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT NS	Polysensitized perennial and seasonal tree nut and peanut allergy	Multiple allergens	Home
	Vovolis, 2013[85]	SLIT (A) wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE Not reported	Polysensitized Olea europaea pollen, Dust mite (D pter-D far)	Multiple allergens	Clinic
	Ventura, 2008[86] Europe	SLIT wo comparator	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Not reported	Polysensitized graminacee, olive, cypress, house dust mite, Anisakis	Single allergen Dust mite (D pter-D far)	NR
	Blazowski, 2008[87]	SLIT wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	Not reported	Not reported	Multiple allergens	Home
	Moral, 2016[88]	SLIT (A) wo comparator	Asthma diagnosis criteria NR Mild to moderate persistent Control status NS	SPT and/or IgE Wheal diameter ≥3mm; IgE > class 2	Both poly and monosensitized	Pollens or Dust mite	Not specified
Mixed age	Roger, 2011[89] Europe	SLIT wo comparator	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Positive SPT (size NS) plus specific IgE class 2 or greater (10.7 kU/l)	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Clinic
	De Castro, 2013[90]	SLIT (T) Control	Asthma diagnosis criteria NR Mild persistent and moderate persistent Controlled	SPT and IgE Wheal diameter > 3mm; or IgE CAP class 3	Both poly and monosensitized	Single allergen Grass	Not specified
Children	Nuhoglu, 2007[91]	SLIT wo comparator	Asthma diagnosis criteria NR Severity Intermittent Controlled	SPT >3mm	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Home and Clinic
	Galip, 2015[92] Europe	SLIT (A) wo comparator	Pulmonary tests (PFT with bronchodilator reversibility of 18%) persistent asthma controlled on daily ICS	SPT wheal 10x10mm	Monosensitized Dust mite (D pter-D far))	Single allergen Dust mite (D pter-D far)	Home Hospital after AE
	Bene, 2016[93] Europe	SLIT (A) wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	NR	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	Not specified

T: Tablet A: Aqueous SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina*

* Authors did not report sensitization status

Table G2.B– Patient Characteristics

Population	Study	Patients	Comparators	Age in years Mean +/- SD (range)	Sex (% Male/ Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean years Affected)
Adults	Dunsky, 2006[84] US	1	SLIT wo comparator	31 years	NR/1	1/NA	NR
	Vovolis, 2013[85]	1	SLIT wo comparator	25 years	NR/1	1/NA	15 years
	Ventura, 2008[86] Europe	1	SLIT wo comparator	39 years	NR/1	1/NA	NR
	Blazowski, 2008[87]	1	SLIT wo comparator	16 years	NR/1	1/NA	NR
	Moral, 2016[88]	93	SLIT wo comparator	NR	NR	NR	NR
Mixed age	Roger, 2011[89] Europe	77	SLIT wo comparator	20.4 (NR)	46/54	77/NA	4.84 years
	De Castro, 2013[90] Europe	98	SLIT Control	NR NR	NR NR	NR NR	NR
Children	Nuhoglu, 2007[91]	39	SLIT wo comparator	8.8 (2.3)	23/16	39/NR	NR
	Galip, 2015[92]	1	SLIT wo comparator	6 years	1/NR	1/NA	3 years
	Bene, 2016[93]	1	SLIT wo comparator	10 years	NR/1	1/NA	NR

Table G3.B – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Dunsky, 2006[84]	SLIT without comparator	NR	NR	NR	NR	NR	NR
	Vovolis, 2013[85]	SLIT without comparator	NR	Targeted: NR Actual: 3 drops /day	NR	Daily	NR	NR
	Ventura, 2008[86]	SLIT without comparator	NR	NR	NR	NR	NR	1 month
	Blazowski, 2008[87]	SLIT without comparator	NR	Targeted: 10 drops, 100 IR/ml Actual: 60 drops, 100 IR/ml	NR	Daily	NR	3 years
	Moral, 2016[88]	SLIT without comparator	NR	Targeted: 300 SRU/day	NR	daily	NR	At least 3 months
Mixed age	Roger, 2011[89]	SLIT without comparator	NR	Targeted: 240 IR 3 times per week Actual: NR	Targeted: 450 IR at the end of ultra-rush induction Actual: NR	3 times per week	NR	2 weeks

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	De Castro, 2013[90]	SLIT (T) Control	Both (SABAs ICS and oral corticosteroids)	Targeted: 2-5 weekly tablets of 1.000 UA each Actual: 2-5 weekly tablets of 1.000 UA each Targeted: NA Actual: NA	NR	Daily	NR	3 years
Children	Nuhoglu, 2007[91]	SLIT without comparator	NR	Targeted: NR Actual: NR	Targeted: NR Actual: 100	3 alternate days a week	NR	3 years
	Galip, 2015[92]	SLIT without comparator	Both	Targeted: 300 IR/ml Actual: 300 IR/ml	NR	Daily	NR	3 years
	Bene, 2016[93]	SLIT wo comparator	NR	300IR	NR	NR	NR	NR

NR: Not reported IR: index reactivity units

Table G4.B– Local Reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Abdominal pain, nausea, vomiting/ Gastrointestinal complaints	Ventura, 2008[86]	Dust mite NS	SLIT (A) wo comparator	1	abdominal pain, nausea, vomiting	1	NR
	Bene, 2016[93]	Dust mite NS	SLIT (T) wo comparator	1	Eosinophilic esophagitis: Patient presented reflux and vomiting 6 weeks after starting SLIT. Did not respond to treatment. Histopathology confirmed diagnosis of eosinophilic esophagitis. Resolved after SLIT discontinuation	1	1
	Roger, 2011[89]	Dust mite Mild to moderate asthma	SLIT (A) wo comparator	77	General malaise, vomiting	1 (1.3%)	1

Table G5.B – Systemic Reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Lower respiratory	Galip, 2015[92]	Dust mite NS	SLIT aqueous wo comparator	2	Wheezing requiring beta agonists and dose reduction of SLIT	1	NA
	Nuhoglu, 2007[91]	Dust mite Mild and Moderate asthma	SLIT tablet wo comparator	39	Asthma attacks	NR	0.44
	De Castro, 2013[90]	Grass and Dust mite Mild and Moderate asthma	SLIT Control	50 48	Worsening of asthma	2% 0	1 0
	Roger, 2011[89]	Dust mite Mild asthma	SLIT (A) without comparator	77	Moderate dyspnea and asthma- causal relationship thought improbable	1 (1.3%)	1
	Blazowski, 2008[87]	Dust mite Intermittent asthma	SLIT aqueous wo comparator	1	Self-resolving wheezing	1	2
Reactions not specified	De Castro, 2013[90]	Grass and Dust mite Mild and Moderate asthma	SLIT Control	50 48	No systemic adverse effects were reported during the 3 years	0 0	0 0
	Roger, 2011[89]	Dust mite Mild and Moderate asthma	SLIT aqueous rush wo comparator	77	Adverse events not specified A little under half the adverse events were reported in the 77 asthmatic patients included in the study, although the profile of adverse events was similar to the overall population of the study.	NR	NR
	Moral, 2016[88]	Pollens and Dust mite	SLIT without comparator	93	Adverse reaction, not specified	26 (28%)	NR

Table G6.B - Anaphylaxis

Study	Allergen and Asthma severity	Arms	N	Description	Reported as patients N (%)	Reported as events N (%)
Blazowski, 2008[87]*	Dust mite Intermittent asthma	SLIT aqueous	1	Anaphylactic shock	1	NR
Vovolis, 2013[85]	Dust mite and Trees NS	SLIT aqueous	1	Flushing, hoarseness, dyspnea, dizziness and mild hypotension	1	NR
Dunsky, 2006[84]	Mold, Animals, Grass, and Weeds NS	SLIT aqueous	1	Anaphylaxis	1	NR

*caused by overdose

Table G7.B – Deaths*

No study reported on deaths.

*Data abstracted ONLY if studies specifically reported on deaths

Appendix H. Sublingual Versus Subcutaneous Immunotherapy

Table H1. Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Study Design Setting
Adults	Mungan, 1999[94] Turkey	SCIT SLIT (A)	Asthma diagnosis per clinical criteria and pulmonary tests (reversibility and FEV >70%) Severity NS Control status NS	SPT and IgE NS	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	RCT Clinic
Mixed age	Li, 2016[95] Asia	SCIT SLIT (A)	Asthma diagnosis per Chinese medical association Pulmonary tests (bronchial provocation test or exercise test positivity) Severity NS Control status presence of symptoms despite optimal treatment and allergen avoidance uncontrolled asthma excluded	SPT and IgE wheal ≥0.25 , IgE>0.35 kU/L	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Unspecified dust mites)	Single allergen Dust mite (NS)	RCT Clinic
	Yukselen, 2012[96] Yukselen, 2013[97]* Turkey	SCIT SLIT (A)	Asthma diagnosis per GINA criteria Mild persistent Control status NS	SPT and IgE SPT >3mm IgE classII or >0.70kU/l	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	RCT Clinic
Children	Keles, 2011[98] Turkey	SCIT SLIT (A)	Asthma diagnosis per GINA criteria and pulmonary tests (reversibility and FEV >70%) Mild persistent and moderate Control status NS	SPT and IgE NS	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	RCT Clinic
	Karakoc-Aydiner, 2015[99] Eifan, 2010[100] Europe	SCIT SLIT (A)	Asthma diagnosis per EPR and GINA criteria Mild persistent and moderate persistent Controlled asthma	SPT and IgE IgE >0.35 positive SPT (size not described)	Monosensitized Dust mite (D pter-D far)	Single allergen Dust mite (D pter-D far)	RCT Clinic
	Cochard, 2009[101] Europe	SCIT SLIT (A)	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE NS	Polysensitized Patient 1: birch, hazel tree, grass mix, rye, plantain, ragweed pollens, *Alternaria*; Patient 2: grass and cereal pollens, dust mites, molds, cat dander	Multiple allergens	Case report Clinic for SCIT NR for SLIT

SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified D pter: *Dermatophagoides pteronyssinus* D far: *Dermatophagoides farina* RCT Randomized controlled trial
* Authors do not specify sensitization status
** This is a second phase, Yukselen, 2013[97], not included because is an open phase Cohort

Table H2. Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Adults	Mungan, 1999[94]	36	SLIT (A) SCIT Placebo	32+/- 7 (Range 18-41) 29 +/- 7 (Range 18-39) 33 +/- 8 (Range 18-46)	13/87 40/60 9/91	15/0 10/0 11/0	5.67+/-4.32 years 6.2 +/-2.97 years 7.27 +/-3.07 years
Mixed age	Li, 2016[95]	90	SCIT + Seretide SLIT (A) + Seretide Seretide	7.6 +/- 1.5 7.4 +/- 1.3 7.1 +/- 1.2	63/37 60/40 63/37	27/3 30/0 30/0	1.7 1.6 1.6
	Yukselen, 2012[96]	32	SCIT + placebo drops SLIT (A) + placebo injections Placebo injections + drops	11+/- 3 9+/- 3 10+/- 3	60/40 50/50 60/40	10/0 11/1 10/1	1 year
Children	Keles, 2011[98]	60	SCIT SLIT (A) SCIT + SLIT Pharmacotherapy	7+/-2 9+/-2 8+/-1 8+/-3	36/74 31/69 56/44 42/58	11/2 13/2 14/0 12/0	NR
	Karakoc-Aydiner, 2015[99] Eifan, 2010[100]	48	SLIT (A) SCIT Pharmacotherapy	6 +/- 2 (Range 5-10) 7 +/- 2 (Range 5-10) 7 +/- 2 (Range 5-10)	47/53 38/62 44/56	16/1 16/2 16/2	2.1 years 2.5 years 2.4 years

Table H3. Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Mungan, 1999[94]	SLIT (A) SCIT Placebo SLIT	conventional therapy	20 drops of 100 IR/ml 0.15-0.75 ml of 10 IR/ml	11316 IR 131 IR	2 times a week Monthly	NR NR	1 year
Mixed age	Li, 2016[95]	SCIT + Seretide SLIT (A) + Seretide Seretide	Both	SCIT conventional 0.1-0.8 mL of 100000 SQ-U/Ml SLIT 3 drops of 333 µg/mL daily	NR	SCIT Weekly SLIT daily	NR	16 weeks
	Yukselen, 2012[96]	SCIT (plus placebo sublingual drops) SLIT (A) (plus placebo subcutaneous injections) Placebo (sublingual and subcutaneous)	conventional therapy	0.2-0.8 ml of 5000 TU/ml 28 drops of 1000 TU/ml	43,770 TU (21,885 TU of Dpt and 21885 TU of Df) 173733 TU (86866.5 TU of Dpt and 86,866.5 TU of Df)	Every 4th week Three times a week	NR NR	1 year

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Eifan, 2010[100]	SLIT (A) SCIT Pharmacotherapy	Only rescue medication	5 drops STU (1000 STU/ml) 100000 SQ U/ml, 1cm³	73876.8 STU 1131540 SQU	3 times per week Monthly	295.5 Der p 1, 295.5 Der f 1(cumulative) 111 Der p 1, 156 Der f 1(cumulative)	1 year
Children	Keles, 2011[98]	SCIT SLIT (A) SCIT (build-up) +SLIT (maintenance) Pharmacotherapy	Only rescue medication	44.12 µg of Der p1 and 62.1 µg of Df1 52.8 µg of Der p1 and 52.8 µg of Df1 43.2 µg of Der p1 and 43.2 µg of Df1	NR	Monthly 3 times a week 3 times a week	44.12 µg of Der p1 and 62.1 µg of Df1 52.8 µg of Der p1 and 52.8 µg of Df1 43.2 µg of Der p1 and 43.2 µg of Df1 (Maintenance phase)	1 year

T: Tablet A: Aqueous BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg: microgram Ag/ml: major protein unit
TU: Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: Index of reactivity unit NR: Not reported DU dosing unit

Table H4. Asthma Control
Asthma symptoms ACT Scores

Study	Allergen	Arms	N	Time of Measure	Value pre Mean+/-SD	Value post	Comparative Values
Li, 2016[95] Asia	Unspecified Dust mites	SCIT + Seretide SLIT (A) + Seretide Seretide	27 30 30	NR	18.84 (3.11) 19.06 (3.51) 18.74 (3.33)	24.75 (1.82) 23.35 (2.13) 23.01 (2.66)	SCIT pre vs post $P < 0.05$ SLIT pre vs post $P < 0.05$ Seretide pre vs post $P < 0.05$

Table H5. Quality of Life
No study reported on quality of life.

Table H6. Medication Use
No study reported on medication use

Table H7. Asthma Exacerbations and Health care Utilization
No study reported on Asthma exacerbations or healthcare utilization.

Table H8. Pulmonary Physiology and Airway Responsiveness

Study	Allergen	Arms	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Li, 2016[95]	Unspecified Dust mites	SCIT + Seretide SLIT (A) + Seretide Seretide	16 weeks	Peak expiratory flow (PEF)	81.79 +/-8.60 80.65 +/-8.60 79.69 +/-8.02	89.56 +/- 4.21 88.77 +/- 6.42 89.95 +/- 5.59	SCIT pre vs post $P < 0.01$ SLIT pre vs post $P < 0.05$ Seretide pre vs post P NR

Study	Allergen	Arms	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Li, 2016[95]	Unspecified Dust mites	SCIT + Seretide SLIT (A) + Seretide Seretide	16 weeks	FEV1	77.25 +/-6.6 77.65 +/-5.71 75.66 +/-4.06	89.79 +/-9.55 87.35 +/-9.96 79.63 +/-7.05	SCIT pre vs post *P* < 0.05 SLIT pre vs post *P* < 0.05 Seretide pre vs post *P* NR
Mungan, 1999[94]	Dust mites	SLIT SCIT Placebo	1 year	Methacholine bronchial provocation test	NR	NR	SLIT pre vs post *P*=NS SCIT pre vs post *P*=NS Placebo pre vs post *P*=NS
Yukselen, 2012[96]	Dust mites	SCIT SLIT Placebo	1 year	HDM-Specific Bronchial provocation	NR	NR	SCIT pre vs post, *P*=0.03 SLIT pre vs post, *P*=0.56 Placebo pre vs post, *P*=0.78 SCIT vs SLI T *P*= 0.91

PFT: Pulmonary Function Test NS: Not significant PEF: Peak Expiratory Flow FEV: forced expiratory volume

Table H9. Immunological Markers

A. IgE

Study	Allergen	Arms	Time of Measure	Outcome/ Unit	Value pre	Value post	Comparative Values
Eifan, 2010[100]	Dust mite	SLIT (A) SCIT Pharmacotherapy	1 year	IgE D.f/ D.pt specific IU/ml	51.1±38.9/ 59.4 ±42.9 63.6±37.7/ 69.8±45.3 60.4±37.7/ 72.4±29.5	NR NR NR	D far specific: SCIT pre versus post *P*=0.03 SCIT versus Pharmacotherapy *P*=0.03 SLIT pre versus post *P*=0.04 Pharmacotherapy pre versus post *P*=NS D pter specific: SCIT versus Pharmacotherapy *P*=0.03
Mungan, 1999[94]	Dust mite	SLIT (A) SCIT Placebo	1 year	IgE D.f/ D.pt specific kU/ml	505.05 311.89 288.40	NR NR NR	No significant changes in all three arms at 12 months compared to baseline
Keles, 2011[98]	Dust mites	SCIT SLIT (A) SCIT+SLIT Pharmacotherapy	1 year	Derp1 specific IgE IU/ml	62+/-52 67+/- 33 83+/-27 73+/- 37	61+/- 53 44+/-32 85+/-34 75+/-41	No significant differences pre vs post in all groups. No significant differences between IT groups and pharmacotherapy
2006 Li, 2016[95]	Unspecified dust mite	SCIT + Seretide SLIT (A) + Seretide Seretide	NR	HDM specific IgE	17.02+/- 9.25 18.62 +/-8.32) 17.89 +/-8.78)	11.12 +/- 8.27 13.07 +/- 9.15 16.07 +/- 9.35	*P* < 0.01 *P* < 0.05 NR

B. IgG4

Study	Allergen	Arms	Time of Measure	Biomarker	Units	Value pre	Value post	Comparative Values
Keles, 2011[98]	Dust mites (D.pt and D.f)	SCIT SLIT (A) SCIT+SLIT Pharmacotherapy	1 year	Derp1 specific IgG4	Ua/ML	0.21+/0.37 0.14+/-0.1 0.11+/-0.03 0.11+/-.11	0.22+/-0.41 5.74+/-4.43 0.70+/-0.45 0.09+/-0.08	SCIT vs Pharmacotherapy p<0.05 SCIT+SLIT vs Pharmacotherapy p<0.05

Table H10. Anaphylaxis

Study	Arms	N	Event description	Reported as patients N (%)	Reported as Events N (%)
Eifan, 2010[100]	SLIT (A) SCIT	16	Flushing, wheezing and dyspnea requiring epinephrine -required treatment discontinuation (SCIT arm)	1 (0.06%)	-

Table H11. Local Reactions

Study	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N(%)
Mungan, 1999[94]	SLIT (A) SCIT Placebo	15 10 11	Reaction at the injection site classified > 5cm (SCIT)	2 (13%)	-
			Buccal pruritus (SLIT)	1 (10%)	-
Eifan, 2010[100]	SLIT (A) SCIT Pharmacotherapy	16	Oral cavity or Oropharynx Itching classified as mild (SLIT)	1 (0.06%)	-
Li, 2016[95]	SCIT + Seretide SLIT (A) + Seretide Seretide	27 30 30	Local AEs grade 1	10 3 NR	NR NR NR
			Local AEs grade 2	1 1 NR	NR NR NR

Table H12. Systemic Reactions

Study	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Eifan, 2010[100]	SLIT (A) SCIT	16	Respiratory reaction- severe asthma symptoms- classified as severe – required treatment discontinuation (SCIT arm)	1 (6.2%)	-
Mungan, 1999[94]	SLIT (A) SCIT Placebo	15 10 11	Respiratory events classified as mild (bronchospasm) in SCIT	1 (10%)	-
			Mild Nausea in SLIT	1 (10%)	-
Keles, 2011[98]	SCIT SLIT (A) SCIT+SLIT Pharmacotherapy	11	Respiratory events classified as moderate- dyspnea and wheezing- required treatment discontinuation (SCIT arm)	2 (18.2%)	-
Li, 2016[95]	SCIT + Seretide SLIT (A) + Seretide Seretide	27 30 30	Unspecified systemic reactions	2 (SCIT) 1 (SLIT)	-

Table H13. Reactions Reported in Non RCTs

Study	Allergen and Asthma severity	N	Arms	Event Description
Cochard, 2009[101]	Case 1 Multiple Athma severity NS	1	SCIT	Recurrent immediate itchy and painful large local reactions at the injection site lasting for 2 to 4 days, in the absence of any systemic side effects – Required treatment discontinuation and switched to SLIT
			SLIT	SLIT ultrarush- Mouth itchiness during build up asthma attacks, during treatment progression- required discontinuation
	Case 2 Multiple Athma severity NS	1	SCIT	shortness of breath and was wheezing required treatment with antihistamine. AE recurred with second dose– Required treatment discontinuation and switched to SLIT
			SLIT	SLIT ultrarush- heavy nasal congestion during build up only with dust mite preparation. Reocurred when intiated followed with increased symptoms of asthma during treatment progression- required discontinuation

Table H14. Deaths

No deaths reported**.**

Appendix I. Risk of Bias Assessment

Subcutaneous Immunotherapy (SCIT)

Table I1 – Cochrane Risk of Bias for RCTs Included for SCIT

Study	Sequence Generation	Allocation Scheme Concealed	Blinding of Participants and Personnel	Blinding of Outcomes Assessor	Incomplete Outcome Data Addressed	Selective Reporting	Other Biases (other threats to validity)	Overall Risk of Bias
Alzakar, 2010[34]	Unclear	Unclear	No	No	No	Yes	Yes	Medium
Altintas, 1999[19]	Unclear	No	No	No	No	Yes	Yes	High
Ameal, 2005[4]	Unclear	Yes	Yes	Yes	No	Yes	Yes	Low
Adkinson, 1997[32] Limb, 2006[33]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Low
Arroabarren, 2015[31]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Baris, 2014[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Blumberga, 2011[13]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Bousquet, 1985[3]	Unclear	Low	No	No	No	Low	No	High
Bousquet, 1988[23]	Yes	No	No	No	No	Yes	Yes	High
Casanovas, 2005[37]	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Medium
Chakraborty, 2006[8]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Creticos, 1996[9]	Yes	No	No	No	Yes	Yes	No	High
Dreborg, 1986[29]	Yes	Yes	No	Unclear	Yes	Yes	Yes	Low
Gallego, 2010[2] Garcia-Robaina, 2006[1]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Garcia-Ortega, 1993[12]	Yes	No	No	No	Yes	Yes	No	High
Hill, 1982[20]	Unclear	No	No	No	No	Yes	Yes	High
Hui, 2014[30]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Low
Ibero, 2006[17]	Unclear	Unclear	No	No	Yes	Yes	Yes	Medium
Kilic, 2011[25]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Kohno, 1998[7]	Unclear	No	No	Unclear	Yes	Yes	Yes	Medium
Lozano, 2014[26]	No	No	No	No	Yes	Yes	Yes	High

Study	Sequence Generation	Allocation Scheme Concealed	Blinding of Participants and Personnel	Blinding of Outcomes Assessor	Incomplete Outcome Data Addressed	Selective Reporting	Other Biases (other threats to validity)	Overall Risk of Bias
Maestrelli, 2004[16]	Unclear	Yes	No	Unclear	Yes	Yes	Yes	Low
Ohman, 1984[10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Olsen, 1997[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Pifferi, 2002[28]	Yes	No	No	Unclear	Yes	Yes	Yes	Medium
Roberts, 2006[39]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Schubert 2009[38]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Tsai, 2010[35]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Van Bever, 1992[18]	Unclear	Yes	No	Unclear	Yes	Yes	No	Medium
Van Metre, 1988[11]	Unclear	No	Yes	Yes	No	Yes	No	High
Valovirta, 1984[21] Valovirta, 2006[22]	Yes	Yes	Yes	Unclear	Low	Yes	Yes	Low
Vidal, 2011[5]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Wang, 2006[15]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Low
Zielen, 2010[27]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium

(in alphabetical order)

Table I2 – ROBINs I Risk of Bias for non-RCTs Included for SCIT

Study	Bias due to Confounding	Bias in Selection of Participants	Bias of Classification of Interventions	Bias due to Departure from intended interventions	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall ROB
Confino-Cohen, 2010[50]	High	Moderate	Low	Low	Low	Serious	Moderate	Serious
Eng, 2006[55]	Probably Not	Moderate	Low	Low	Moderate	Low	Low	Moderate
Gozde Kanmaz, 2011[47]	High	Critical	Serious	Low	Low	Low	Low	Serious
Quiralte,2013[40]	High	Moderate	Low	Low	Low	Moderate	Low	Moderate
Rank, 2008[41]	Yes	Serious	Serious	Moderate	No information	Low	Moderate	Serious
Santos, 2015[54]	High	Moderate	Low	Low	Unclear	Moderate	Low	Moderate
Smits, 2007[51]	Probably Not	Moderate	Low	Low	Low	Low	Low	Low

(in alphabetical order)

Table I3 – WHO assessment for Case Series and Case Reports Included for SCIT

Study	How was the Adverse Event Classified?	Was the Adverse Event Related to the Intervention?	Causality
Cardona, 2014[53]	Dose related and time related	Yes	Probably/likely
Copenhaver, 2011[49]	Dose related and time related	Yes	Probably/likely
Dong, 2017[56]	Dose related and time related	Yes	Probably/likely
Garde, 2005[102]	Dose related	Not reported	Unassessible/Unclassifiable
Kartal, 2015[48]	Not clear	Yes	Unassessible/Unclassifiable
Lim,2017[57]	Dose related and time related	Yes	Probably/likely
Kim, 2011[44]	Dose related and time related	Yes	Certain
Ozden, 2009[46]	time related	Yes	Probable/likely
Rank, 2014[42]	Dose related	Yes	Certain
Sana, 2013[43]	Not dose related	Yes	Possible
Sanchez-Morillas, 2005[45]	time related	Yes	Possible
Santos, 2015[54]	Dose related and time related	Not reported	Probably/likely

(in alphabetical order)

Sublingual Immunotherapy (SLIT)

Table I4 – Cochrane Risk of Bias for RCTs Included for SLIT

Study	Sequence Generation	Allocation Scheme Concealed	Blinding of Participants and Personnel	Blinding of Outcomes Assessor	Incomplete Outcome Data Addressed	Selective Reporting	Other Biases (other threats to validity)	Overall Risk of Bias
Bahceciler, 2001[73]	Yes	Yes	No	No	Yes	Yes	No	Medium
Bufe, 2009[82]	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Medium
de Blay, 2014[59]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Calderon, 2006[67]	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low
Corzo, 2014[81]	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Low
Dahl, 2006[66]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Medium
Devillier, 2016[63]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium

Study	Sequence Generation	Allocation Scheme Concealed	Blinding of Participants and Personnel	Blinding of Outcomes Assessor	Incomplete Outcome Data Addressed	Selective Reporting	Other Biases (other threats to validity)	Overall Risk of Bias
Gomez, 2004[65]	Yes	Unclear	Yes	Unclear	Yes	No	No	Medium
Ippoliti, 2003[78]	Yes	No	Yes	Unclear	Yes	No	Yes	Medium
La Grutta, 2007[74]	Unclear	No	No	No	No	No	Yes	High
Lue, 2006[76]	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Medium
Maloney, 2016[62]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Marogna, 2009[70]	Yes	Yes	No	No	Yes	Yes	No	Medium
Marogna, 2010[71]	Yes	No	No	No	Yes	Yes	No	High
Marogna, 2013[68]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Low
Mosges, 2010[83]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	High
Niu, 2006[77]	Yes	Yes	Yes	Unclear	No	No	Yes	Medium
Pham-Thi, 2007[72]	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low
Shao, 2014[80]	Unclear	No	No	Unclear	Yes	Yes	Yes	Medium
Stelmach, 2009[75]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Low
Virchow, 2016[58]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Voltolini, 2010[69]	Yes	Yes	No	Unclear	Yes	Yes	No	Medium

(in alphabetical order)

Table I5 – ROBINs I Risk of Bias for non-RCTs Included for SLIT

Study	Bias due to Confounding	Bias in Selection of Participants	Bias of Classification of Interventions	Bias due to Departure from intended interventions	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall ROB
De Castro, 2013[90]	Low	Low	Low	Low	Low	Moderate	Moderate	Low
Nuhoglu, 2007[91]	High	Moderate	Low	Low	Unclear	Low	Low	Moderate
Roger, 2011[89]	Probably Not	Moderate	Low	Low	Low	Moderate	Low	Low

(in alphabetical order)

Table I6 – WHO assessment for Case Series and Case Reports Included for SLIT

Study	How was the Adverse Event Classified?	Was the Adverse Event Related to the Intervention?	Causality
Bene, 2016[93]	Ends with withdrawal	Yes	Probable/likely
Blazowski, 2008[87]*	Dose related	Yes	Certain
Dunsky, 2006[84]	Dose related and time related	Yes	Certain
Galip, 2015[92]	Dose related	Yes	Certain
Moral, 2016[88]	Dose related and time related	Yes	Probable/likely
Ventura, 2008[86]	Ends with withdrawal	Yes	Probable/likely
Vovolis, 2013[85]	Dose related	Yes	Probable/likely

(in alphabetical order)

*caused by overdose

Table I7 – Cochrane Risk of Bias for RCTs for SCT vs. SLIT

Study	Sequence generation	Allocation scheme concealed	Blinding of participants and personnel	Blinding of outcomes	Incomplete outcome data	Selective reporting	Free of other biases (other threats to validity)	Overall Risk of Bias
Karakoc-Aydiner, 2015[99] Eifan, 2010[100]	Unclear	Yes	No	No	Yes	Yes	Yes	Low
Keles 2011[98]	Yes	No	No	No	Yes	Yes	Yes	Medium
Li, 2016[95]	Unclear	Unclear	No	No	Yes	Yes	Yes	Medium
Mungan,1999[94]	Unclear	No	No	No	Yes	Yes	Yes	Medium
Yukselen, 2012[96]	Yes	Yes	Yes	No	Yes	Yes	Yes	Medium

(in alphabetical order)

Appendix J. References

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