Effective Health Care Program

Comparative Effectiveness Review
Number 111

Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review

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Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review

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Errata, "Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review."

The following errors appeared in the Comparative Effectiveness Review, "Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review." These errors did not affect the overall conclusions of the report.

In the Methods section, the definition of single and multiple allergen was missing. It should read:

> "In this review, multiple allergen immunotherapy was defined as the use of extracts containing more than one allergen species, including cross-reacting allergens. Single allergen immunotherapy was defined by the use of a single allergen species, and not by a class of allergens.
>
> Allergists may apply different definitions of single and multiple allergen immunotherapies to our findings. Multiple allergen immunotherapies can be defined as the use of extracts containing more than one allergen class, whereas single allergen immunotherapy can refer to the use of closely related allergens within the same class. For example, a study using a grass mix allergen (or tree mix, or 2 dust mite species) could be considered a single allergen study, whereas a multiple allergen study could use different classes of allergens, such as tree and grass."

Lastly, in Table 27 (Body of evidence for sublingual immunotherapy affecting rhinitis/rhinoconjunctivitis symptoms), the direction of change for Tseng 2008 and deBot 2011 appeared as positive when these two studies, in fact, showed a negative direction of change.

In the Executive Summary, Page ES-11, we said, "The strength of evidence is low that subcutaneous immunotherapy is superior to sublingual immunotherapy for control of allergic rhinitis and conjunctivitis symptoms." This is an error since the strength of evidence for this outcome is moderate, as stated in tables in the full report that refer to this outcome.

Again, these errors did not affect the overall conclusions of the report.

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10061-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.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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

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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 email list to learn about new program products and opportunities for input.

We welcome 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, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review

Structured Abstract

Objectives. Allergic rhinitis is highly prevalent in North America, affecting 20 to 40 percent of the population. Nearly 9 percent of Americans suffer from asthma, with more than half having evidence of atopy. This comparative effectiveness review describes the effectiveness and safety of subcutaneous immunotherapy and sublingual immunotherapy (off-label use of subcutaneous-aqueous allergens for sublingual desensitization) compared with other therapies for treatment of allergic rhinoconjunctivitis and asthma.

Data sources. We searched the MEDLINE®, Embase, LILACS, and CENTRAL databases from the beginning of each database through May 21, 2012.

Review methods. Two reviewers independently selected randomized controlled trials according to established study inclusion criteria. Disagreements were resolved by consensus. Paired reviewers assessed the risk of bias of each study and extracted details about the population, intervention(s), and outcomes of interest. The results were summarized by immunotherapy type (sublingual or subcutaneous), allergen, and outcomes. Studies exclusively enrolling children were reviewed separately. The strength of the body of evidence was graded and summarized.

Results. We included 74 references that investigated the efficacy and safety of subcutaneous immunotherapy, 60 studies that investigated the efficacy and safety of sublingual immunotherapy, and 8 studies that compared the two modes of delivery. All 142 studies were randomized controlled studies. The majority of studies were at medium risk of bias due to design choices. The strength of evidence is high that subcutaneous immunotherapy reduces asthma symptoms, rhinitis symptoms, conjunctivitis symptoms, asthma medication use, asthma plus rhinoconjunctivitis medication use, and rhinoconjunctivitis-specific quality of life. The strength of evidence is moderate that subcutaneous immunotherapy reduces rhinoconjunctivitis medication use, relative to usual care, which includes pharmacotherapy. Likewise, the strength of evidence is high that sublingual immunotherapy reduces asthma symptoms. The strength of evidence is moderate that sublingual immunotherapy reduces rhinitis/rhinoconjunctivitis symptoms, combined symptom scores, conjunctivitis symptoms, and medication useusage relative to usual care, and improves allergy-specific quality of life. In studies comparing subcutaneous with sublingual immunotherapy, strength of evidence supporting the superiority of subcutaneous immunotherapy for reducing allergic rhinitis and conjunctivitis symptoms, and the superiority of sublingual immunotherapy for reducing medication use, is low. We identified 13 pediatric studies of subcutaneous immunotherapy, 18 pediatric studies of sublingual immunotherapy, and 3 pediatric studies comparing subcutaneous and sublingual immunotherapy. The strength of evidence is moderate that subcutaneous immunotherapy reduces asthma symptoms and rhinitis symptoms in comparison to usual care. The strength of evidence is low that subcutaneous immunotherapy reduces conjunctivitis symptoms, medication scores, combined symptom-medication scores, or improves quality of life relative to usual care. The strength of evidence is high that sublingual immunotherapy reduces asthma symptoms, and

moderate that it reduces rhinitis/rhinoconjunctivitis symptoms, combined asthma plus rhinitis/rhinoconjunctivitis symptoms, conjunctivitis symptoms, and decreases medication use. While local reactions were frequent with both treatment regimens, there were rare reports of anaphylaxis in the subcutaneous immunotherapy studies, and no anaphylaxis reported in the sublingual immunotherapy studies.

Conclusions. With some variation across outcomes, the overall body of evidence consistently provides moderate to high support for the effectiveness and safety of both subcutaneous and sublingual immunotherapy for the treatment of allergic rhinitis and asthma. The evidence to support the use of immunotherapy in children is somewhat weaker than the evidence supporting its use in adults. The superiority of one route of administration over the other is not known.

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Executive Summary

Background

Allergic rhinitis is a widespread clinical problem, estimated to affect 20 to 40 percent of the population in the United States.[1-5] Inhalant allergens, such as plant pollens, characteristically cause seasonal rhinoconjunctivitis and/or asthma; whereas, cat dander, cockroaches, or dust mite allergens may induce symptoms year-round, and are associated with perennial rhinitis and/or asthma. The prevalence of asthma in the United States is approximately 9 percent, and approximately 62 percent of individuals with asthma show evidence of also having atopy (i.e., one or more positive-specific IgE levels).[6,7] The medical management of patients with allergic rhinitis and asthma includes allergen avoidance, pharmacotherapy, and immunotherapy.[4,5]

Allergen-specific immunotherapy (SIT) is typically recommended for patients whose allergic rhinoconjunctivitis and asthma symptoms cannot be controlled by medication and environmental controls, for patients who cannot tolerate medications, or for patients who do not comply with chronic medication regimens.[8,9] Currently, two forms of specific immunotherapy are used clinically in the United States. The U.S. Food and Drug Administration (FDA) has approved the use of allergen extracts for subcutaneous administration (subcutaneous immunotherapy) for the treatment of seasonal and perennial allergic rhinitis and allergic asthma. In the United States, a patient with allergies receives subcutaneous injections of an allergen-containing extract, comprised of the relevant allergens to which the patient is sensitive, in increasing doses, in an attempt to suppress or eliminate allergic symptomatology. Considerable interest has also evolved in using sublingual immunotherapy as an alternative to subcutaneous injection immunotherapy. Sublingual immunotherapy involves placement of the allergen under the tongue for local absorption to desensitize the allergic individual over a period of months to years and diminish allergic symptoms. In 1996, an Immunotherapy Task Force, assembled by the World Allergy Organization, cited the emerging clinical data on sublingual immunotherapy, recognized its potential as a viable alternative to subcutaneous therapy, and encouraged continued clinical investigation to characterize optimal techniques.[10] Over the past two decades, sublingual forms of immunotherapy have gained favor in Europe; sublingual tablet immunotherapy has been approved by the European regulatory authorities. In the United States, there are currently no FDA-approved sublingual forms of immunotherapy. In the absence of FDA-approved sublingual forms of immunotherapy, some researchers and physicians in the United States are exploring the off-label use of subcutaneous aqueous allergens for sublingual desensitization. An increasing number of U.S. physicians are employing this alternate desensitization approach in the treatment of allergic respiratory conditions based on European and U.S. studies, and on the European Medicines Agency's approval of certain oral products; however, due to differing standardization of potency in Europe and the United States, doses have been hard to translate between countries.

Scope and Key Questions

Objectives

The primary objective of this comparative effectiveness review is to evaluate the efficacy, effectiveness, and safety of SIT (including both subcutaneous and sublingual immunotherapy) that are presently available for use by clinicians and patients in the United States. We addressed the following Key Questions (KQs):

KQ1. What is the evidence for the efficacy and effectiveness of SIT in the treatment of allergic rhinoconjunctivitis and/or asthma?

KQ2. What is the evidence for safety of SIT in patients with allergic rhinoconjunctivitis and/or asthma?

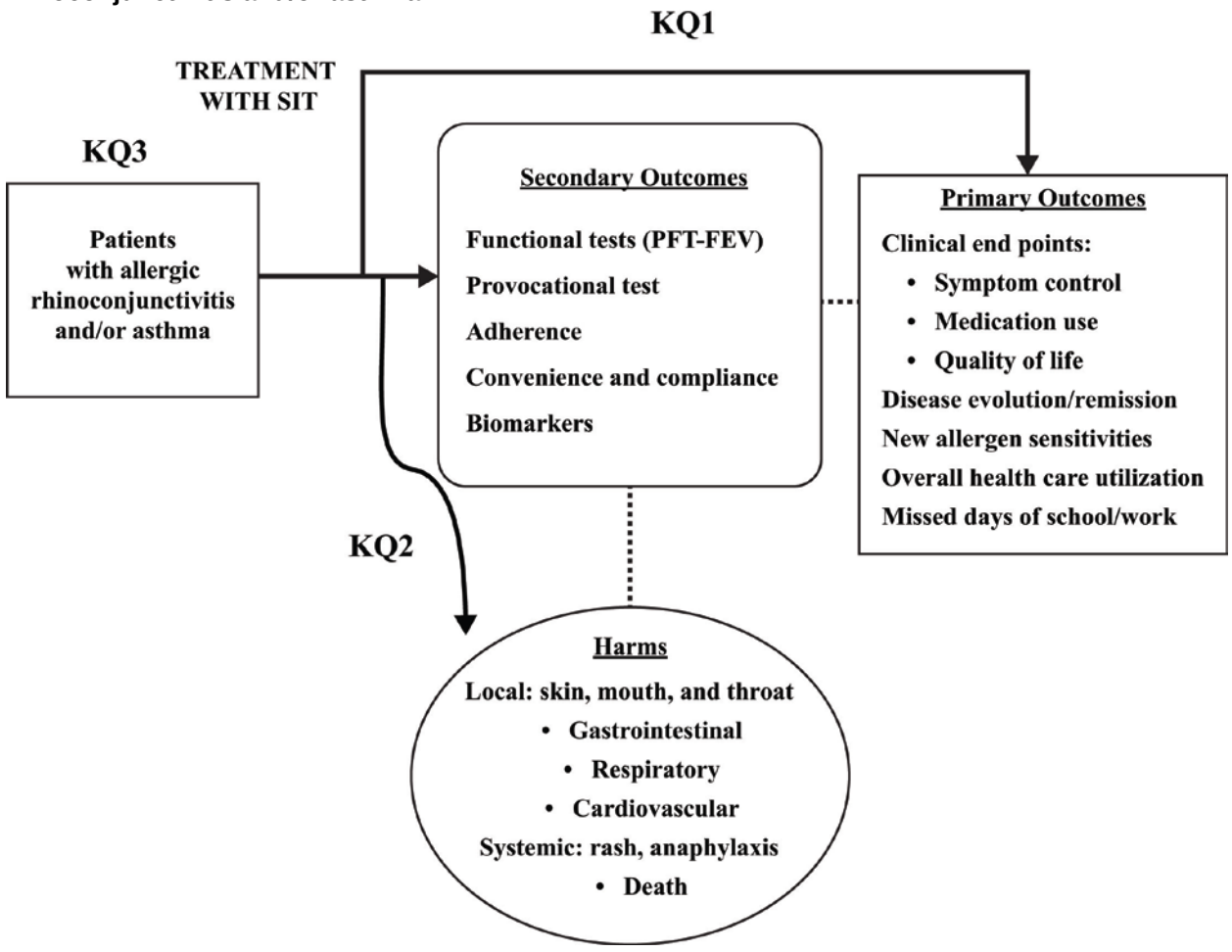
KQ3. Is the safety and effectiveness of SIT different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma? Specifically:

- Children
- Adults
- Elderly
- Pregnant women
- Minorities
- Inner-city and rural residents
- Monosensitized individuals
- Patients with severe asthma

Analytic Framework

Our analytic framework illustrates our approach to this systematic review and displays the interventions and comparators of interest, as well as the key primary and secondary outcomes (Figure A).

Figure A. Analytic framework for allergen-specific immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma



KQ = Key Question; PFT-FEV = pulmonary function test- forced expiratory volume; SIT = allergen-specific immunotherapy

The analytic framework depicts the impact of treatment of allergic rhinitis and asthma. It shows the KQs within the context of the inclusion criteria described in the following sections. It depicts how allergen-specific immunotherapy in this specific population (KQ3) may improve clinical outcomes (KQ1) and functional tests or chemical biomarkers. The potential harms (KQ2) of specific immunotherapy are shown in the framework as well.

Methods

Input From Stakeholders

With the input of a key informant panel, and staff at the Agency for Healthcare Research and Quality (AHRQ) and the Scientific Resources Center, we developed the KQs. The KQs compare how the two delivery routes of immunotherapy affect intermediate outcomes, long-term clinical outcomes, and adverse events. For additional input, we recruited a panel of technical experts, which included experts on the treatment of allergies and asthma in the adult and pediatric populations and then finalized the protocol.

Data Sources and Selection

We reviewed titles and then abstracts to identify randomized controlled trials (RCTs) on the effects of SIT. We included only articles published in English. Abstracts were reviewed independently by two investigators, and were excluded if both investigators agreed that the article met one or more of the exclusion criteria; disagreements were resolved by consensus. For inclusion in this review, we required that the RCTs enrolled patients with allergic rhinoconjunctivitis and/or allergic asthma due to airborne allergies, and that these diagnoses were confirmed by objective testing. The trials had to test subcutaneous immunotherapy or sublingual immunotherapy alone or in combination with usual care, which included pharmacotherapy and environmental interventions. We included trials if the comparators were placebo, other SIT regimens, or pharmacotherapy. For inclusion, the trials had to report at least one of the following: symptoms, medication use, results of provocation tests, quality of life, harms of treatment, adherence measures, convenience measures, or the long-term effects of treatment, including prevention of sequelae of allergic disease or the development of new sensitivities. Studies were excluded if they tested specific sublingual formulations that are not available in the United States, or if no similar U.S. allergen is available for off-label use. An example is our exclusion of studies of sublingual tablets. We also excluded articles in which oral immunotherapy was immediately swallowed without prolonged mucosal contact, as this type of immunotherapy is not currently in clinical use. We also excluded studies that did not clearly report the dose of allergen delivered. Differences regarding article inclusion were resolved through consensus adjudication; a third reviewer audited a random sample to ensure consistency in the reviewing process.

Data Extraction and Quality Assessment

We created standardized forms for data extraction to maximize consistency in identifying pertinent data for synthesis. Each article underwent duplicate review by study investigators for data abstraction, with the second reviewer confirming the accuracy of the first reviewer's data abstraction. Reviewer pairs were formed to ensure clinical and methodological expertise. Reviewers were not masked to the author, institution, or journal. In most instances, data were abstracted from the published text or tables. If possible, relevant data were also abstracted from figures. Differences in opinion were resolved through consensus adjudication and by discussion during team meetings.

Reviewers extracted detailed information on study characteristics, study participants, interventions, primary and secondary outcome measures and their methods of ascertainment, and safety outcomes. For studies that recorded outcomes at multiple time points, we used the outcome data from the final time point reported. For studies which treated and assessed subjects during a single season, we extracted the outcomes at peak pollen seasons when available. All information from the article review process was entered into the DistillerSR database by the individual completing the review.

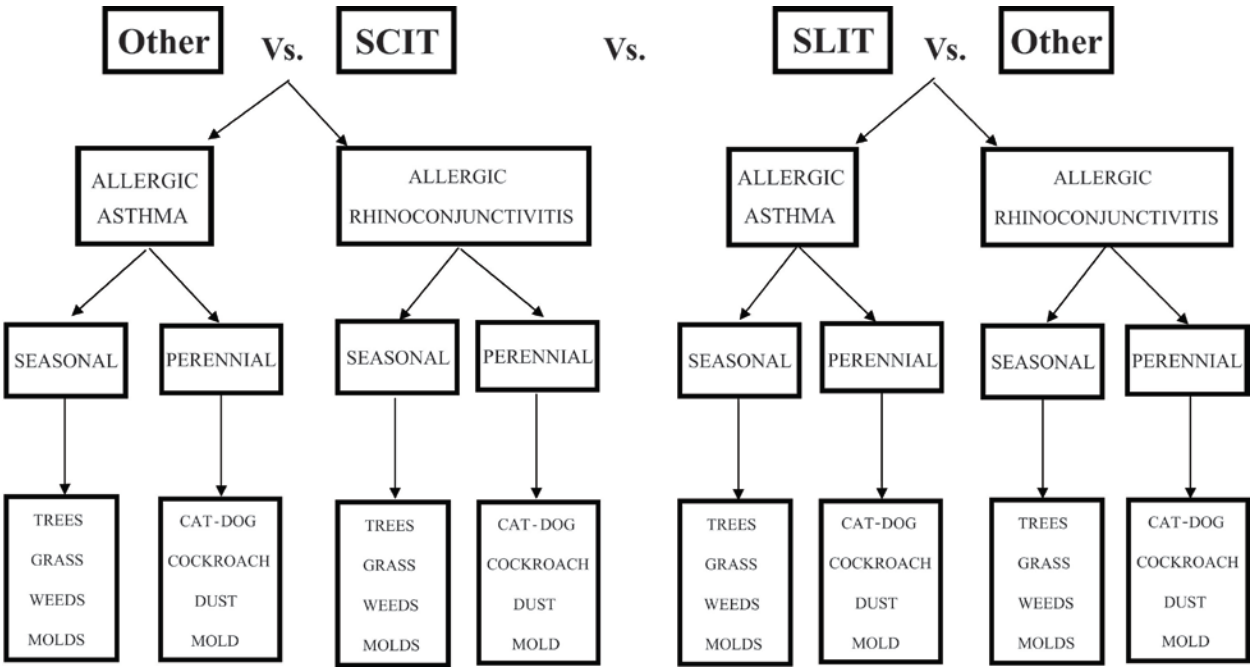
Two reviewers independently assessed the risk of bias in each article and came to consensus about the overall rating. We used a modification of the Cochrane Collaboration tool for assessing risk of bias from the "Cochrane Handbook for Systematic Reviews of Interventions."[11] We assessed six categories of potential bias: (1) lack of randomization, (2) lack of allocation concealment, (3) inadequate blinding, (4) incomplete data reporting, (5) selective reporting, and

(6) other sources of bias including the funding source. Studies were categorized as having a low, moderate, or high risk of bias depending on their adequacy across the six categories.

Data Synthesis and Analysis

We distributed the studies by intervention, disease, and allergen, and addressed the KQs within each intervention and disease strata (Figure B).

Figure B. Algorithm for the approach and classification of the studies



SCIT = subcutaneous immunotherapy; SIT = allergen specific immunotherapy; SLIT = sublingual immunotherapy

We created a set of detailed evidence tables containing information about each primary and secondary outcome that was extracted from eligible studies, and stratified the tables according to KQ. Given the substantial heterogeneity between studies and the lack of reporting of measures of variability, we did not quantitatively pool the data on efficacy. We summarized the safety of specific immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma by extracting data on the harms or adverse events reported in the included studies. The safety data reported in this systematic review include only information from the RCTs that met the criteria for inclusion in the review. The adverse events of specific immunotherapy were divided into two categories: local reactions (reactions that occur at the site of introduction of allergen) and systemic reactions (reactions that occur distant to the site of introduction of the allergen). These data could not be pooled quantitatively, either, due to heterogeneity.

At the completion of our review, we graded the quantity, quality, and consistency of the best available evidence addressing KQs 1, 2, and 3 by adapting an evidence grading scheme recommended by the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[12,13] We graded the evidence for each comparison for each outcome. Our grading incorporated the risk of biases in the trials, the consistency of the direction of the effect across studies for a given comparison and outcome, the relevance of the collection of trials to the question of interest (directness), and the magnitude of the effects reported in the trials. We could

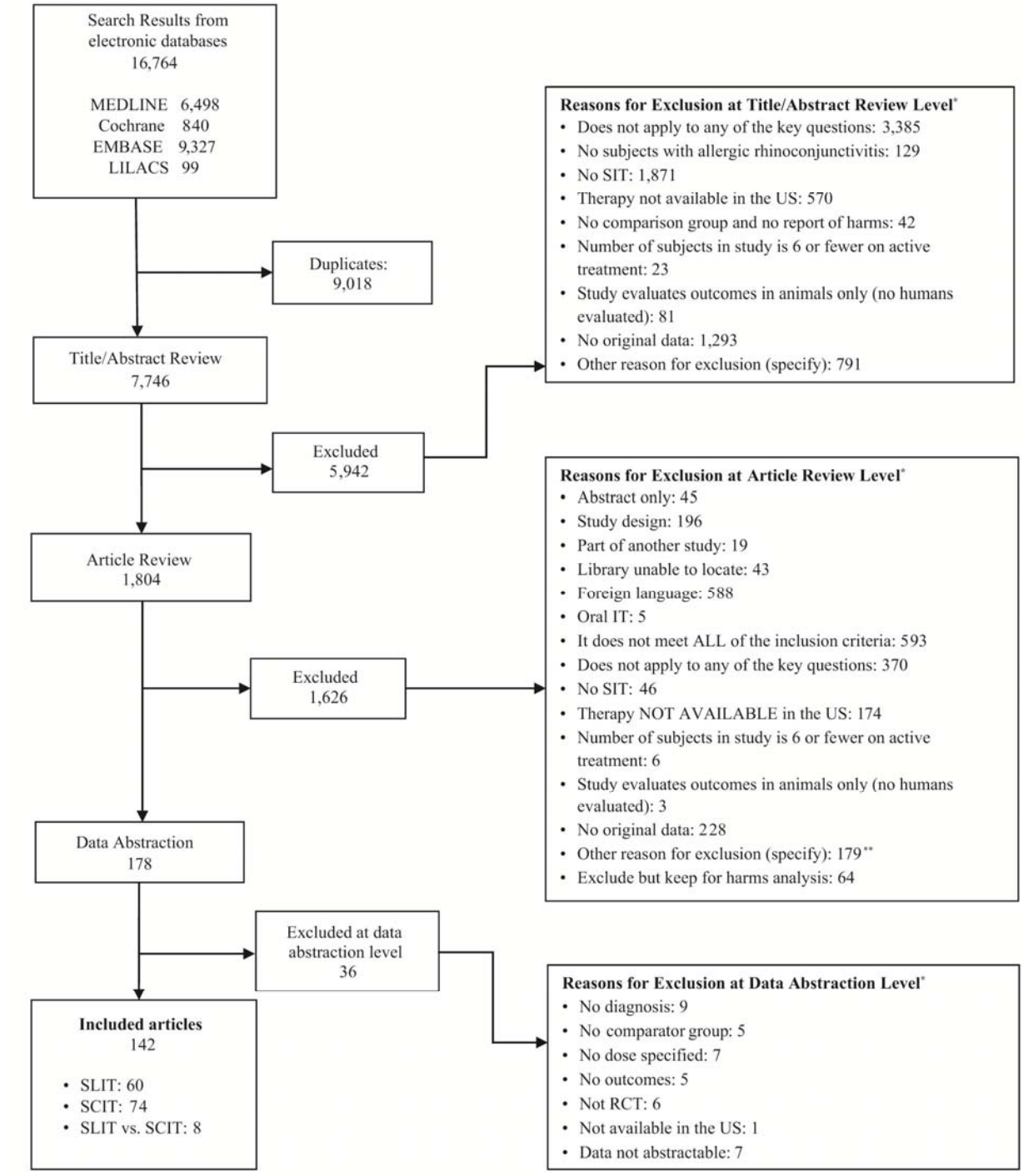
not comment on the precision of the effect sizes as there were seldom measures of variability within the individual studies. The magnitude of effect in a trial was considered "weak" if there was less than a 15 percent difference in post-to-pre change comparing the SIT group and the comparator group, a 15 to 40 percent difference was considered "moderate," and a greater than 40 percent difference was considered "strong."

We assigned evidence grades for each outcome as follows: (1) high grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); (2) moderate grade (indicating moderate confidence that the evidence reflects the true effect, although future research may change our confidence in the estimate of the effect and may change the estimate); (3) low grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) insufficient (evidence is unavailable). The investigator responsible for each section assigned the evidence grades, and the team reviewed the grades and came to consensus. We did not assign evidence grades for indirect outcome measures, such as pulmonary function test results and provocation tests (including nasal, conjunctival, and bronchial provocation tests).

Results

Our search identified 7,746 citations. After the necessary exclusions, 142 articles were included in the review. All of the included studies were RCTs. We included 74 references that investigated the efficacy and safety of subcutaneous immunotherapy, 60 studies that investigated the efficacy and safety of sublingual immunotherapy, and 8 studies that compared subcutaneous immunotherapy and sublingual immunotherapy. Figure C shows the results of our literature search.

Figure C. Literature search



RCT = randomized controlled trial; SCIT = subcutaneous immunotherapy; SIT = specific immunotherapy; SLIT = sublingual immunotherapy

* Total may exceed number in corresponding box, as articles were excluded by two reviewers at this level.

** Other reasons: Control group is healthy population, routes of administration not included, abandoned interventions, outcomes not reported, no comparator group, continued medical education reports, editorials or reviews, studies about mechanism or action, other allergies (food, aspirin).

Study Characteristics

The primary diagnoses of the subjects in the included articles were allergic rhinoconjunctivitis and/or asthma. The majority of studies included adults only (52%), followed by studies enrolling only children (24%); studies of mixed adult and pediatric participants were least frequent. Study sizes ranged from 15 to 511 patients. Twenty-three studies (20%) had fewer than 30 patients and twenty-six studies (18%) had more than 100 patients. The majority of the subcutaneous immunotherapy studies (51 studies or 69%) had 50 subjects or fewer, whereas 60 percent of sublingual immunotherapy studies (36 studies) enrolled at least 50 subjects. The majority of studies evaluated seasonal allergens (subcutaneous immunotherapy: 59%, sublingual immunotherapy: 67%), followed by perennial allergens (subcutaneous immunotherapy: 41%, sublingual immunotherapy: 30%), while least common were mixed seasonal and perennial allergens (subcutaneous immunotherapy: 2%, sublingual immunotherapy: 3%). Nearly all studies had at least a medium risk of bias (subcutaneous immunotherapy: 80%, sublingual immunotherapy: 85%). Forty-eight percent of subcutaneous studies and 61 percent of sublingual studies had industry support in the form of either funding and/or supplies.

Population Characteristics

The age range at the time of randomization was 3 to 72 years in the subcutaneous immunotherapy studies and 4 to 74 years in the sublingual immunotherapy studies. Only one study reported race. The duration of allergic rhinoconjunctivitis and/or asthma prior to enrollment was reported in 48 percent of the studies. Twenty-two percent of the studies reported that patients had been affected for more than 5 years. In 22 percent of the studies, patients had been affected for 1 to 5 years.

Intervention Characteristics

The duration of treatment ranged from one season to 5 years; the majority of studies treated the participants for less than 3 years. Thirty-five percent of studies treated participants for less than 1 year. There was substantial heterogeneity in the doses of immunotherapy administered to participants, and the studies used a variety of units to report dosing.

Subcutaneous Immunotherapy

Key Question 1. What is the evidence for the efficacy and effectiveness of subcutaneous immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma?

The majority of the subcutaneous immunotherapy trials used a single allergen for treatment. In the trials testing subcutaneous immunotherapy against placebo injections or usual pharmacological measures for patients with asthma, the strength of evidence is high that subcutaneous immunotherapy reduces asthma symptoms, medication use, and combined asthma plus rhinoconjunctivitis medication use. The strength of evidence is moderate that subcutaneous immunotherapy reduces asthma plus rhinitis/rhinoconjunctivitis symptoms. The strength of evidence is low that subcutaneous immunotherapy reduces asthma (with or without rhinitis) combined symptom-medication scores. Although we did not grade the evidence for indirect outcomes, we observed that subcutaneous immunotherapy consistently decreased specific

bronchial reactivity to allergen challenges. No consistent benefit was observed for pulmonary-function test results and nonspecific bronchial reactivity.

Regarding the use of subcutaneous immunotherapy for control of allergic rhinoconjunctivitis, we found that the strength of evidence is high that subcutaneous immunotherapy reduces rhinitis/rhinoconjunctivitis symptoms; conjunctivitis symptoms; combined nasal, ocular, and bronchial symptoms; combined rhinoconjunctivitis plus asthma medication use; and improves disease-specific quality of life. The strength of evidence is moderate that subcutaneous immunotherapy reduces rhinitis/rhinoconjunctivitis medication use. The strength of evidence is low that subcutaneous immunotherapy reduces combined symptom-medication scores (Table A).

Key Question 2. What is the evidence for safety of subcutaneous immunotherapy in patients with allergic rhinoconjunctivitis and/or asthma?

Not all of the studies reported safety data and the lack of a consistent reporting system and grading system for the adverse outcomes made it impossible to pool safety data across studies. Forty-five studies of subcutaneous immunotherapy reported safety data. Local reactions, reported in 5 percent to 58 percent of patients and 0.6 percent to 54 percent of injections, were more common than systemic reactions. Most local reactions were mild. The most common systemic reactions were respiratory reactions, occurring in up to 46 percent of patients and following 15 percent of injections. General symptoms (such as headache, fatigue, arthritis) also occurred frequently and affected up to 44 percent of patients. The majority of the systemic reactions were either mild or unspecified. Gastrointestinal reactions, reported in only one study, were the least frequent reactions. Thirteen anaphylactic reactions were reported in four trials. No deaths were reported (Table B).

Key Question 3. Is the safety and effectiveness of subcutaneous immunotherapy different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma?

Insufficient data exist to describe the strength of evidence regarding efficacy or safety of subcutaneous immunotherapy in the following subpopulations: the elderly, pregnant women, racial and ethnic minorities, inner-city residents, rural residents, and individuals with severe asthma. However, the evidence from a few studies suggests that subcutaneous immunotherapy may be more beneficial in patients with mild asthma than in those with severe asthma. There were no consistent differences in efficacy when considering only the trials enrolling mono-sensitized individuals and the trials enrolling poly-sensitized participants. The data were sufficient to comment on the pediatric subpopulation.

Efficacy of Subcutaneous Immunotherapy in the Pediatric Subpopulation

We included 13 RCTs, enrolling 920 children and comparing subcutaneous immunotherapy with placebo injections or usual pharmacological measures. As observed in the general population, the majority of studies used a single allergen for subcutaneous immunotherapy. The strength of evidence was moderate that subcutaneous immunotherapy reduces asthma symptoms. The strength of evidence was low that subcutaneous immunotherapy reduces asthma medication use, combined asthma plus rhinitis/rhinoconjunctivitis medication use, and asthma/rhinitis/rhinoconjunctivitis symptom-medication scores. We found a moderate strength of evidence to support the use of subcutaneous immunotherapy for reducing

rhinitis/rhinoconjunctivitis symptoms in children. The strength of evidence was low that subcutaneous immunotherapy reduces conjunctivitis symptoms and improves quality of life in children with rhinitis/rhinoconjunctivitis (Table C).

Safety of Subcutaneous Immunotherapy in the Pediatric Population

Inconsistent reporting of adverse events in the pediatric subcutaneous immunotherapy articles made it impossible to pool safety data across studies. However, local reactions were the most common adverse reactions in children receiving subcutaneous immunotherapy. There were no reports of anaphylaxis or death.

Sublingual Immunotherapy

Key Question 1. What is the evidence for the efficacy and effectiveness of sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma?

In the trials testing sublingual immunotherapy against placebo drops or usual pharmacological measures, the overall strength of evidence is moderate that sublingual immunotherapy improves allergic rhinitis and asthma outcomes. The strength of evidence is high that sublingual immunotherapy reduces asthma symptoms. The strength of evidence is moderate that sublingual immunotherapy reduces the following clinical outcomes: rhinitis/rhinoconjunctivitis symptoms, combined asthma plus rhinitis/rhinoconjunctivitis symptoms, combination medication plus symptom scores, conjunctivitis symptoms, and medication use, and improves quality of life. We observed that sublingual immunotherapy consistently improved measures of pulmonary function in the allergic asthmatic population (Table D).

Key Question 2. What is the evidence for safety of sublingual immunotherapy in patients with allergic rhinoconjunctivitis and/or asthma?

Forty-three studies of sublingual immunotherapy provided safety data. Local reactions were commonly reported and were described as mild. Systemic reactions were described infrequently; no life-threatening reactions, anaphylaxis, or deaths were reported in these trials. The strength of evidence is insufficient for definitive statements about the safety of sublingual immunotherapy although few serious events were reported (Table E).

Key Question 3. Is the safety and effectiveness of sublingual immunotherapy different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma?

Insufficient data exist to describe the strength of evidence regarding efficacy or safety of sublingual immunotherapy in the following subpopulations: the elderly, pregnant women, racial and ethnic minorities, inner-city residents, rural residents, and individuals with severe asthma. The data were sufficient to comment on the pediatric subpopulation.

Efficacy of Sublingual Immunotherapy in the Pediatric Subpopulation

We included 18 RCTs, enrolling 1,579 children, comparing sublingual immunotherapy with placebo drops or usual pharmacological measures. The strength of evidence is high that sublingual immunotherapy reduces asthma symptoms. The strength of evidence is moderate that sublingual immunotherapy reduces rhinitis/rhinoconjunctivitis symptoms, combined asthma plus rhinitis/rhinoconjunctivitis symptoms, conjunctivitis symptoms, and reduces medication use. The strength of evidence is low that sublingual immunotherapy reduces combined medication plus symptoms scores. There is insufficient evidence to determine the impact of sublingual immunotherapy on disease-specific quality of life. The overall strength of evidence is moderate, that sublingual immunotherapy in children and adolescents improves symptom control, when considering all domains with pertinent clinical outcomes (Table F).

Safety of Sublingual Immunotherapy in the Pediatric Population

The inconsistent reporting of adverse events in the pediatric sublingual immunotherapy studies made it impossible to pool safety data across studies. Local reactions were common, but mild. No life-threatening reactions, anaphylaxis, or deaths were reported in these trials. The strength of evidence is insufficient for definitive statements about the safety of subcutaneous immunotherapy or sublingual immunotherapy in children, although few serious events were reported.

Subcutaneous Versus Sublingual Immunotherapy

Key Question 1. What is the evidence for the efficacy and effectiveness of subcutaneous versus sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma?

Eight RCTs, published between 1989 and 2010, reported on the efficacy and safety of sublingual immunotherapy and subcutaneous immunotherapy when compared directly. Only three of the eight studies reported head-to-head statistical comparisons of the clinical outcomes of interest. The strength of evidence is moderate that subcutaneous immunotherapy is superior to sublingual immunotherapy for control of allergic rhinitis and conjunctivitis symptoms. The strength of evidence is low that sublingual immunotherapy is superior to subcutaneous immunotherapy for reducing medication use. There is insufficient evidence to favor either route of delivery for reducing asthma symptoms and asthma medicine use.

Key Question 2. What is the evidence for safety of subcutaneous versus sublingual immunotherapy in patients with allergic rhinoconjunctivitis and/or asthma?

The safety of sublingual immunotherapy and subcutaneous immunotherapy was assessed in all eight of the included articles. The recording and reporting of the adverse events was neither uniform nor comparable across studies. Local reactions were common and were all of mild or moderate severity. There was one report of anaphylaxis with subcutaneous immunotherapy. There were no reported deaths.

Key Question 3. Is the safety and effectiveness of subcutaneous versus sublingual immunotherapy different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma?

Insufficient data exist to describe the strength of evidence regarding efficacy or safety of sublingual versus subcutaneous immunotherapy in these subpopulations: the elderly, pregnant women, racial and ethnic minorities, inner-city residents, rural residents, and individuals with severe asthma.

Three RCTS, enrolling 135 children and adolescents, reported on the efficacy and safety of sublingual immunotherapy and subcutaneous immunotherapy when compared directly. The strength of evidence is low to support subcutaneous over sublingual immunotherapy in children and adolescents for reducing asthma symptoms, allergic rhinitis/rhinoconjunctivitis symptoms, or decreasing medication use. Local reactions were reported in both groups. No systemic reactions were reported in patients receiving sublingual immunotherapy. Among children receiving subcutaneous immunotherapy, one anaphylaxis event and three respiratory systemic reactions were reported.

Discussion

For this review of the effectiveness, efficacy, and safety of specific immunotherapy, we summarized data from 142 randomized controlled trials: 74 of subcutaneous immunotherapy, 60 of sublingual immunotherapy, and 8 comparing subcutaneous to sublingual therapy. The studies had considerable heterogeneity in the outcomes reported, scoring of outcomes, and safety data reported, which precluded quantitative pooling of the data. The majority of studies had a moderate risk of bias due to the design choices that were made.

Summary of Results

In our analysis of subcutaneous immunotherapy, key evidence was examined to determine the efficacy and effectiveness of subcutaneous immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma. We reviewed pertinent direct clinical outcomes, such as symptoms, medication use, and quality of life. There is sufficient evidence to support the overall effectiveness and safety of both subcutaneous and sublingual immunotherapy for the treatment of allergic rhinitis and asthma.

Regarding asthma outcomes, this review provides supportive evidence subcutaneous immunotherapy improves several asthma and rhinitis/rhinoconjunctivitis outcomes. There is high-grade evidence that subcutaneous immunotherapy reduces asthma symptoms and asthma medication use. Regarding allergic rhinoconjunctivitis outcomes, we found high grade evidence that subcutaneous immunotherapy reduces rhinitis/rhinoconjunctivitis symptoms; conjunctivitis symptoms; combined nasal, ocular, and bronchial symptoms; combined asthma plus rhinitis/rhinoconjunctivitis medication use; and improves disease-specific quality of life. Overall, our findings are consistent with findings from previous systematic reviews.[14-16] The majority of the studies included in this review used a single allergen for immunotherapy. In the United States, it is common practice to include multiple allergens in subcutaneous immunotherapy extracts. However, only a few trials have investigated the use of multiple allergen regimens for immunotherapy.

We note that few systematic reviews of subcutaneous immunotherapy have focused on studies in children. A systematic review by Roder et al. reviewed immunotherapy for allergic

rhinoconjunctivitis in children and adolescents and identified six studies of subcutaneous immunotherapy that showed conflicting results for clinical efficacy.[17] For this review, we reviewed studies in pediatric subpopulations separately. Although the evidence supports the use of subcutaneous immunotherapy to improve asthma and allergic rhinitis outcomes in children, we found fewer pediatric studies, and the strength of evidence was lower in the pediatric subpopulation than in the mixed adult and pediatric population. As observed in the mixed population, the majority of the pediatric subcutaneous immunotherapy studies used a single allergen.

Similarly, the overall strength of evidence is moderate that sublingual immunotherapy improves allergic rhinitis and asthma outcomes. There is high-grade evidence that sublingual immunotherapy reduces asthma symptoms. There is moderate-grade evidence that sublingual immunotherapy reduces combined rhinitis/rhinoconjunctivitis symptoms, asthma plus rhinitis/rhinoconjunctivitis symptoms, combination medication plus symptom scores, conjunctivitis symptoms, medication use, and improves quality of life.

In the pediatric studies, the overall strength of evidence is moderate that sublingual immunotherapy improves allergic rhinitis and asthma outcomes. There is moderate-grade evidence to support that sublingual immunotherapy reduces rhinitis/rhinoconjunctivitis symptoms, combined asthma plus rhinitis/rhinoconjunctivitis symptoms, conjunctivitis symptoms, and decreases medication use. The strength of evidence is low that sublingual immunotherapy reduces combination medication use plus symptoms. The strength of evidence is insufficient to support sublingual immunotherapy use for improving disease-specific quality of life.

In studies comparing subcutaneous to sublingual immunotherapy, the evidence is insufficient to draw a conclusion about the superiority of one mode of delivery over the other.

The available safety data supports the safety of specific immunotherapy, although local reactions were commonly reported for subcutaneous and sublingual immunotherapy. Serious, life-threatening reactions were rare, and no deaths were reported. The pediatric safety data are consistent with the overall safety results reported for subcutaneous and sublingual immunotherapy. While local reactions were common, only one anaphylaxis event was reported in a child receiving subcutaneous immunotherapy in a study comparing subcutaneous and sublingual immunotherapy.

There is consistency in the observed benefits across outcomes for both sublingual and subcutaneous immunotherapy, and in the mixed and pediatric-only populations. The direction of effect largely favors immunotherapy across all outcomes.

Applicability

The results of this systematic review are applicable to patients with allergic rhinoconjunctivitis and/or asthma. We included only studies that confirmed the diagnosis of allergy, either by skin or in vitro testing. Furthermore, asthma studies were included only if the studies used objective measures to confirm asthma diagnosis. We included only studies in which the specific immunotherapy formulations used (or close substitutes) are available to clinicians in the United States, so these results should be applicable to practitioners in the United States.

The reviewed outcomes reflect important clinical outcomes for patients with environmental allergies. The majority of outcomes were direct measures of disease symptomatology, which should make the findings of our review meaningful to clinicians and to patients. Some surrogate measures, such as pulmonary function testing, were also included. While pulmonary function

testing is an indirect measure of asthma outcomes, it is used frequently by clinicians in the United States.

However, the following should be considered regarding the applicability of the evidence described in this report. The majority of the included trials used a single allergen for immunotherapy; hence, it is difficult to determine the extent to which this evidence applies to U.S. practitioners using multiple allergen regimens. Based on the findings from a few studies that found subcutaneous immunotherapy to be more beneficial in patients with mild asthma than with severe asthma, the use of subcutaneous immunotherapy to treat asthma is probably most applicable to mild asthmatics. The majority of sublingual immunotherapy studies in this review included subjects with allergic rhinitis/rhinoconjunctivitis and/or mild asthma. Hence, although it may appear from this review that sublingual immunotherapy may be safer than subcutaneous immunotherapy, the safety data from these subgroups of patients must not be extrapolated to the more severely affected patients. There is little evidence supporting the use of immunotherapy in patients with severe asthma.

While a separate sub-analysis of pediatric studies was performed for this review, several studies reported outcomes on a mixed population of adults and children without stratifying the outcomes by age group, so we could not say definitively to which population the results apply. Furthermore, the dosing regimens and durations of treatment reported in these studies varied widely. Therefore, this body of evidence is insufficient for us to comment specifically on target maintenance dose or on duration of sublingual therapy. This may, however, be interpreted as supporting the effectiveness of immunotherapy across a broad range of doses.

There is no clear consensus on what is considered a clinically relevant improvement in symptoms. While some clinicians may suggest that a 15 percent change could reflect real and significant improvement in symptoms in some patients, Canonica et al reported that "the minimal clinically relevant efficacy should be at least 20 percent higher than placebo."[18] We would expect less difference in symptom improvement when comparing immunotherapy to medications. Our systematic review included both studies using placebo and other comparators, such as medications. We chose to consider a less than 15 percent difference as a weak magnitude of effect, a 15 percent to 40 percent difference as a moderate magnitude of effect, and a greater than 40 percent difference as a strong magnitude of effect. We applied this scheme to all graded outcomes in this review.

Our analysis adds to the available information about the strength of evidence for the efficacy and safety of allergen immunotherapy for the treatment of asthma and allergic rhinoconjunctivitis. These findings are relevant to clinicians who provide care for patients affected by these medical conditions. The findings are also relevant to patients making decisions regarding therapy, as they findings can help inform patients on the efficacy and safety of allergen immunotherapy. Guideline developers may also find our review useful for making recommendations about the use of allergen immunotherapy in adults and children.

Limitations

We encountered several challenges during our review process. We included only RCTs in this review; however, the studies varied substantially in their risk of bias. While all studies used randomization, several studies did not specify whether allocations schemes were concealed, or if the type of intervention was concealed from participants and outcome assessors. The majority of subcutaneous and sublingual immunotherapy studies received industry support financially or in the form of supplies. The study authors rarely reported the clear role or extent of involvement of

the sponsors. For these reasons, several studies were considered to have a moderate or high risk of bias. The potential risk of bias played an important role in determining the strength of the evidence for each direct outcome.

The body of literature reviewed has much heterogeneity. The clinical outcomes reported varied from study to study, and there were no consistent scoring or grading systems for reporting pertinent primary outcomes, such as symptoms or medication use. The study authors used varying criteria for diagnosing asthma and assessing asthma severity and control. Some of the asthma criteria may overestimate, while other criteria may underestimate, the degree of asthma control. Some studies that reported combined asthma and rhinoconjunctivitis scores demonstrated significant improvement. It is possible that a preferential effect of immunotherapy on one of these disease processes may have highly influenced the combined scores. Studies with multiple allergens presented a similar dilemma; response to one allergen may have determined the overall clinical score; therefore, the true effect of desensitization with each allergen remains unclear. The heterogeneity of the data on symptoms and medication use precluded pooling the data for further analysis.

The same issues of heterogeneity existed with the safety data reported in the studies; the adverse events were reported with different denominators from study to study. The lack of a consistent reporting and grading system made it impossible to pool data. In further regards to the safety data, although it may appear from this review that sublingual immunotherapy may be safer than subcutaneous immunotherapy, it should be noted that there are few studies of sublingual immunotherapy for treating patients with moderate or severe asthma, which may affect the incidence of more severe reactions. Furthermore, our study reports only the safety data from RCTs, and, therefore, is not a comprehensive review of the incidence of adverse events. A comprehensive review would require the review of observational studies and case reports.

There were also deficiencies in the statistical reporting in the included studies. Most of the studies had small sample sizes; so, relevant statistical information on continuous outcomes, such as scores, were frequently unavailable (i.e., standard deviation, standard error, or confidence intervals). Therefore, precision of the point estimates could not be assessed. As a result, we used the magnitude of effect in place of precision when grading the strength of evidence for each outcome. In the six studies that compared subcutaneous and sublingual immunotherapy head-to-head, only three reported direct statistical comparisons between the groups for the clinical outcomes of interest.

There are concerns that there may be publication bias in the specific immunotherapy literature, as positive outcomes are more likely to be published than negative outcomes. While our study did not formally assess this, publication bias is a concern in this body of literature. In an attempt to identify unpublished studies, we requested information from the relevant pharmaceutical companies, but we did not receive any requested information packets. Therefore, we did not report on any unpublished studies.

Future Research

Additional RCTs are needed to examine the efficacy, effectiveness, and safety of SIT. The RCTs should be conducted with attention to the design elements that reduce bias, such as clear concealment of allocation and masking of the intervention throughout the study, to allow for more definitive conclusions. Future studies will benefit from standardized methods to report symptoms and symptom scoring, adverse events, and dosing quantity, frequency, and formulation. Published guidelines for allergen immunotherapy clinical trials recommend that the

combined symptom-medication score be used as the primary outcome measure;[18] future studies should be encouraged to comply with these guidelines.[19-21]

There is a specific need for studies investigating the efficacy and safety of multiple allergen regimens, as multiple regimens are commonly used in the United States. There is increasing discussion in the scientific community about the clinical use and efficacy of single-allergen versus multiple-allergen therapy, and there are insufficient numbers of studies which compare these head-to-head. Future studies are needed to directly compare the effectiveness of single-allergen versus multiple-allergen regimens for desensitization. On the other hand, studies restricting immunotherapy to a single allergen will allow for a greater understanding of dose effect, dosing strategy effect, and effect of treatment duration on relevant clinical outcomes.

Studies including patients with asthma should clearly describe how patients are diagnosed with asthma. Restricting asthma severity in studies to mild, moderate, or severe would be helpful in assessing whether there is a subgroup of patients with asthma that may benefit from immunotherapy. Adequately powered trials with appropriate subgroups of patients and utilizing correct methodology are needed to address the efficacy and safety of allergen immunotherapy in specific subpopulations (e.g., pregnant women, monosensitized versus polysensitized patients, patients with severe asthma, urban vs. rural patients).

There is a need to document with future research whether immunotherapy has a disease-modifying activity. Especially in the pediatric population, there is a need to determine if immunotherapy can prevent or modify the atopic march in children at high risk for allergic rhinitis and asthma. Additional considerations for pediatric studies include identifying the optimal age for initiation of immunotherapy and evaluating the differential effects of immunotherapy based on the developmental stage of children and adolescents.

Although our review and others have found sublingual immunotherapy effective for improving symptoms of allergic rhinoconjunctivitis and asthma, there are several unanswered questions. The target maintenance dose, dosing strategies, and the necessary duration of treatment for sublingual immunotherapy with various allergens have not yet been fully determined.

Finally, there is a need for studies that directly compare sublingual to subcutaneous immunotherapy to strengthen the evidence base in children and adults. Future studies comparing subcutaneous to sublingual immunotherapy should use doses previously shown to be effective in earlier, high-quality studies, and direct statistical comparisons between the outcomes of the two groups would be useful for ensuring a fair comparison of the two therapies.

Conclusions

In summary, we found sufficient evidence to support the effectiveness and safety of subcutaneous and sublingual immunotherapy for the treatment of allergic rhinitis and asthma, particularly using single-allergen immunotherapy regimens in adults and children. Strengthening the evidence for the effectiveness and safety of multiple allergen regimens should be high priority for future studies. There are far fewer pediatric studies than adult studies; hence, the evidence is less strong for the pediatric population. Additional pediatric studies may strengthen the evidence for the effectiveness and safety of allergen immunotherapy in the pediatric population. When comparing subcutaneous with sublingual immunotherapy, the existing evidence is insufficient and inconclusive. Additional trials are needed to establish the efficacy and safety of the interventions when directly compared in the usual care settings, given the expectation of differences in adherence.

Table A. Subcutaneous immunotherapy: Summary of allergens, comparators, and main results per outcome

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Asthma Studies						
Asthma symptoms	16	1,178	Dust mite (7) *Cladosporium* (2) *Alternaria* (1) Timothy (1) Ragweed (1) Rye (1) Cat (1) Multiple (2)	SCIT vs. Placebo (12) vs. Pharmacotherapy (3) vs. No SCIT (1) vs. SCIT continuation (1) SCIT cluster vs. conventional (1)	The SCIT group showed greater improvement than the comparators in all studies.	**High** that SCIT improves asthma symptoms more than comparators
Asthma plus rhinitis/ rhinocon-junctivitis symptoms	5	175	*Parietaria* (1) *Alternaria* (1) Birch (1) Timothy (1) Cat (1)	SCIT vs. Placebo (4) vs. Pharmacotherapy (1)	The SCIT groups consistently showed greater improvement than the comparators in all studies.	**Moderate** that SCIT improves rhinoconjunctivitis symptoms more than comparators
Asthma medication scores	12	1,062	Dust mite (6) Ragweed (1) Rye (1) *Cladosporium* (1) Birch (1) Multiple (2)	SCIT vs. Placebo (8) vs. Pharmacotherapy (3) vs. No SIT (1)	9 studies showed greater reduction in medication use in the SCIT group; 5 were statistically significant (3 when compared with placebo, and 2 when compared with pharmacotherapy). 5 studies showed no significant difference between groups. 1 study did not report statistics. 4 studies did not report results from direct comparison between groups.**	**High** that SCIT improves asthma medication scores more than comparators
Asthma plus rhinitis/ rhinocon-junctivitis medication scores	5	203	*Parietaria* (1) Birch (1) Timothy (1) *Cladosporium* (1) *Alternaria* (1)	SCIT vs. Placebo (4) vs. Pharmacotherapy (1)	All studies showed a significant reduction in asthma and rhinoconjunctivitis medication consumption in the SCIT group when compared with controls.	**High** that SCIT improves asthma plus rhinitis/ rhinoconjunctivitis medication scores more than comparators

Table A. Subcutaneous immunotherapy: Summary of allergens, comparators, and main results per outcome (continued)

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Asthma Studies (continued)						
Combined asthma symptom-medication scores	6	196	Dust mite (2) *Alternaria* (2) Cat (1) *Cladosporium* (1)	SCIT vs. Placebo (5) vs. Pharmacotherapy (1) vs. SCIT (1)–placebo controlled	All placebo controlled studies demonstrated significant improvement in the SCIT group. The other study showed no significant difference.	**Low** that SCIT improves combined asthma symptom and medication scores more than comparators
Rhinitis/Rhinoconjuctivitis Studies						
Rhinitis/ rhinocon-junctivitis symptoms	26	1,764	Dust mite (4) Timothy (4) Ragweed (3) *Parietaria* (2) Grass mix (2) *Alternaria* (2) Tree (2) *Cladosporium* (1) Cat (1) Multiple (5)	SCIT vs. Placebo (23) vs. Pharmacotherapy (2) vs. SCIT (4)	23 studies showed greater improvement in symptoms favoring the SCIT group; 19 were statistically significant (18 when compared with placebo, and 1 when compared with pharmacotherapy). 7 studies showed no statistically significant difference.	**High** that SCIT improves rhinitis/ rhinoconjunctivitis symptoms more than comparators
Conjunctivitis symptoms	14	1,104	Timothy (4) Grass mix (2) *Parietaria* (1) *Cladosporium* (1) *Alternaria* (2) Cat (1) Multiple (3)	SCIT vs. Placebo (11) vs. SCIT (2)–both placebo controlled vs. Pharmacotherapy (1)	13 studies showed greater improvement in symptoms favoring the SCIT group; 6 were statistically significant. 8 studies showed no statistically significant difference.	**High** that SCIT improves conjunctivitis symptoms more than comparators

Table A. Subcutaneous immunotherapy: Summary of allergens, comparators, and main results per outcome (continued)

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Rhinitis/Rhinoconjuctivitis Studies (continued)						
Combined symptom score (bronchial, nasal, ocular; rhinitis studies only)	6	591	Grass mix (2) *Alternaria* (1) Timothy (1) Mountain cedar (1) Dust mite (1)	SCIT vs. Placebo (6) vs. SIT (1)	5 studies showed greater improvement in symptoms in the SCIT group than in the comparator group. 1 study showed improvement in the SCIT arm only when comparing pretreatment with post-treatment scores.**	**High** that SCIT improves combined symptom scores more than comparators
Rhinitis/rhino-conjunctivitis medication scores	10	564	Dust mite (2) Timothy (2) Ragweed (1) *Parietaria* (1) Grass mix (2) Tree (1) Multiple (1)	SCIT vs. Placebo (8) vs. SCIT (3)–all were placebo controlled vs. pharmacotherapy (1)	All studies showed greater reduction in medication consumption in the SCIT arm; 7 of the studies were statistically significant (6 when compared with placebo, and 1 when compared with pharmacotherapy).	**Moderate** that SCIT improves rhinitis/ rhinoconjunctivitis medication scores more than comparators
Rhinitis/rhinocon-junctivitis plus asthma medication scores (rhinitis studies only)	11	768	*Parietaria* (3) Timothy (2) Grass mix (2) Ragweed (1) *Alternaria* (1) Dust mite (1) Multiple (1)	SCIT vs. Placebo (11) vs. SCIT (1)–placebo controlled	9 studies showed significant reduction in asthma and rhinoconjunctivitis medication consumption in the SCIT group. 2 studies showed no difference.	**High** that SCIT improves rhinitis/ rhinoconjunctivitis plus asthma medication scores more than comparators
Combined rhinitis symptom-medication score	6	400	Grass mix (1) Ragweed (1) *Alternaria* (2) Date tree (1) Grass (1)	SCIT vs. Placebo (5) vs. SCIT (2), (1 conventional, 1 crude)	4 studies demonstrated significant improvement in the SCIT group. 2 studies showed no difference.	**Low** that SCIT improves combined rhinitis medication scores more than comparators

Table A. Subcutaneous immunotherapy: Summary of allergens, comparators, and main results per outcome (continued)

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Rhinitis/Rhinoconjuctivitis Studies (continued)						
Disease-specific quality of life	6	889	*Alternaria* (2) *Parietaria* (1) Timothy (1) Grass mix (1) Multiple (1)	SCIT vs. Placebo (4) vs. Pharmacotherapy (1) vs. SCIT (1)–placebo controlled	All studies showed greater improvement in quality of life favoring the SCIT group. 4 studies reported statistically significant improvement in disease-specific quality of life when compared with placebo. The other 2 studies found no improvement.	**High** that SCIT improves disease-specific quality of life more than comparators
Secondary Outcomes						
Pulmonary function test results	13	1,024	Dust mite (6) Cat (2) Birch (2) Ragweed (1) *Cladosporium* (1) Multiple (1)	SCIT vs. Placebo (9) vs. Pharmacotherapy (2) vs. No SCIT (1) SCIT cluster vs. conventional (1)	There were variable and inconsistent findings.	Not graded
Specific allergen bronchial reactivitiy	17	514	Dust mite (9) Cat (3) Ragweed (1) Birch (1) *Cladosporium* (1) Dog (1) Multiple (1)	SCIT vs. Placebo (15) vs. Pharmacotherapy (2)	11 studies demonstrated significant decreases in bronchial reactivity favoring the SCIT group over the comparison group. 6 studies showed no difference.	Not graded

Table A. Subcutaneous immunotherapy: Summary of allergens, comparators, and main results per outcome (continued)

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Secondary Outcomes (continued)						
Nonspecific bronchial reactivity	16	750	Dust mite (7) Cat (3) Multiple (2) Birch (2) Timothy (1) *Alternaria* (1)	SCIT vs. Placebo (10) vs. Pharmacotherapy (5) vs. Conventional (1)	Two studies demonstrated significant decreases in bronchial reactivity favoring the SCIT group over the comparison group.	Not graded

SCIT = subcutaneous immunotherapy; SIT = allergen-specific immunotherapy

*****This column presents a summary of the relevant findings. Numbers in this column may not match the total numbers of studies included per outcome; for some outcomes, studies reported more than one comparison per outcome (e.g., different dosage groups).

**Results from pre-post comparisons did not contribute to the evidence grades, as their design was not as strong as head-to-head comparisons. We included these results in the tables for informational purposes only.

Table B. Subcutaneous immunotherapy: Summary of safety per location of adverse events

Reaction	Allergen (Number of Studies)	Number of Patients in Studies Reporting Adverse Events	Number of Patients With Adverse Events	Range of Adverse Events	Severity
Local reactions (reported as patients): 16 studies	Dust mite (4) *Alternaria* (2) *Cladosporium* (2) Grass mix (2) Ragweed (2) Cat (2) Timothy (1) Tree mix (1) 1 study reported AEs in the control arm.	SCIT arm: 854 patients	SCIT arm: 290 patients presenting with AEs	SCIT arm: Range 5% to 58%	Unspecified (19%) Mild (77%) Moderate (3%) Severe (1%)
		Control arm: 7 patients (in 1 study)	Control arm:1 patient presenting with AEs	Control arm: 14%	Unspecified (100%)
Local reactions (reported as events): 11 studies	Dust mite (2) Cat (2) Dog (1) Grass mix (1) Timothy (1) Ragweed (1) *Parietaria* (1) *Alternaria* (1) Multiple (1) 5 studies reported AEs in the control arm.	SCIT arm: 235 patients–3,717 injections	SCIT arm: 438 reactions reported	SCIT arm: Range 0.6% to 54%	Unspecified (29%) Mild (68%) Moderate (3%)
		Control arm: 86 patients–462 injections (in 3 studies)	Control arm: 16 reactions reported	Control arm: Range 2.1% to 3%	Unspecified (75%) Mild (25%)
		410 patients in 1 study that reported harms for the whole study; 133 patients in 3 studies that did not report number of injections SCIT arm: 64 Control arm: 59	2 studies reported 593 reactions 2 studies reported events by time of presentation	Percentage or range not quantifiable	Moderate (59%) Unspecified (41%)

Table B. Subcutaneous immunotherapy: Summary of safety per location of adverse events (continued)

Reaction	Allergen (Number of Studies)	Number of Patients in Studies Reporting Adverse Events	Number of Patients With Adverse Events	Range of Adverse Events	Severity
Cutaneous reactions (reported as patients): 10 studies	Timothy (3) Dust mite (2) *Cladosporium* (1) *Alternaria* (1) *Parietaria* (1) Cat (1) Multiple (1) 2 studies reported AEs in the control arm.	SCIT arm: 556 patients	SCIT arm: 47 patients presenting with AEs	SCIT arm: Range 2% to 25%	Unspecified (66%) Mild (11%) Moderate (23%)
		Control arm: 48 patients (in 2 studies)	Control arm: 13 patients presenting with AEs	Control arm: Range 16% to 33%	Unspecified (23%) Mild (77%)
Respiratory reactions (reported as patients): 15 studies	Dust mite (6) Timothy (3) *Alternaria* (1) *Parietaria* (1) Multiple (2) 6 studies reported AEs in the control arm. 2 studies reported AEs ONLY in the control arm.	SCIT arm: 834 patients	SCIT arm: 180 patients presenting with AEs	SCIT arm: Range 1% to 46%	Unspecified (71%) Mild (19%) Moderate (3%) Severe (7%)
		Control arm: 208 patients (in 6 studies)	Control arm: 44 patients presenting with AEs	Control arm: Range 1% to 31%	Unspecified (91%) Mild (9%)
Respiratory reactions (reported as events): 5 studies	Dust mite (1) Birch (1) *Cladosporium* (1) *Alternaria* (1) Cat (1) 4 studies reported AEs in the control arm.	SCIT arm: 54 patients–1,271 injections	SCIT arm: 58 reactions reported	SCIT arm: Range 0.3% to 2.9%	Mild (95%) Moderate (5%)
		Control arm: 26 patients–1,271 injections (in 6 studies)	Control arm: 32 reactions reported	Control arm: Range 0.2% to 2.45%	Mild (16%) Moderate (84%)
		85 patients in 2 studies did not report number of injections. SCIT arm: 45 Control arm: 40	188 reactions reported in these 2 studies SCIT arm: 91 Control arm: 97	Percentage not quantifiable	Mild (83%) Moderate (17%)

Table B. Subcutaneous immunotherapy: Summary of safety per location of adverse events (continued)

Reaction	Allergen (Number of Studies)	Number of Patients in Studies Reporting Adverse Events	Number of Patients With Adverse Events	Range of Adverse Events	Severity
GI reactions (reported as patients): 1 study	Timothy (1) No studies reported AEs in the control arm.	SCIT arm: 20 patients	SCIT arm: 1 patient presenting with AEs	5%	Mild (100%)
General symptoms (reported as patients): 14 studies	Timothy (5) Ragweed (2) Dust mite (2) Grass mix (2) Cat (1) *Cladosporium* (1) *Parietaria* (1) 7 studies reported AEs in the control arm.	SCIT arm: 624 patients	SCIT arm: 190 patients presenting with AEs	SCIT arm: Range 3.5% to 44%	Unspecified (74%) Mild (12%) Moderate (10%) Severe (4%)
		Control arm: 217 patients (in 6 studies)	Control arm: 52 patients presenting with AEs	Control arm: Range 3.5% to 35%	Unspecified (83%) Mild (5%) Moderate (10%) Severe (2%)
General symptoms (reported as events): 2 studies	Birch (1) Grass mix (1) 1 study reported AEs in the control arm.	SCIT arm: 48 patients	SCIT arm: 78 reactions reported	Percentage or range not quantifiable	Mild (100%)
		Control arm: 22 patients (in 1 study)	Control arm: 81 reactions reported	Percentage or range not quantifiable	Mild (100%)

Table B. Subcutaneous immunotherapy: Summary of safety per location of adverse events (continued)

Reaction	Allergen (Number of Studies)	Number of Patients in Studies Reporting Adverse Events	Number of Patients With Adverse Events	Range of Adverse Events	Severity
Unspecified reactions (reported as patients): 10 studies	Ragweed (3) Dust mite (2) Timothy (2) Cat (1) Grass mix (1) 2 studies reported AEs in the control arm. 1 study reported AEs ONLY in the control arm.	SCIT arm: 373 patients	SCIT arm: 79 patients presenting with AEs	SCIT arm: Range 2% to 53%	Unspecified (36%) Mild (24%) Moderate (32%) Severe (8%)
		Control arm: 103 patients (in 1 study)	Control arm: 12 patients presenting with AEs	Control arm: Range 10% to 17%	Unspecified (50%) Moderate (34%) Severe (16%)
Unspecified reactions (reported as events): 3 studies	*Cladosporium* (1) Cat (1) Multiple (1) No studies reported AEs in the control arm.	59 patients in 3 studies that did not report number of injections	64 reactions reported	0.3 to 2.8 events per patient	Unspecified (100%)
Anaphylactic reactions: 4 studies	Dust mite (2) Timothy (1) *Cladosporium* (1) No studies reported AEs in the control arm.	SCIT arm: 205 patients	SCIT arm: 13 reactions reported	SCIT arm: Range 0.7% to 26%	Severe (100%)

AE = adverse event; GI = gastrointestinal; SCIT = subcutaneous immunotherapy

Table C. Subcutaneous immunotherapy: Summary of allergens, comparators, and main results per outcome in the pediatric population

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Asthma Studies						
Asthma symptoms	6	550	Dust mite (1) *Cladosporium* (1) Rye (1) *Alternaria* (1) Multiple (2)	SCIT vs. Placebo (4) vs. Pharmacotherapy (2)	The SCIT group showed greater improvement than the comparison group in all studies.	**Moderate** that SCIT improves asthma symptoms more than comparators
Asthma medication scores	4	470	Dust mite (1) Rye (1) Multiple (2)	SCIT vs. Placebo (2) vs. Pharmacotherapy (2)	2 studies showed significant reduction in medication consumption in the SCIT arm when compared with pharmacotherapy. 1 study did not find significant differences. 1 study did not report results from direct comparison between groups.**	**Low** that SCIT improves asthma medication scores more than comparators
Asthma plus rhinitis/rhino-conjunctivitis medication scores	2	80	*Cladosporium* (1) *Alternaria* (1)	SCIT vs. Placebo (2)	Both studies showed significant reduction in asthma and rhinoconjunctivitis medication consumption in the SCIT group.	**Low** that SCIT improves asthma plus rhinitis/ rhinoconjunctivitis medication scores more than comparators

Table C. Subcutaneous immunotherapy: Summary of allergens, comparators, and main results per outcome in the pediatric population (continued)

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Asthma Studies (continued)						
Asthma or asthma plus rhinoconjunctivitis combined symptom-medication scores	2	85	Dust mite (1) *Alternaria* (1)	SCIT vs. Placebo (1) vs. SCIT (1)–placebo placebo controlled	Both studies showed significant improvement in the SCIT group, when compared with placebo.	**Low** that SCIT improves asthma or asthma plus rhinoconjunctivitis combined symptom-medication scores more than comparators
Rhinitis/Rhinoconjunctivitis Studies						
Rhinitis/ rhinoconjunctivitis symptoms	3	285	*Alternaria* (1) *Cladosporium* (1) Birch (1)	SCIT vs. Placebo (3)	All studies showed greater improvement in symptoms in the SCIT group.	**Moderate** that SCIT improves rhinitis/ rhinoconjunctivitis symptoms more than comparators
Conjunctivitis symptoms	3	285	*Alternaria* (1) *Cladosporium* (1) Birch (1)	SCIT vs. Placebo (3)	All studies showed greater improvement in symptoms in the SCIT group compared with placebo.	**Low**
Disease-specific quality of life	2	350	*Alternaria* (2) Multiple (1)	SCIT vs. Placebo (1) vs. Pharmacotherapy (1)	Both studies reported significant improvement in disease-specific quality of life in the SCIT arm.	**Low**

SCIT = subcutaneous immunotherapy

*****This column presents a summary of the relevant findings. Numbers in this column may not match the total numbers of studies included per outcome; for some outcomes, studies reported more than one comparison per outcome (e.g. different dosage groups).

**Results from pre- post comparisons did not contribute to the evidence grades, as their design was not as strong as head-to-head comparisons. We included these results in the tables for informational purposes only.

Table D. Sublingual Immunotherapy: Summary of allergens, comparators, and main results per outcome

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Symptom Scores						
Asthma symptoms	13	625	Dust mite (7) *Alternaria* (2) Grass mix (1) Tree mix (1) Birch (1) *Parietaria* (1)	SLIT vs. Placebo (12) vs. Inhaled steroids (1) vs. SLIT (1) (placebo controlled)	All placebo controlled studies demonstrated significant improvement in the SLIT group. The remaining study showed improvement in both arms.	**High** that SLIT improves asthma symptoms more than comparators
Rhinitis or rhino-conjunctivitis symptoms	35	2,658	Grass mix (10) Dust mite (8) *Parietaria* (3) Cedar (3) Timothy (2) Ragweed (2) Birch (2) Olive (1) Cat (1) Tree mix (1) Multiple (2)	SLIT vs. Placebo (32) vs. Pharmacotherapy (2) vs. SLIT (2) (placebo controlled)	All studies showed greater improvement in symptoms in the SLIT group when compared with placebo.	**Moderate** that SLIT improves rhinitis or rhinoconjunctivitis symptoms more than comparators
Asthma plus rhinitis or rhino-conjunctivitis symptoms	5	308	*Alternaria* (1) Birch (1) Tree mix (1) Dust mite (1) Multiple (1)	SLIT vs. Placebo (4) vs. SLIT (3) (2 placebo controlled, 1 pharmacotherapy controlled)	4 studies demonstrated significant improvement in the SLIT group. 1 study found no improvement in symptoms (placebo controlled).	**Moderate** that SLIT improves asthma plus rhinitis or rhinoconjunctivitis symptoms more than comparators

Table D. Sublingual Immunotherapy: Summary of allergens, comparators, and main results per outcome (continued)

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Symptom Scores (continued)						
Conjunctivitis symptoms	13	1,074	Grass mix (3) Dust mite (2) Timothy (1) Ragweed (1) *Parietaria* (2) Cedar (1) Olive (1) Multiple (2)	SLIT vs. Placebo (12) vs. SLIT (1) (placebo controlled)	11 studies showed greater improvement in symptoms in the SLIT group when compared with placebo. 2 studies showed no significant results.	**Moderate** that SLIT improves conjunctivitis symptoms more than comparators
Medication Scores						
Medication use	38	2,724	Grass mix (9) Dust mite (8) *Parietaria* (4) Cedar (3) Timothy (2) Ragweed(2) Birch (2) *Alternaria* (2) Tree mix (2) Olive (1) Multiple (3)	SLIT vs. Placebo (33) vs. Pharmacotherapy (2) vs. SLIT (5) (placebo controlled)	17 studies showed reduction in medication consumption in the SLIT group when compared with placebo (11 were statistically significant). 4 studies showed a significant reduction in medication consumption in the SLIT group when compared with pharmacotherapy. 12 studies did not show any benefit. 5 studies showed improvement in the SLIT arm only when comparing initial with final scores.**	**Moderate** that SLIT improves medication use more than comparators
Combined Symptom and Medication Scores						
Combined medication plus symptoms scores	19	1,462	Cedar (5) *Parietaria* (3) Grass mix (3) Dust mite (1) *Alternaria* (1) Ragweed (1) Multiple (5)	SLIT vs. Placebo (12) vs. Pharmacotherapy (2) vs. Nothing (2) vs. SLIT (3) (1 placebo controlled, 1 pharmacotherapy controlled, 1 no SLIT controlled)	10 studies showed greater improvement in the SLIT group than in the comparator group. 5 studies did not find a significant difference between comparators. 4 studies showed improvement in the SLIT arm only when comparing initial with final scores.**	**Moderate** that SLIT improves combined medication plus symptoms scores more than comparators

Table D. Sublingual Immunotherapy: Summary of allergens, comparators, and main results per outcome (continued)

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Combined Symptom and Medication Scores (continued)						
Disease-specific quality of life	8	819	Cedar (4) Dust mite (2) Grass mix (1) Multiple (1)	SLIT vs. Placebo (8)	4 studies reported significant improvement in disease-specific quality of life when compared with placebo. 2 studies showed no difference. 2 studies reported significant improvement in the SLIT group when comparing initial with final quality of life scores.**	**Moderate** that SLIT improves disease-specific quality of life more than comparators
Other Outcomes						
Pulmonary function testing	14	1,375	Dust mite (4) Multiple (5)	SLIT vs. Placebo (14)	SLIT consistently improves measure of pulmonary function in the allergic asthmatic population.	**Not graded**
Allergen challenges	10				SLIT consistently improves response to challenges in the allergic population.	**Not graded**

SLIT = sublingual immunotherapy

*****This column presents a summary of the relevant findings. Numbers in this column may not match the total numbers of studies included per outcome; for some outcomes, studies reported more than one comparison per outcome (e.g. different dosage groups).

**Results from pre- post comparisons did not contribute to the evidence grades, as their design was not as strong as head-to-head comparisons. We included these results in the tables for informational purposes only.

Table E. Sublingual Immunotherapy: Summary of safety per location of adverse events

Reaction	Allergen (Number of Studies)	Number of Patients in Studies Reporting Adverse Events	Number of Patients With Adverse Events	Range of Adverse Events	Severity
Local reactions (reported as patients) 37 studies	Grass mix (10) Dust mite (9) Tree (8) Multiple (5) *Parietaria* (2) *Alternaria* (1) Ragweed (1) Cat (1) 23 studies reported AEs in the control (placebo) arm.	SLIT arms: 2,342	SLIT arms: 560	Range: 0.2% to 97%	Unspecified (35%) Mild (65%)
		Placebo arms: 884 (in 23 studies)	Placebo arms: 142	Range: 3% to 38.5%	Unspecified (23%) Mild (77%)
Local reactions (reported as events or percentage) 2 studies	Timothy (1) Grass mix (1)	56 patients in 1 study did not report number of injections SLIT: 28, Control: 28 80 patients in 1 study did not report number of events SLIT: 80 (SLIT vs. SLIT)	380 reactions reported in this study in the SLIT arm Number of reactions not reported	4.75 events per patient Total percent of adverse events for both arms: 6%	Mild (100%) Unspecified (100%)
Upper respiratory reactions (reported as patients) 18 studies	Grass mix (6) Dust mite (5) Trees (3) *Parietaria* (1) Multiple (1) 12 studies reported AEs in the control (placebo) arm; 2 studies had AEs ONLY in the placebo arm.	SLIT arms: 1,023	SLIT arms: 340	SLIT arms: 3% to 92%	Unspecified (74%) Mild (24%) Severe (2%)
		Placebo arms: 513 (in 12 studies)	Placebo arms: 223	Placebo arms: 1.6% to 93%	Unspecified (95%) Mild (4.9%) Moderate (0.1%)

Table E. Sublingual Immunotherapy: Summary of safety per location of adverse events (continued)

Reaction	Allergen (Number of Studies)	Number of Patients in Studies Reporting Adverse Events	Number of Patients With Adverse Events	Range of Adverse Events	Severity
Lower respiratory reactions (reported as events) 14 studies	Dust mite (4) Grass mix (5) Trees (1) Cat (1) Multiple (2) 9 studies reported AEs in the control (placebo) arm; 2 studies had AEs ONLY in the placebo arm.	SLIT arms: 1,071	SLIT arms: 159	Range: 0.3% to 69%	Unspecified (91%) Mild (6%) Moderate (1%) Severe (2%)
		Placebo arms: 473 (in 9 studies)	Placebo arms: 139	Range: 3% to 67%	Unspecified (94%) Mild (4%) Moderate (1%) Severe (1%)
Cutaneous reactions (reported as patients) 13 studies	Grass mix (4) Dust mite (3) Trees (2) Multiple (3) 7 studies reported AEs in the control (placebo) arm; 1 study had AEs ONLY in the placebo arm.	SLIT arms: 1,158	SLIT arms: 142	Range: 0.7% to 57%	Unspecified (94%) Mild (6%)
		Placebo arms: 476 (in 6 studies)	Placebo arms: 132	Range: 2% to 65%	Unspecified (98%) Mild (2%)
GI reactions (reported as patients) 19 studies	Grass mix (7) Dust mite (5) Trees (2) *Parietaria* (1) Ragweed (1) Multiple (3) 9 studies reported AEs in the control (placebo) arm.	SLIT arms: 1,611	SLIT arms: 342	Range: 0.3% to 74%	Unspecified (91%) Mild (9%)
		Placebo arms: 651 (in 9 studies)	Placebo arms: 244	Range: 3% to 73%	Unspecified (100%)
		1 study with 60 patients did not report number of doses or number of events.		Percentage or range not quantifiable	Unspecified (100%)

Table E. Sublingual Immunotherapy: Summary of safety per location of adverse events (continued)

Reaction	Allergen (Number of Studies)	Number of Patients in Studies Reporting Adverse Events	Number of Patients With Adverse Events	Range of Adverse Events	Severity
Cardiovascular reactions (reported as patients) 2 studies	Grass mix (1) Cypress (1) 1 study reported AEs in the control (placebo) arm.	SLIT arms: 65	SLIT arms: 2	Range: 2% to 4%	Mild (100%)
		Placebo arms: 30 (in 1 study)	Placebo arms: 1	Range: 2% to 4%	Mild (100%)
Ocular reactions (reported as patients) 11 studies	Grass mix (3) Dust mite (3) Trees (2) *Parietaria* (1) Multiple (1) 7 studies reported AEs in the control (placebo) arm; 1 study had AEs ONLY in the placebo arm.	SLIT arms: 710	SLIT arms: 279	Range: 1.5% to 73.4%	Unspecified (97%) Mild (1%) Severe (2%)
		Placebo arms: 518 (in 7 studies)	Placebo arms: 258	Range: 3% to 65%	Unspecified (99%) Mild (1%)
General symptoms (reported as patients) 17 studies	Grass mix (5) Dust mite (6) *Parietaria* (1) Trees (1) Timothy (1) Multiple (2) 10 studies reported AEs in the control (placebo) arm; 1 study had AEs ONLY in the placebo arm.	SLIT arms: 763	SLIT arms: 149	Range: 1% to 60%	Unspecified (74%) Mild (22%) Moderate (4%)
		Placebo arms: 435 (in 10 studies)	Placebo arms: 21	Range: 6% to 67%	Unspecified (86%) Mild (13%) Moderate (1%)
		2 studies with 116 patients did not report number of doses or number of events.		Percentage not quantifiable	Moderate (50%) Unspecified (50%)
Anaphylactic reactions	No studies reported anaphylactic reactions.				

AE = adverse event; GI = gastrointestinal; SLIT = sublingual immunotherapy

Table F. Sublingual Immunotherapy: Summary of allergens, comparators, and main results per outcome in the pediatric population

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Symptom Scores						
Asthma symptoms	9	471	Dust mite (7) Tree mix (1) *Parietaria* (1)	SLIT vs. Placebo (9) vs. SLIT (1) (placebo controlled)	All studies demonstrated significant improvement in the SLIT group.	**High** that SLIT improves asthma symptoms more than comparators
Rhinitis or rhino-conjunctivitis symptoms	12	1,065	Grass mix (2) Dust mite (6) *Parietaria* (2) Olive (1) Tree mix (1)	SLIT vs. Placebo (10) vs. Control (1) vs. SLIT (1) (placebo controlled)	5 studies showed greater improvement in symptoms in the SLIT group when compared with placebo. 3 studies showed no significant results. 4 studies did not report results from direct comparison between groups, but 3 studies showed improvement in the SLIT arm only when comparing initial to final scores.**	**Moderate** that SLIT improves rhinitis or rhinoconjunctivitis symptoms more than comparators
Asthma plus rhinitis or rhino-conjunctivitis symptoms	1	98	Tree mix (1)	SLIT vs. SLIT (1) (placebo controlled)	This study demonstrated significant improvement in the SLIT group.	**Moderate** that SLIT improves asthma plus rhinitis or rhinoconjunctivitis symptoms more than comparators
Conjunctivitis symptoms	5	513	Dust mite (2) Olive (1) Tree mix (1) *Parietaria* (1)	SLIT vs. Placebo (4) vs. SLIT (1) (placebo controlled)	2 studies showed greater improvement in symptoms in the SLIT group when compared with placebo. 3 studies showed no significant results.	**Moderate** that SLIT improves conjunctivitis symptoms more than comparators

Table F. Sublingual Immunotherapy: Summary of allergens, comparators, and main results per outcome in the pediatric population (continued)

Outcome	Number of Studies	Number of Participants	Allergen (Number of Studies)	Comparator (Number of Studies)	Findings*	Strength of Evidence
Medication Scores						
Medication use	13	1,078	Dust mite (6) Grass mix (2) *Parietaria* (2) Olive (1) Tree mix (1) Multiple (1)	SLIT vs. Placebo (12) vs. Control (1) vs. SLIT (1) (placebo controlled)	9 studies showed significant reduction in medication consumption in the SLIT group. 4 studies did not show any benefit.	**Moderate** that SLIT improves medication use more than comparators
Combined Symptom and Medication Scores						
Combined medication plus symptoms	2	329	Grass mix (1) Dust mite (1)	SLIT vs. Control (2)	1 study showed greater improvement in the SLIT group than in the comparator. 1 study showed no difference.	**Low** that SLIT improves combined medication plus symptoms scores more than comparators
Other Outcomes						
Disease-specific quality of life	2	461	Dust mite (1) Grass mix (1)	SLIT vs. Placebo (8)	1 study showed no improvement in disease-specific quality of life. 1 study showed no difference.	**Insufficient** that SLIT improves disease-specific quality of life more than comparators

SLIT = sublingual immunotherapy

*****This column presents a summary of the relevant findings. Numbers in this column may not match the total numbers of studies included per outcome; for some outcomes, studies reported more than one comparison per outcome (e.g. different dosage groups).

**Results from pre- post comparisons did not contribute to the strength of evidence grades, as their design was not as strong as head-to-head comparisons. We included these results in the tables for informational purposes only.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
FDA	Food and Drug Administration
KQ	Key Question
RCT	Randomized controlled trial
SIT	Allergen-specific immunotherapy
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy

Introduction

The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program requested a comparative effectiveness review of "Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma." The topic was selected through the Effective Health Care Program nomination process.

Background

Allergic rhinitis is a common clinical problem affecting as many as 20 to 40 percent of the general population in North America.[1-5] Allergens such as tree, grass, and weed pollens characteristically cause seasonal rhinoconjunctivitis and/or asthma, whereas cat dander, cockroach, or dust mite allergens may induce symptoms year-round and are associated with perennial rhinitis and/or asthma. The prevalence of asthma in the general U.S. population is approximately 9 percent, and approximately 62 percent of individuals with asthma have evidence of atopy (i.e., one or more positive specific IgE).[6,7]

The medical management of patients with allergic rhinitis and asthma includes allergen avoidance, pharmacotherapy, and immunotherapy.[4,5,8] Pharmacotherapies for allergic rhinitis symptoms include topical nasal corticosteroid or cromolyn preparations and/or antihistamines and decongestants. These must be used daily to provide effective control, raising critical issues related to long-term compliance, safety, and cost. Similarly, the long-term use of inhaled steroids for asthma control poses risks, especially if used together with nasal steroids to control seasonal or perennial respiratory conditions. Furthermore, long-acting bronchodilators have the potential to cause cardiovascular complications including arrhythmias and sudden death, and leukotriene antagonists have been associated with neuropsychiatric disturbances.[9-11]

Allergen specific immunotherapy (SIT) is typically recommended for patients whose allergic rhinoconjunctivitis and asthma symptoms cannot be controlled by environmental control and pharmacotherapy, those who cannot tolerate their medications, or those who do not comply with chronic medication regimens.[12,13] Over the years, allergen specific immunotherapy has proven to be safe.[14-16] The U.S. Food and Drug Administration (FDA) approved the use of subcutaneous allergen extracts (subcutaneous immunotherapy) for the treatment of seasonal and perennial allergic rhinitis, allergic asthma, and venom sensitivity. The same aqueous materials can also be administered orally (sublingual immunotherapy), although this not an approved use of these materials in the United States and such use would be considered off-label. An increasing number of U.S. physicians are attempting to employ this alternate desensitization approach in the treatment of allergic respiratory conditions based on European and U.S. studies and the European Medicines Agency approval of certain oral products; however due to differing standardization of potency in the Europe and United States, doses have been extremely hard to translate between countries.

Subcutaneous immunotherapy, as a treatment for allergic diseases, was first introduced by Noon and Freeman in 1911 as a means of treating grass-induced allergic symptomatology.[17] In the United States, a patient with allergies receives increasing doses of an allergen-containing extract, comprised of the relevant allergens to which the patient is sensitive, to suppress or eliminate allergic symptomatology. With continued administration, it is expected that the treatment regimen will make the patient tolerant to the offending allergen and suppress future untoward responses to the allergen(s) through modulation of the patient's immune system.[18-21]

Chemical modifications of allergens have been attempted to enhance efficacy, improve safety, and foster compliance with immunotherapy. Many of these approaches have been unsuccessful as the allergenicity (potential to cause an untoward allergic reaction) and immunogenicity (potential to induce a beneficial clinical effect) have changed in parallel, with little change in the risk-benefit ratio. However, recent approaches with modified and recombinant allergens, immunostimulatory adjuvants, T-cell tolerizing constructs, and improved oral approaches have shown promise for treatment of allergic respiratory disease.[21-25]

Oral immunotherapy was first proposed as a treatment for allergic disease in the early 1900s. In 1996, a task force assembled by the World Allergy Organization on Immunotherapy cited the emerging clinical data on oral immunotherapy and its potential as a viable alternative to subcutaneous therapy; this encouraged continued clinical investigation to characterize optimal techniques.[26] In this context, oral immunotherapy has been administered as an oral aqueous immunotherapy where the allergen is mixed with a diluent and swallowed; as an oral-sublingual immunotherapy where the allergen is placed under the tongue as an aqueous solution or as a dissolvable tablet for local absorption; and as an oral-encapsulated immunotherapy where the allergen is placed in a liposome, or polymer, or microencapsulated carrier and swallowed with pH-dependent release of the allergen to the gut lymphoid tissue.

Interest has also increased considerably related to using sublingual immunotherapy as an alternative to subcutaneous therapy 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 for allergy shots), and possibly shorter time to achieve effect.[27,28] Over the past decade, sublingual forms of immunotherapy have gained favor in Europe; sublingual tablet immunotherapy has been approved by the European regulatory authorities but is not available in the United States

Rationale for Comparative Effectiveness Review

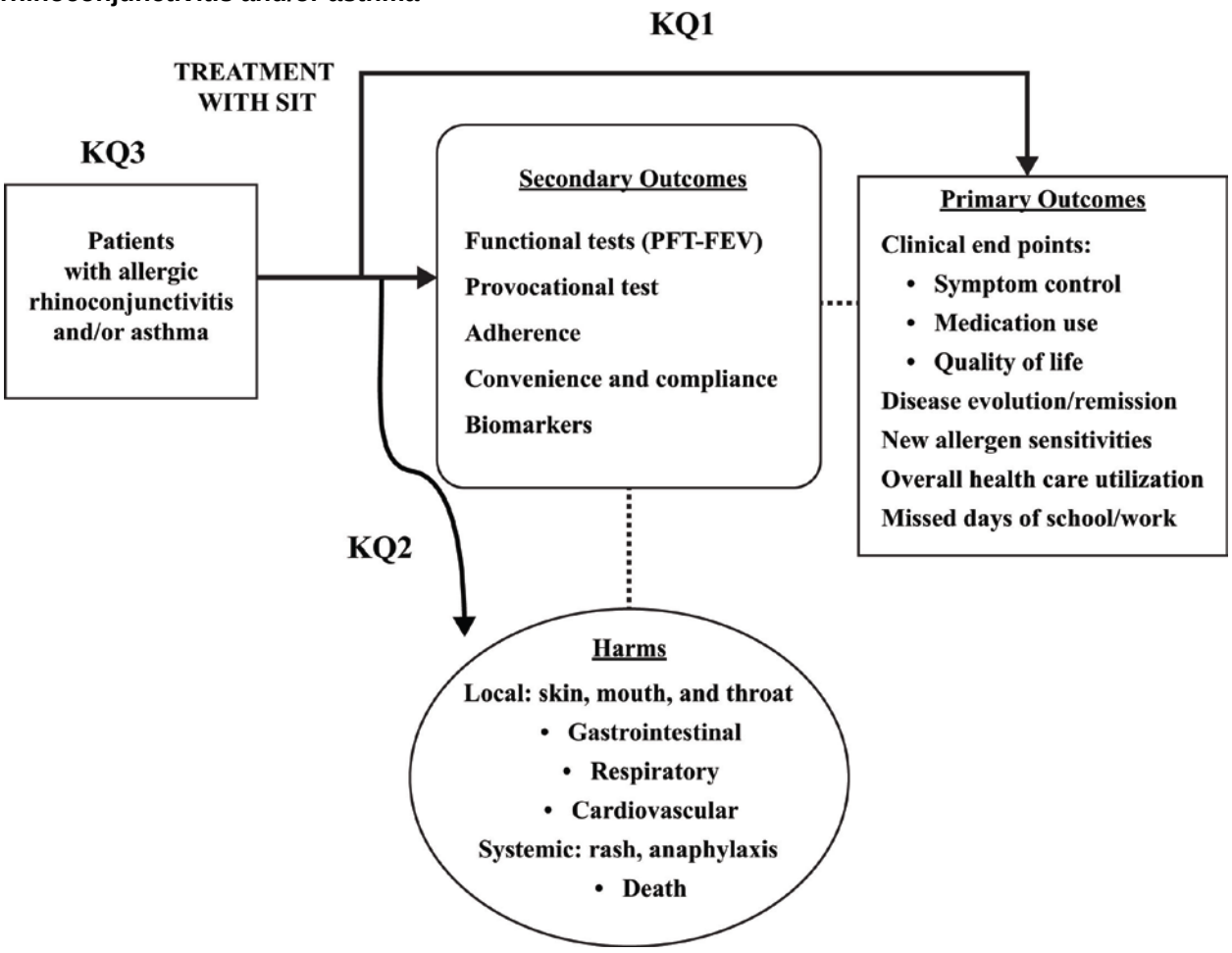
Although subcutaneous immunotherapy is used worldwide and sublingual immunotherapies are used broadly in Europe, Latin America, and Asia, sublingual immunotherapy has not been approved by the FDA for use in the United States. Based on U.S. manufacturer package inserts, allergen extracts are sold for skin testing and for preparation of immunotherapy solutions for parenteral administration. Thus, use of these allergenic extracts as sublingual treatment agents is "off-label" in the United States and third-party payers have generally not paid for sublingual immunotherapy. In addition, there is no standardized information on how to prepare an oral extract with licensed allergenic extracts or information on the effective dose. No sublingual allergen tablets are sold in the United States. This comparative effectiveness review addresses the comparative efficacy, effectiveness, and safety of the subcutaneous therapies, presently available for use by clinicians and patients in the United States, as well as the "off-label use" for possible sublingual applications.

Conceptual Model

Our conceptual model for the systematic review is presented in Figure 1. This figure depicts the Key Questions (KQs) addressed in this review. The figure illustrates how SIT administered to patients with respiratory allergies may result in intermediate outcomes including changes in immunologic parameters and long-term outcomes such as improvement of symptoms and quality of life and reduction of health care costs. However, adverse events may occur at any point after treatment is administered. We approached the synthesis of this body of literature by addressing

the KQs described below, separately, for the studies evaluating sublingual immunotherapy, for the studies evaluating subcutaneous immunotherapy, and for the studies that compared sublingual immunotherapy with subcutaneous immunotherapy.

Figure 1. Analytic framework for allergen-specific immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma



KQ = Key Question; PFT-FEV = pulmonary function test- forced expiratory volume; SIT = allergen-specific immunotherapy

The analytic framework (Figure 1) depicts the impact of treatment for allergic rhinitis and/or asthma. It depicts the KQs within the context of the inclusion criteria described in the following sections. The framework represents how allergen-specific immunotherapy in these specific populations (KQ3) may improve clinical outcomes (KQ1) and/or be reflected in changes in functional tests or chemical biomarkers. Finally, the potential for harms (KQ2) of specific immunotherapy are illustrated in the framework.

Key Questions

This review includes our evaluation of the efficacy, effectiveness, and safety of both sublingual immunotherapy, subcutaneous immunotherapy and the comparison of both. The KQs to be explored are as follows:

Key Question 1. What is the evidence for the efficacy and effectiveness of SIT in the treatment of allergic rhinoconjunctivitis and/or asthma?

Key Question 2. What is the evidence for safety of SIT in patients with allergic rhinoconjunctivitis and/or asthma?

Key Question 3. Is the safety and effectiveness of SIT different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma? Specifically:

- Children
- Adults
- The elderly
- Pregnant women
- Minorities
- Inner-city and rural residents
- Monosensitized individuals
- Patients with severe asthma

Methods

Our Evidence-based Practice Center (EPC) established a team and a work plan to develop this evidence report. The project involved recruiting key informants and technical experts, formulating and refining the questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review and public comment.

Topic Development

The topic for this report was nominated in a public process. At the beginning of the project, we recruited a panel of key informants to give input on key steps including the selection and refinement of the questions to be examined. The panel included internal experts from the Johns Hopkins University with expertise in evaluating the efficacy and safety of immunotherapy and external experts with expertise in immunotherapy research and patient care.

In preparation for this report, we reviewed existing systematic reviews on this topic as well as guidelines prepared by key professional societies about the use of these therapies. With input from the key informants, staff of AHRQ, and the Scientific Resources Center, we developed the KQs. Our draft KQs were posted on AHRQ's website for public comment in April 2011. We then refined the KQs based on feedback received.

The final KQs focus on the comparisons of the methods of immunotherapy delivery, their ability to affect intermediate outcomes, long-term clinical outcomes, and adverse effects. We drafted a protocol to address these KQs and then recruited a panel of technical experts, which included experts on the treatment of allergies on the adult and pediatric population, including asthma experts. With input from the technical expert panel and representatives from AHRQ, we finalized the protocol.

Search Strategy

We searched the following databases for primary studies for the periods in parentheses: MEDLINE® (from 1950 to May 21 2012), Embase (from 1947 to May 21 2012), the Cochrane Central Register of Controlled Trials (to May 21 2012), and LILACS (Latin American and Caribbean Health Sciences Literature, from 1982 to May 21 2012). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH), terms, and text words of key articles identified *a priori* (Appendix A). We also reviewed the reference lists of each included articles and relevant review articles.

To identify additional studies, we reviewed public registries of clinical trials, including the International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/default.aspx) and ClinicalTrials.gov (www.clinicaltrials.gov). We also assessed medical and statistical reviews, as well as the FDA status of the included medications, using the Food and Drug Administration website.

The results of the searches were downloaded and imported into ProCite® version 5 (ISI Research Soft, Carlsbad, CA). We scanned for exact article duplicates; author/title duplicates, and title duplicates using the duplication check feature in ProCite. From ProCite, the articles were uploaded to DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based software package developed for systematic review and data management. This database was used to track the search results at the levels of abstract review, article inclusion/exclusion, and data abstraction.

We requested Scientific Information Packets from the relevant pharmaceutical companies so as to be able to include gray literature in this review.

Study Selection

The abstract review phase was designed to identify randomized controlled trials (RCTs) reporting on the effects of SIT on intermediate outcomes, long-term clinical outcomes, and/or adverse events and side effects (Appendix B). We included only articles published in English due to volume of literature and lack of resources to translate all the languages encountered. Abstracts were reviewed independently by two investigators and were excluded if both investigators agreed that the article met one or more of the exclusion criteria (Table 1). Differences between investigators regarding abstract inclusion or exclusion were resolved through consensus adjudication.

Articles promoted on the basis of abstract review underwent another independent parallel review to determine if they should be included for data abstraction (Appendix B). Differences regarding article inclusion were resolved through consensus adjudication. A third reviewer audited a random sample of abstract and article reviews to ensure consistency in the reviewing process.

Studies utilizing sublingual formulations not currently available or in which similar off label use allergens are not available in the United States such as sublingual tablets, were not included in this review. We also excluded articles in which oral immunotherapy was immediately swallowed without prolonged mucosal contact, as this type of immunotherapy is not currently in clinical use.

Table 1. Study inclusion and exclusion criteria

PICO Criteria	Inclusion and Exclusion Criteria
Population and condition of interest (Appendix C, Population)	Studies enrolled patients with allergic rhinoconjunctivitis and/or allergic asthma due to airborne allergies. Allergic rhinoconjunctivitis must have been confirmed by skin tests or RAST and asthma must confirmed by pulmonary lung function (FEV; methacholine challenge). Studies included adults, the elderly, pregnant women, individuals with severe asthma, monosensitized individuals, minorities, inner-city residents, and rural residents.
Interventions (Appendix C, Interventions)	The intervention was SIT alone or with usual care. SIT preparation must be available for use in the United States No study of SIT was excluded because of timing or duration of treatment. We excluded studies where dosage units were NOT specified

Table 1. Study inclusion and exclusion criteria (continued)

PICO Criteria	Inclusion and Exclusion Criteria
Comparisons of interest (Appendix C, Comparators)	We included studies that compared SIT (subcutaneous immunotherapy or sublingual immunotherapy) to any of the following: 1. Placebo 2. Any other SIT (any form available in the United States) 3. Pharmacotherapy (positive control) 4. Environmental control 5. Usual care (for example, environmental control, pharmacotherapy) Studies where SIT was used alone or in combination with any other treatment and compared with the listed comparators or any other treatment
Outcomes (Appendix C, Outcomes Explanations)	We included studies that reported the following outcomes: Primary outcomes 1. Symptom scores (for rhinitis, conjunctivitis, or asthma) 2. Medication scores 3. Combined symptom and medication scores 4. Quality of life 5. Safety or harms Secondary outcomes 1. Functional test results (PFT, FEV) 2. Provocational test results (for nasal, conjunctival, or bronchial challenges) 3. Adherence and convenience 4. Long-term effects of SIT (disease modification-prevention of sequelae or new sensitivities)
Timing and Setting	We did not impose any limitation on timing or setting.
Study design	We included only randomized, controlled trials

FEV = forced expiratory volume; PFT = pulmonary function testing; RAST = radioallergosorbent test; SIT = allergen specific immunotherapy

All of the articles had to meet four basic criteria to be included: the allergic diagnosis had to be confirmed, the study had to include a relevant comparison group, the dose of allergen had to be specified, and the study had to report the outcomes of interest.

The studies compared the outcomes of patients receiving immunotherapy to the outcomes of patients that did not receive immunotherapy. The comparator arms sometimes included administration of a placebo and uniformly included pharmacotherapy for symptom control, which can be considered to be usual care. The majority of immunotherapy arms also permitted concurrent use of pharmacotherapy.

In this review, multiple allergen immunotherapy was defined as the use of extracts containing more than one allergen species, including cross-reacting allergens. Single allergen immunotherapy was defined by the use of a single allergen species, and not by a class of allergens.

Allergists may apply different definitions of single and multiple allergen immunotherapies to our findings. Multiple allergen immunotherapies can be defined as the use of extracts containing more than one allergen class, whereas single allergen immunotherapy can refer to the use of closely related allergens within the same class. For example, a study using a grass mix allergen

(or tree mix, or 2 dust mite species) could be considered a single allergen study, whereas a multiple allergen study could use different classes of allergens, such as tree and grass.

Data Abstraction

We used a systematic approach for extracting data to minimize the risk of bias in this process. By creating standardized forms for data extraction, which were pilot tested, we sought to maximize consistency in identifying all pertinent data available for synthesis. Each article underwent double review by study investigators for data abstraction. The second reviewer confirmed the first reviewer's data abstraction for completeness and accuracy. Reviewer pairs were formed to assure clinical and methodological expertise. A third reviewer re-reviewed a random sample of articles by the first two reviewers to ensure consistency in the data abstraction of the articles. Reviewers were not masked to the articles' authors, institution, or journal. In most instances, data were abstracted from the text or tables in the article. If possible, relevant data were also abstracted from figures. Differences in opinion were resolved through consensus adjudication and in difficult cases, during team meetings.

For all articles, reviewers extracted information on general study characteristics (for example, study design, study period, and followup); study participants (for example, age, sex, race, disease, inclusion criteria, allergens, and duration of disease); interventions (for example, doses, frequency of use, and duration of use); primary and secondary outcome measures, their the method of ascertainment, and the results of each outcome; and safety (Appendix B). For studies that recorded outcomes at multiple time points, we used the outcome data from the final time point reported. However, some studies treated and assessed subjects for only one season; in these single season studies, the values reported at peak pollen seasons were used when available.

All information from the article review process was entered into the DistillerSR database by the individual completing the review. Reviewers entered comments into the system whenever applicable. The DistillerSR database was used to maintain and clean the data, as well as to create detailed evidence tables and summary tables.

Quality Assessment

Two reviewers independently assessed the risk of bias in each article and came to consensus about the overall rating. We used a modification of the Cochrane Collaboration Tool for Assessing Risk of Bias from the Cochrane Handbook for Systematic Reviews of Interventions.[29] This tool was used to assess potential sources of bias:

1. Was there random allocation of subjects?
2. Was the allocation scheme concealed?
3. Was the intervention concealed from study personnel and participants?
4. Was incomplete data adequately addressed?
5. Were there other important sources of bias?

We did not assess selective outcome reporting in this body of literature. We did, however, assess a sixth item: the participation of the sponsor company in the study design and interpretation.

For each bias category, reviewers entered "Yes" if item posed a low risk of bias, "No" if item posed a high risk of bias, or "Unclear" (Appendix C).

- **Good (low risk of bias). 0–1 point.** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a formal randomized controlled design; a clear description of the

population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.

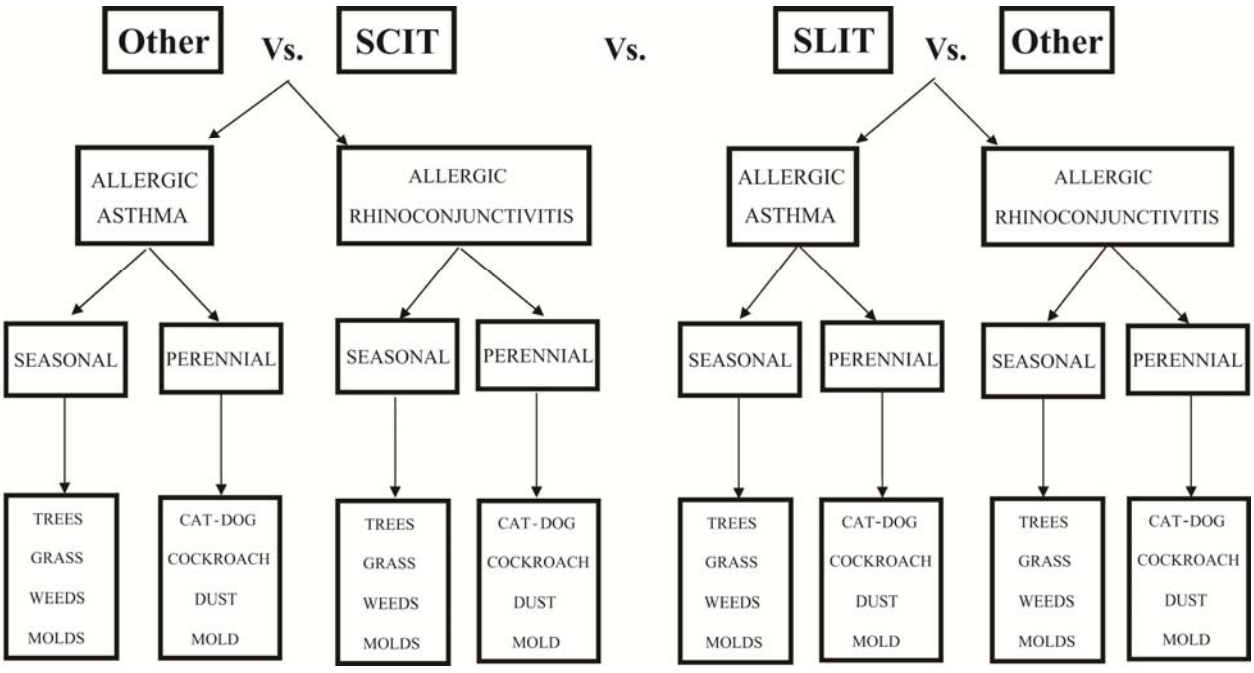
- **Fair (moderate risk of bias). 2–3 points.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias). 4–6 points.** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

We reviewed all of the studies that had only one point in the overall quality assessment and made some reassignments. Studies remained in the **Good (low risk of bias)** category if the single point was due to sponsorship or "other sources of bias"; studies were assigned to the **Fair (moderate risk of bias)** category if the single point came from lack of allocation concealment, lack of blinding or incomplete data reporting.

Data Analysis and Synthesis

We distributed the studies by intervention, disease, and allergen KQ following the following diagram, and addressed the KQs within each intervention and disease strata (Figure 2).

Figure 2. Algorithm for the approach and classification of the studies



SCIT = subcutaneous immunotherapy; SIT = allergen specific immunotherapy; SLIT = sublingual immunotherapy

We created a set of detailed evidence tables containing information extracted from eligible studies and stratified the tables according to KQ. Once these evidence tables were created, we

rechecked selected data elements against the original articles. If there was a discrepancy between the data abstracted and the data appearing in the article, this discrepancy was brought to the attention of the investigator in charge of the specific dataset and the data were corrected in the final evidence tables. Given the substantial heterogeneity between studies and the lack of reporting of measures of variability, we did not quantitatively pool the data.

We summarized the safety of sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma by abstracting the harms or adverse events reported in the included studies. The adverse events recorded with sublingual immunotherapy were divided into two general categories. Local reactions are reactions that occur at the site of introduction of allergen. In the case of sublingual immunotherapy, these are reactions that occur in the oral cavity, such as mouth irritation, itching, swelling, and pain. The reactions may or may not require treatment and can range from mild to severe. Systemic reactions are allergic reactions that occur distant to the site of introduction of the allergen and can include any system of the body: cutaneous, ocular, gastrointestinal, or respiratory. These reactions may or may not require treatment, and some may require hospitalization. Severity can range from mild to life-threatening. The most severe potential systemic reactions with allergen-specific immunotherapy include anaphylaxis and death.

Studies used different methods for reporting safety data. The two most common methods were number of patients experiencing adverse events and number of adverse events experienced throughout study period. Due to the heterogeneity observed in the different studies, the safety outcomes are presented only descriptively.

Data Entry and Quality Control

Each data element was reviewed by at least two reviewers. The second reviewers were generally more experienced members of the research team. In addition, two additional investigators audited a random sample of the reviews to identify any problems with data abstraction. If problems were recognized in a reviewer's data abstraction, the problems were discussed at a meeting with the reviewers. In addition, research assistants used a system of random data checks to assure data abstraction accuracy.

Rating Body of Evidence

At the completion of our review, we graded the quantity, quality, and consistency of the best available evidence addressing the three KQs by adapting by the Grading of Recommendation Assessment, Development and Evaluation (GRADE) Working Group, adapted by AHRQ in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=328&pageaction=displayproduct) and published in the Journal of Clinical Epidemiology.[30,31]

We applied evidence grades to the collection of trials for each comparison and for each outcome. We found that some articles reported only the post- to pre- comparisons within the intervention arm. We show these results in our evidence tables and summary tables, however, those results did not contribute to the evidence grades as this is a less strong design than the head-to-head comparisons. In our grade assignments, we considered the limitations of each individual study's quality (using the risk of bias classification), the consistency of the direction of the effect across studies, the directness of the body of evidence to the question of interest, and the magnitude of the effects reported across trials. We could not comment on the precision of the

effect sizes as there were seldom measures of variance within the individual studies. We did not use the reported statistical significance of the differences between groups to grade the evidence as this was not consistently reported. We could not generate confidence intervals for these data as these were largely continuous outcomes. We calculated the percent change in outcomes in the intervention arm, and also the percent change in the comparator arm; the magnitude of effect was based on the difference between comparators.

There is no clear consensus on what is considered a clinically relevant improvement in symptoms. While some clinicians may suggest that a 15 percent change could reflect real and significant improvement in symptoms in some patients, Canonica et al state that "the minimal clinically relevant efficacy should be at least 20 percent higher than placebo."[10] We would expect less difference in symptom improvement when comparing immunotherapy to medications. Our systematic review included both studies using placebo and other comparators (such as medications). We chose to classify magnitude of effect as weak if there was less than a 15 percent difference in percent change between the SIT group and comparator arm; a 15 to 40 percent difference was called moderate, and greater than 40 percent was considered a strong effect. We applied this scheme to all graded outcomes in this review. We did not grade the evidence for indirect outcomes such as pulmonary function testing and provocational studies.

The investigator responsible for each section assigned an evidence grade for each disease (asthma, allergic rhinitis, and rhinoconjunctivitis) and each treatment comparison. The team reviewed these and came to a consensus. We assigned evidence grades as:

1. High grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect);
2. Moderate grade (indicating moderate confidence that the evidence reflects the true effect and future research may change our confidence in the estimate of the effect and may change the estimate);
3. Low grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and
4. Insufficient (evidence is unavailable or no relevant trials).

We adhered to the following system to assign the overall grade of evidence for each outcome. High grade evidence is at least 2 trials having low risk of bias, at least 1 of which has a strong magnitude of effect and the overall body of evidence is largely consistent. Moderate grade evidence is 1 trial having a low risk of bias with a strong magnitude of effect; or 2 or more trials with medium risk of bias having strong magnitudes of effect, or 1 trial having low risk of bias with moderate magnitude of effect plus 1 trial having medium risk of bias with strong magnitude of effect and an overall body of evidence that is largely consistent. Low grade evidence was assigned if there was evidence but it did not meet the criteria for the above categories. Evidence was insufficient if there were no relevant trials or data were insufficient.

If the evidence did not meet the criteria to be rated as high then it was graded as moderate IF it met criteria for moderate, if not then it was graded as low. A body of evidence was considered consistent if the direction of effect was the same for all studies for a given comparison and outcome.

The safety data reported in this systematic review include only events reported in RCTs. Evidence grades on the safety of SIT using only this data would be invalid since the grades would not be based on the entirety of the evidence, as safety events are more completely captured in observational studies. Given this, we chose not to grade the safety data. Additionally,

the lack of consistency on the reporting of adverse events and the differences in the severity grading systems made the safety data difficult to synthesize.

Applicability

Throughout the report, we discuss the applicability of the results as the degree to which the study population, interventions, outcomes, and settings are typical of treatment of individuals with allergic rhinitis and asthma in usual care settings (for example, outpatient treatment by internists, family physicians, pediatricians, allergists, and otolaryngologists).

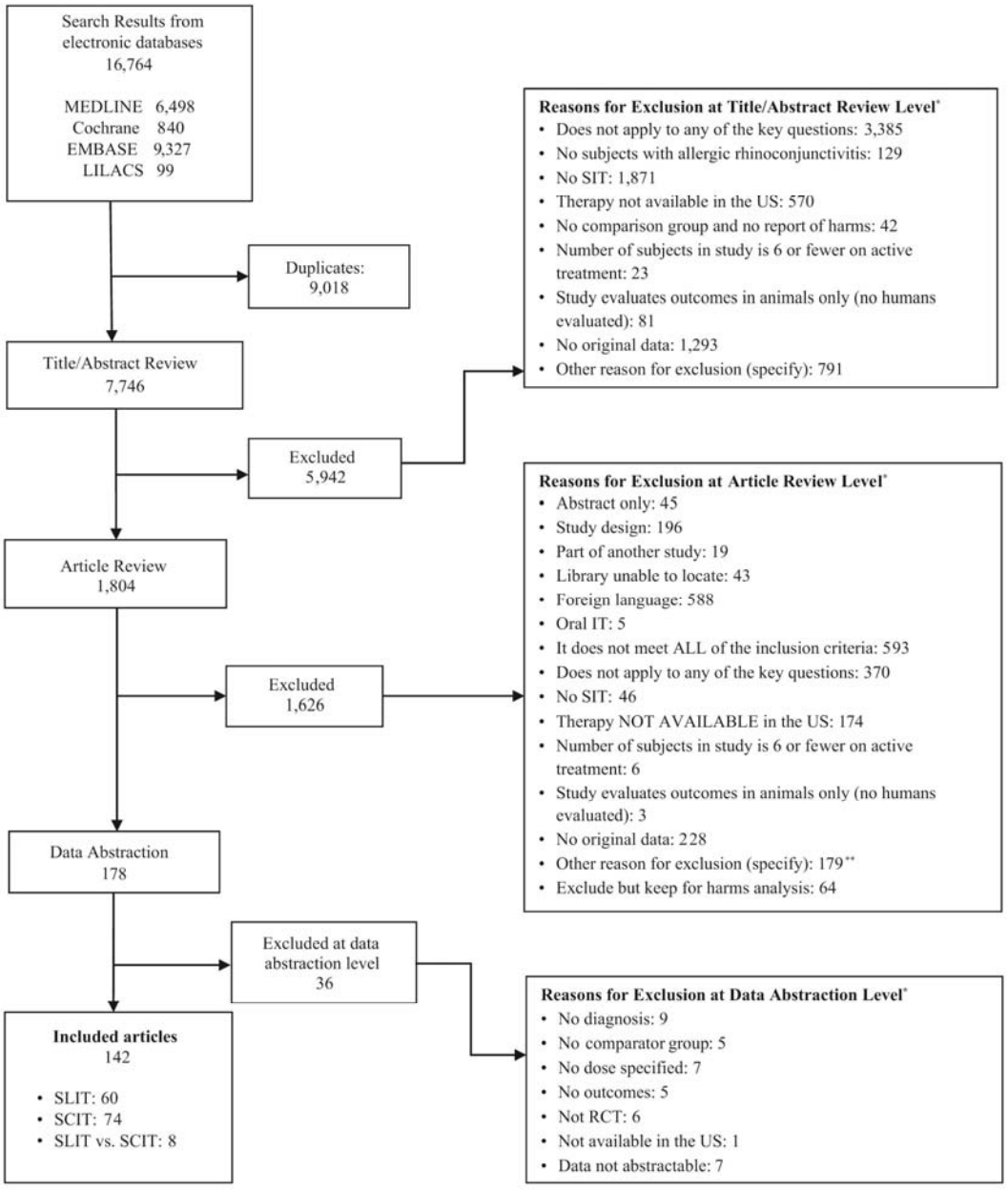
Peer Review and Public Commentary

A draft of the evidence report was reviewed by the peer reviewers, AHRQ representatives, and the Eisenberg Center.

Results

The literature search identified 7,746 citations. During the abstract review process, we excluded 5,942 citations which did not meet eligibility criteria. At the level of full-text article review, we excluded another 1,626 and included 178 articles for data abstraction. At this level we excluded 36 articles and included 142 articles for the final analysis (Figure 3).

Figure 3. Literature search



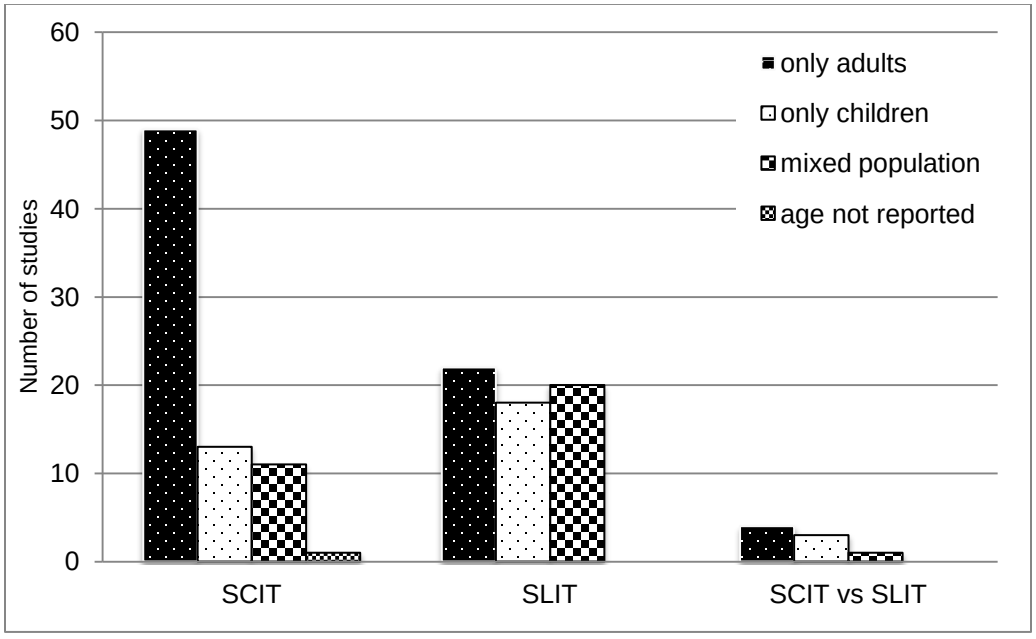
RCT = randomized controlled trial; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy
* Total may exceed number in corresponding box, as articles were excluded by two reviewers at this level.
** Other reasons: Control group is healthy population, routes of administration not included, abandoned interventions, outcomes not reported, no comparator group, continued medical education reports, editorials or reviews, studies about mechanism or action, other allergies (food, aspirin).

Summary of Findings

All studies included were randomized controlled trials. We included 74 references that investigated the efficacy and safety of subcutaneous immunotherapy (SCIT), 60 studies that investigated the efficacy and safety of sublingual immunotherapy (SLIT), and eight studies compared subcutaneous immunotherapy and sublingual immunotherapy, with only 3 of these studies reporting findings from head-to-head comparisons between both forms of SIT. Appendixes D, E, F, and G include details of all studies included; and Appendix H provides a listing of excluded articles with reasons for exclusions.

Seventy-five studies (52%) included only adults and 34 studies (24%) included only children. Thirty two studies (22%) included both adults and children (mixed population). One study in the SCIT intervention did not specify the age of the population studied[32] (Figure 4).

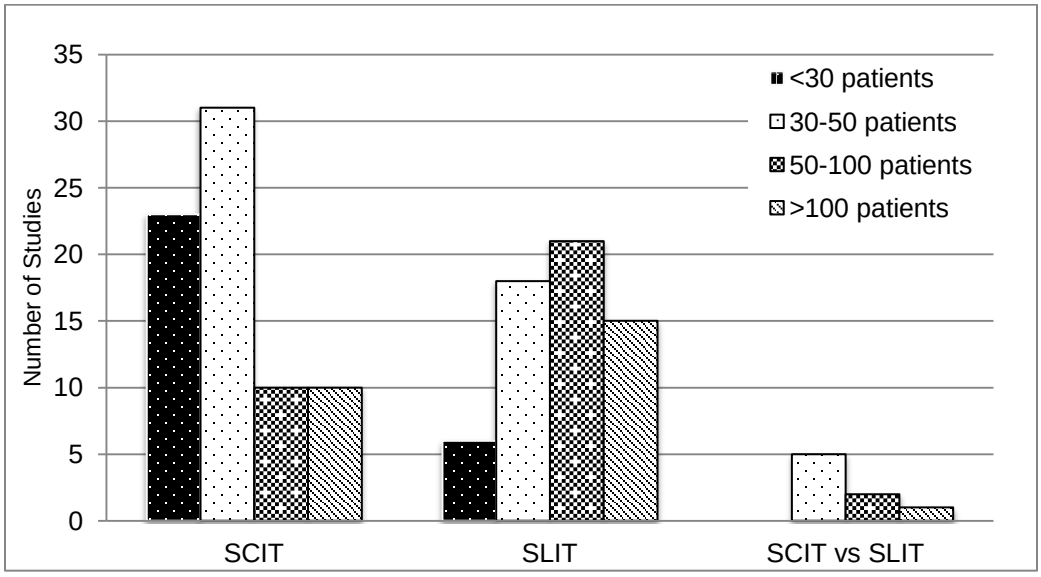
Figure 4. Count of studies including children, adults, or both



SCIT = subutaneous immunotherapy; SLIT = sublingual immunotherapy

We had no limits on study size; the number of patients randomized in the studies ranged from 15 to 511. Twenty nine studies (20%) had fewer than 30 patients and twenty-six studies (18%) had more than 100 patients. The majority of the SCIT studies (54 studies or 73%) had 50 subjects or fewer, whereas 60 percent of SLIT studies (36 studies) enrolled at least 50 subjects. (Figure 5).

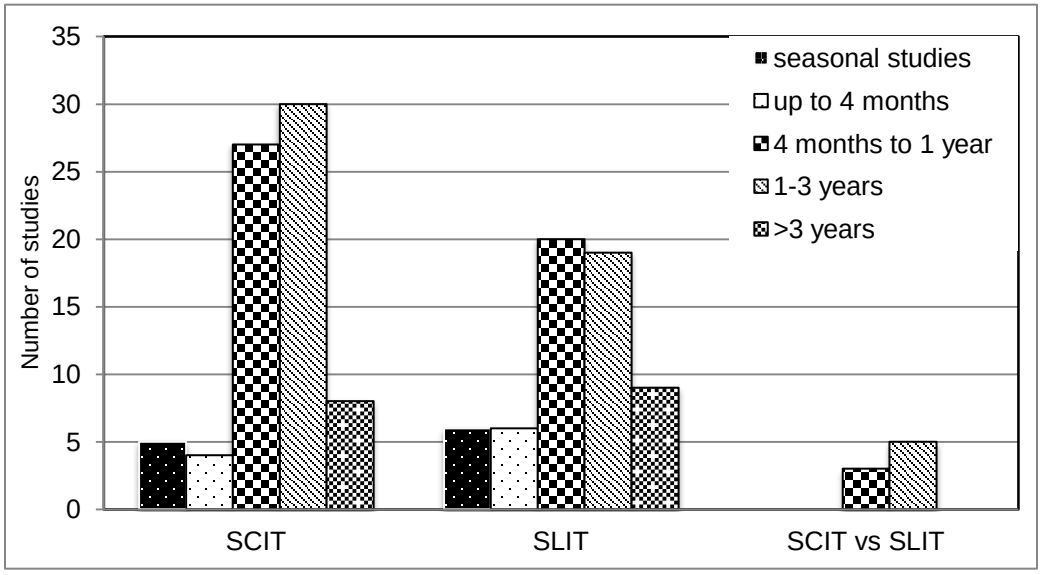
Figure 5. Count of studies by number of enrolled participants



SCIT = subutaneous immunotherapy; SLIT = sublingual immunotherapy.

We had no limitations based on duration of treatment. Only ten studies (7%) treated patients for up to 4 months (16 weeks), 50 studies (35%) treated patients for up to one year, 54 studies (38%) had a duration between 1 and 3 years, and 17 studies; 9 treating with sublingual immunotherapy and 8 treating with subcutaneous immunotherapy had a duration longer than 3 years. One study treated patients with subcutaneous immunotherapy for 4 years.[33] Eleven studies (9%) were seasonal, meaning that the patients were followed only through the allergy season; 5 were studies of subcutaneous immunotherapy and 6 were sublingual immunotherapy (Figure 6).

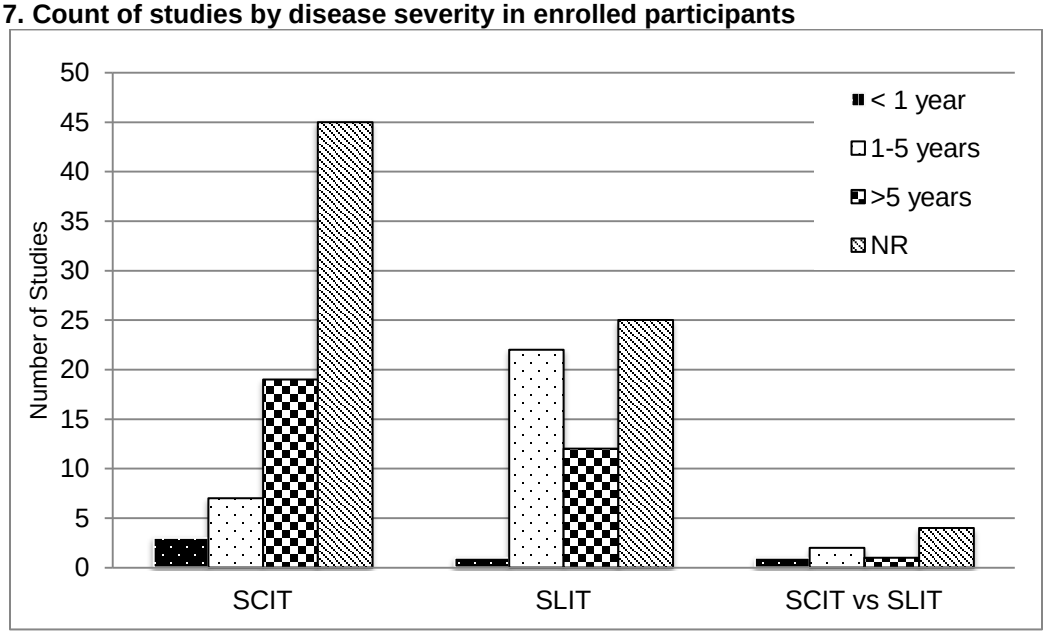
Figure 6. Count of studies by duration of treatment



SCIT = subutaneous immunotherapy; SLIT = sublingual immunotherapy

Since immunotherapy is not usually the first treatment, the number of years with disease is often a criterion for inclusion in clinical trials. However, 74 of the included studies (52%) did not report years with disease. In the rest, this was specified as an inclusion criterion. In 22 percent of the studies, patients had the disease for 1 to 5 years; in 22 percent of the studies patients had the disease for more than 5 years. In only five studies, patients had the disease for less than a year (Figure 7).

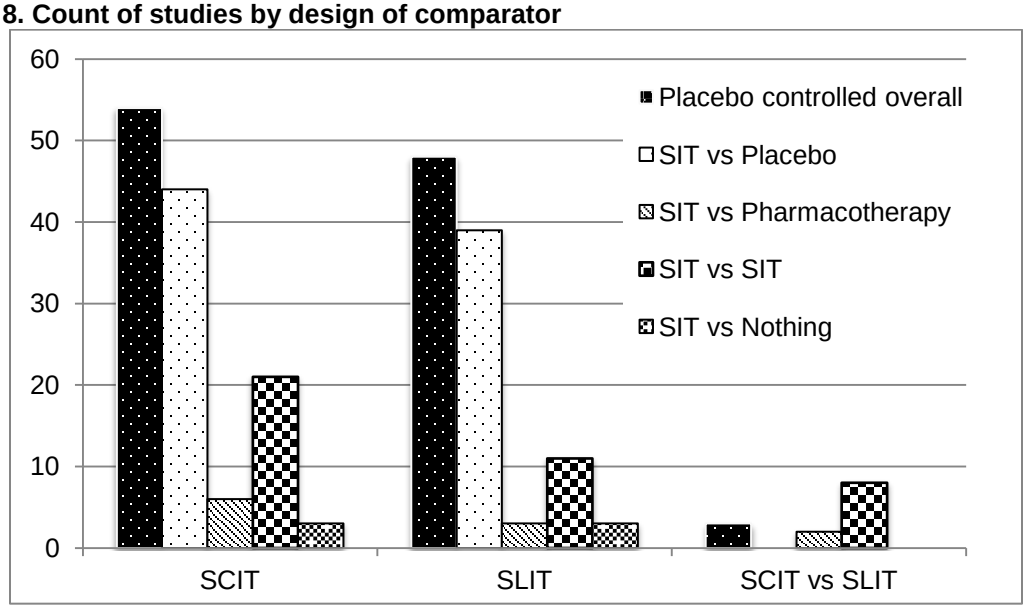
Figure 7. Count of studies by disease severity in enrolled participants



NR = not reported; SCIT = subutaneous immunotherapy; SLIT = sublingual immunotherapy

Numerous studies were designed as immunotherapy versus placebo (73% of the SCIT studies and 80% of the SLIT studies), but some of the studies comparing different immunotherapy regimens (e.g., low dose vs. high dose, coseasonal vs. continuous, cluster vs. classic) included a placebo arm, increasing the number of overall placebo controlled studies to 105 studies (74%); 54 SCIT studies, 48 SLIT studies and 3 SLIT versus SCIT studies [34-36] had a placebo arm. Very few studies were designed to compare SIT versus pharmacotherapy: only 6 SCIT studies,[37-42] 3 SLIT studies,[43-45] and 2 SLIT versus SCIT studies[37,46] included a pharmacotherapy arm (Figure 8).

Figure 8. Count of studies by design of comparator



SCIT = subutaneous immunotherapy; SIT = allergen specific immunotherapy; SLIT = sublingual immunotherapy

The majority of the studies allowed the use of pharmacotherapy (conventional or rescue therapy) as needed; 75 percent of the SCIT studies (remaining 25% were not reported), 98 percent of the SLIT studies and 100 percent of the SLIT versus SCIT studies (see Intervention Characteristics tables in Appendixes D, E and F).

Non-English Literature

Our search identified 590 articles written in languages other than English. These articles were reviewed by two investigators, following the same procedure that all the other articles. This was done after the results of the English language articles were known. After title and abstract review, we excluded 525 references and included 65 for full article review. From these 65 articles, we excluded 44 based on language plus other criteria: did not study SIT, were review articles, used oral or nasal immunotherapy, or did not apply to our KQs. For the remaining 21 articles, we used Google's Web-based translation services, Google Translate® (http://translate.google.com)[47] to translate the article to determine if their results were comparable to those in the English language literature. The translation service did not work on eight articles. Among the remaining articles, five were not RCTs. In the nine RCTs (three Spanish, two German, two French, one Polish, one Japanese), the results were concordant with the results in the English-language literature.

Subcutaneous Immunotherapy

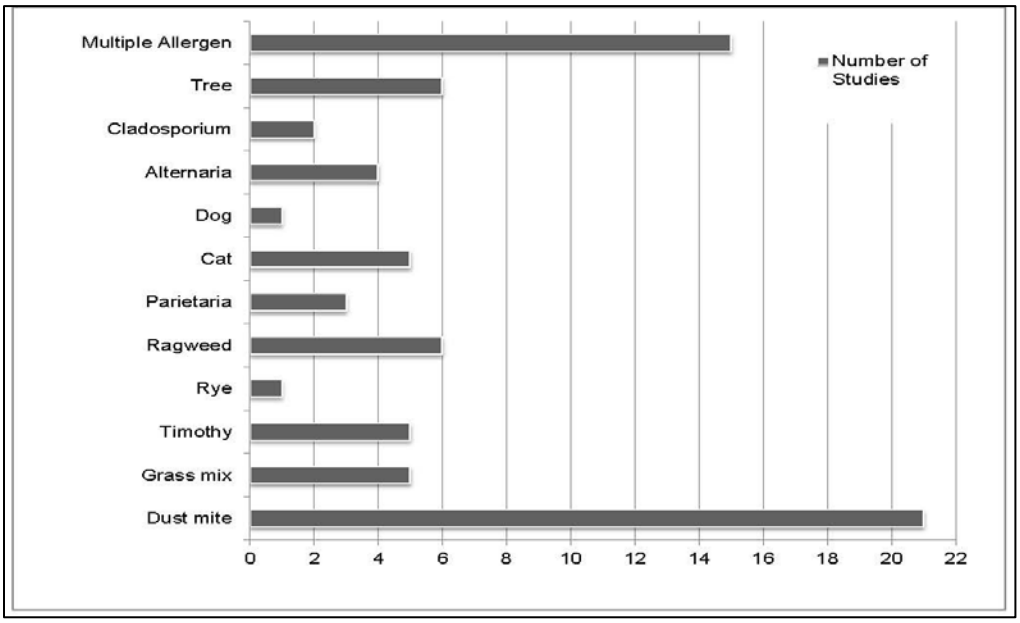
Study Characteristics

These 74 articles, with 4350 subjects, were published between 1967 and 2012. The publications originated from Europe (56 studies or 76%), North America (12 studies or 16%), Asia (5 studies or 7%), South America (1 study or 1%), and Australia (1 study or 1%) (Appendix D, Evidence Table D1). Thirty-five studies (50%) had at least some industry support, although 18 studies (25%) had no identified funding source (Appendix D, Evidence Table D1). Twenty one studies (28%) had a low risk of bias. Fifty-two percent (39 studies) were rated as having a medium risk of bias, and 14 studies (20%) were considered to have a high risk of bias (Appendix D, Evidence Table D4).

The primary diagnoses of the subjects were asthma in 19 studies,[41,48-6465] rhinitis in ten studies,[32,66-74] rhinoconjunctivitis in 14 studies,[37,75-87] asthma with rhinitis in 18 studies,[33,38-40,88-101] and asthma with rhinoconjunctivitis in 13 studies[42,102-113] (Appendix D, Evidence Table D1).

By design, all the studies required subjects to have positive allergy skin test results and/or positive in-vitro specific IgE test results. Forty two studies (57%) required that the subjects had not received previous immunotherapy. Eighteen (24%) focused on monosensitized individuals.[41,48,53,66,77,79,84,88,90-92,95-97,99,102,103,108] The majority of studies (44 studies or 59%) evaluated seasonal allergens including trees, grasses, weeds, and seasonal molds, followed by perennial allergens in 28 studies (38%); only 2 studies (3%) included both seasonal and perennial allergens. Forty-eight studies used a single allergen, whereas the remaining 26 studies used multiple allergens. The most common allergen studied was dust mite (21 studies or 31%) (Figure 9).

Figure 9. Subcutaneous immunotherapy studies by type of allergen



Population Characteristics

The age range of participants in the subcutaneous immunotherapy studies was 3 to 72 years (Appendix D, Evidence Table D2). Twenty-four studies reported the mean or minimum duration of disease among the enrolled participants. Mean duration of disease ranged from 1 year to 24 years. All but twelve studies reported gender; all studies reporting gender included male and female patients. Only one study reported the race of the participants.[65]

Key Question 1. What is the evidence for the efficacy and effectiveness of subcutaneous immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma?

Evidence for the Efficacy and Effectiveness of Subcutaneous Immunotherapy in the Treatment of Asthma

In this section we report findings from the 74 references that investigated the safety and efficacy of subcutaneous immunotherapy in the Treatment of Asthma

Key Points

Relative to placebo or control treatment:

- High grade evidence supports that subcutaneous immunotherapy improves asthma symptom control, based on 16 randomized controlled trials with 1178 subjects.
- Moderate grade evidence supports that subcutaneous immunotherapy improves asthma plus rhinitis/rhinoconjunctivitis symptoms, based on five randomized controlled trials with 175 subjects.
- High grade evidence supports that subcutaneous immunotherapy reduces asthma medication use, based on 12 randomized controlled trials with 1062 subjects.
- High grade evidence supports that subcutaneous immunotherapy reduces asthma plus rhinitis/rhinoconjunctivitis medication use, based on five randomized controlled trials with 203 subjects.
- Low grade evidence supports that subcutaneous immunotherapy improves asthma/rhinitis/rhinoconjunctivitis symptom control and medication use, based on six randomized controlled trials with 196 subjects.

Asthma and Asthma/Rhinoconjunctivitis Symptoms

Asthma symptom scores alone, or combined asthma with rhinitis/rhinoconjunctivitis symptom scores were reported in 20 asthma studies.[39,40,48,49,52,53,56,58-61,64,65,89,95,98,101,110-112] (Appendix D, Evidence Tables D5 and D6). Eighteen studies evaluated asthma symptom scores (Appendix D, Evidence Table D6). The number of participants in each study ranged from 16 to 300. The duration of assessment ranged from 3 months to 6 years. Twelve studies compared subcutaneous immunotherapy to placebo; three studies compared subcutaneous immunotherapy to pharmacotherapy; one study compared subcutaneous immunotherapy to a control group which did not receive SIT; one study compared SCIT using a cluster schedule versus a conventional schedule; and another compared SCIT duration of 3 years versus 5 years. Various measures of asthma symptoms were used. Although the scoring system was not always described, some studies used self-reported symptoms using an ordinal scale. Other measures of asthma symptoms include time to first increase in symptoms,[61] mean percentage of days and nights with asthma,[40]

number of asthma exacerbations per year,[53] and comparison of number of subjects who were improved, unchanged, or deteriorated.[64] Across studies, the immunotherapy group showed an improvement in asthma symptoms scores ranging from 17 to 84 percent greater than the comparison group.

Thirteen of sixteen studies (81%) reported statistical comparisons between subcutaneous immunotherapy and the comparison group.[40,48,52,53,56,59,61,65,98,101,111,112,64] Majority of the studies used a single allergen for immunotherapy. The most common single allergen was dust mite in seven studies.[52,53,56,58-60,98] Seven of the sixteen studies (44%) demonstrated significant improvement in asthma symptoms from subcutaneous immunotherapy when compared with placebo,[56,61,101,112] pharmacotherapy,[40,53] or another control group,[52] with the absolute difference in asthma symptoms between groups ranging from 17 to 79 percent. Of note, one of these was a study of perennial allergic asthma and the investigators specifically reported data for patients only allergic to *D. pteronyssinus*; when patients who were sensitized to more than one perennial allergen were included in the analysis, no significant benefit was observed.[52] Of the remaining six studies that compared groups, two studies demonstrated significant improvement in the subcutaneous immunotherapy group when symptom scores were compared before and after immunotherapy.[65,98] In one of these studies, the placebo group also had a significant reduction in symptom scores.[65]

Three studies (19%) did not report statistical comparisons between the immunotherapy and the comparison groups.[49,58,60] Two of these studies reported significant improvement in symptom scores for the immunotherapy group, whereas no significant changes in symptom scores were observed in the comparison groups of both studies.[58,60] The third study was a 2-year study in which patients were treated with preseasonal immunotherapy only in the first year of the study.[49] Symptom scores were recorded before, during, and after the pollen season for both years; however the investigators did not report a direct comparison of the symptom scores between the first and second year.

Six of 16 studies (38%) reporting asthma symptom scores were large studies with 90 to 300 participants.[40,48,52,56,59,65] Among the large studies with low or moderate risk of bias, three studies investigated dust mite allergen,[52,56,59] one investigated ragweed allergen,[48] and one investigated multiple allergens.[65] Only two of these studies, both investigating dust mites, demonstrated significant improvement in asthma symptoms, when compared with the comparison group.[52,56] Of note, one of these studies reported that this significant improvement was observed exclusively in a subgroup of subjects whose only perennial allergen sensitivity was to *D. pteronnysinus*; there was no significant improvement in the whole study population, which included individuals with other perennial allergen sensitivity.[52] Two high quality studies, including one large study, reported no significant improvement in asthma symptoms following treatment with subcutaneous immunotherapy when the immunotherapy group was compared with the placebo group.[65,111] In fact, in the larger study by Adkinson et al, the placebo group had a greater reduction in symptoms than the immunotherapy group.[65] Allergen doses varied across studies with no clear association between dose and symptom response.

These 16 studies reporting asthma symptom scores included 1178 participants. The overall strength of evidence is high grade to support the use of subcutaneous immunotherapy to improve asthma symptom scores (Table 2).

One blinded study by Tabar et al. compared subcutaneous immunotherapy using a cluster immunotherapy schedule against a conventional schedule.[38] After 1 year of immunotherapy, both groups demonstrated significant improvement in asthma symptoms scores compared with pre-

treatment scores. At the end of the first year, patients were re-randomized to receive either 3 years or 5 years of subcutaneous immunotherapy; this latter study was an unblinded randomized trial.[113] After 5 years, no significant difference was observed in the global asthma symptom scores between treatment groups. This study was not included in the evidence grading because both treatment groups received subcutaneous immunotherapy.

Table 2. Body of evidence for subcutaneous immunotherapy and asthma symptom scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Maestrelli 2004[59]	Dust mite	SCIT Placebo	95	Medium	+	Direct	Moderate
Olsen 1997[60]	Dust mite	SCIT Placebo	31	Low	+	Direct	Strong
Pichler, 1996[98]	Dust mite	SCIT Placebo	30	Medium	-	Direct	Weak
Wang 2006[56]	Dust mite	SCIT Placebo	132	Low	+	Direct	Moderate
Bousquet 1988[52]	Dust mite	SCIT Control (No SIT)	150	Medium	+	Direct	Strong
Kohno 1998[58]	Dust mite	SCIT Pharmaco-therapy	16	Medium	+	Direct	Strong
Pifferi 2002[53]	Dust mite	SCIT Pharmaco-therapy	29	Medium	+	Direct	Strong
Dreborg 1986[111]	Cladosporium	SCIT Placebo	30	Low	+	Direct	Moderate
Malling 1986[64]	Cladosporium	SCIT Placebo	23	High	+	Direct	Could not determine*
Nouri-Aria 2003[101]	Timothy	SCIT Placebo	44	Low	+	Direct	Strong
Hill 1982[49]	Rye	SCIT Placebo	20	High	+	Direct	Strong
Creticos 1996[48]	Ragweed	SCIT Placebo	90	Medium	+	Direct	Moderate
Ohman, 1984[61]	Cat	SCIT Placebo	17	Low	+	Direct	Could not determine*
Adkinson 1997[65]	Multiple	SCIT Placebo	121	Low	-	Direct	Moderate
Cantani 1997[40]	Multiple (dust mite, rye, parietaria)	SCIT Pharmaco-therapy	300	High	+	Direct	Could not determine*
Kuna 2011 [112]	Alternaria	SCIT Placebo	50	Medium	+	Direct	Moderate

+ = positive; - = negative; SCIT = subcutaneous immunotherapy SIT = allergen-specific immunotherapy
*Not enough data were provided in the article to calculate the magnitude of effect.

Five asthma studies reported asthma plus rhinoconjunctivitis symptom scores, each using a different allergen; these included three studies investigating pollen,[39,89,101] one study investigating *Alternaria*,[95] and one study investigating cat allergen.[110] All were small studies ranging from 24 to 49 participants. Four were placebo-controlled trials with low[95] or moderate risk of bias.[89,101,110] Three of these demonstrated significant improvement in pooled symptom scores with subcutaneous immunotherapy when compared directly with placebo.[89,95,101] One study demonstrated significant improvement in pre- versus post-treatment symptom scores in the subcutaneous immunotherapy arm.[110] The single study comparing subcutaneous immunotherapy

to pharmacotherapy demonstrated a significant improvement in combined symptom scores in the subcutaneous immunotherapy arm when compared with pharmacotherapy; however this study was graded as having a high risk of bias.[39] The immunotherapy group showed improvement ranging from 21 to 68 percent greater than the comparison group.

These five studies reporting asthma plus rhinoconjunctivitis symptom scores included 175 participants. The overall strength of evidence is moderate to support the use of subcutaneous immunotherapy to improve combined asthma and rhinoconjunctivitis symptom scores (Table 3).

Table 3. Body of evidence for subcutaneous immunotherapy for asthma plus rhinitis/rhinoconjunctivitis symptom scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Ariano 2006[39]	*Parietaria*	SCIT Pharmaco-therapy	30	High	+	Direct	Strong
Arvidsson 2002/2004[89]	Birch	SCIT Placebo	49	Medium	+	Direct	Could not determine*
Horst 1989[95]	*Alternaria*	SCIT Placebo	24	Low	+	Direct	Could not determine*
Nouri-Aria, 2003[101]	Timothy	SCIT Placebo	44	Low	+	Direct	Moderate
Varney 1997[110]	Cat	SCIT Placebo	28	Medium	+	Direct	Strong

+ = positive; SCIT = subcutaneous immunotherapy

*Not enough data were provided in the article to calculate the magnitude of effect.

Asthma Medication Use and Asthma Plus Rhinitis/Rhinoconjunctivitis Medication Use

Asthma medication scores, or asthma plus rhinitis/rhinoconjunctivitis medication scores were reported in 17 asthma studies.[40,42,48,49,52,53,56,59,60,65,98 39,64,89,101,111,112] (Appendix D, Evidence Tables D7 and D8). The number of participants in each study ranged from 20 to 300. The duration of assessment ranged from 4 months to 6 years. The majority of the studies used a single allergen for immunotherapy; dust mite was the most commonly used allergen. Methods of assessing medication consumption varied across studies. Some studies reported calculated scores, with different scoring scales across studies. Other measures of asthma medication consumption include number of days during which medications were used,[53] proportion of subjects who did not use bronchodilators,[59] comparison of number of subjects who were improved, unchanged, or deteriorated, [64] number of patients taking medications,[98] amount of medication used per week,[60] and sum of daily medication doses.[111]

Twelve studies reported medication scores for asthma alone.[40,42,48,49,52,53,56,59,60,64,65,98] The most prevalent single allergen studied was dust mite in six studies.[52,53,56,59,60,98] Eight studies compared subcutaneous immunotherapy to placebo,[48,49,56,59,60,64,65,98] three studies compared subcutaneous immunotherapy to pharmacotherapy,[40,42,53] and one study compared it to a control group which did not receive immunotherapy.[52] Two placebo controlled studies; one of dust mite allergy[98] and one of rye pollen allergy[49] did not report results of relevant statistical analyses.

Eight studies reported results from direct comparisons between the immunotherapy group and the comparison group.[40,42,48,52,53,56,64,65] Of these, 3 reported a significant difference in medication consumption in favor of the immunotherapy group when compared with pharmacotherapy[40,53] or a control group.[52] The allergens investigated by these studies included

dust mite in all 3 studies [40,52,53] as well as parietaria and ryegrass pollen in one study.[40] The remaining 5 studies found no significant difference in medication use between the immunotherapy group and the comparison groups. This included 4 placebo controlled studies investigating ragweed,[48] dust mite,[56] *Cladosporium*,[64] and multiple allergens,[65] and one study investigating birch pollen allergy which a comparison group that was treated with nasal steroids.[42] One study demonstrated significant reduction in medication use in both the immunotherapy and placebo groups after treatment, with no difference between groups.[65]

Only the results of post-treatment compared with pre-treatment measures were reported by 2 placebo-controlled studies; both studied dust mite immunotherapy and demonstrated significant improvement in medication consumption only in the immunotherapy groups.[59,60] These 12 studies reporting asthma medication consumption included 1062 participants. The overall strength of evidence is high grade that subcutaneous immunotherapy reduces asthma medication use (Table 4).

Table 4. Body of evidence for subcutaneous immunotherapy affecting asthma medication scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Maestrelli 2004 [59]	Dust mite	SCIT Placebo	95	Medium	+	Direct	Weak
Olsen 1997[60]	Dust mite	SCIT Placebo	31	Low	+	Direct	Moderate
Pichler 1996[98]	Dust mite	SCIT Placebo	30	Medium	-	Direct	Moderate
Wang, 2006[56]	Dust mite	SCIT Placebo	132	Low	+	Direct	Strong
Bousquet 1988[52]	Dust mite	SCIT Control(No SIT)	150	Medium	+	Direct	Strong
Pifferi 2002[53]	Dust mite	SCIT Pharmacotherapy	29	Medium	+	Direct	Strong
Creticos 1996[48]	Ragweed	SCIT Placebo	90	Medium	+	Direct	Weak
Hill 1982[49]	Rye grass	SCIT Placebo	20	High	+	Direct	Moderate
Rak 2001/ 2005[42]	Birch	SCIT Pharmacotherapy	41	Medium	NR	Direct	Could not determine*
Malling 1986[64]	*Cladosporium*	SCIT Placebo	23	High	NR	Direct	Could not determine*
Adkinson 1997[65]	Multiple	SCIT Placebo	121	Low	+	Direct	Weak
Cantani 1997[40]	Multiple (dust mite, *Parietaria*, rye grass)	SCIT Pharmacotherapy	300	High	+	Direct	Could not determine*

+ = positive; NR = not reported; SCIT = subcutaneous immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Five studies reported asthma plus rhinoconjunctivitis medication scores, each investigating a different allergen; these included three studies that investigated pollen immunotherapy[39,89,101] and two studies investigated mold immunotherapy.[111,112] Studies ranged from 30 to 50 participants. The single study which compared immunotherapy with pharmacotherapy had a high risk of bias.[39] All five studies demonstrated a significant reduction in asthma and rhinoconjunctivitis medication consumption in the immunotherapy group when compared with the comparison

groups. The immunotherapy group experienced a 14 to 83 percent greater reduction in combined asthma and rhinoconjunctivitis medication consumption than the comparison group. These five studies reporting combined asthma plus rhinoconjunctivitis medication scores included 203 participants. The overall strength of evidence is high that subcutaneous immunotherapy reduces asthma and rhinoconjunctivitis medication consumption (Table 5).

Table 5. Body of evidence for subcutaneous immunotherapy affecting asthma plus rhinitis/rhinoconjunctivitis medication scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Ariano 2006[39]	*Parietaria*	SCIT Pharmaco-therapy	30	High	+	Direct	Strong
Arvidsson 2002/ 2004[89]	Birch	SCIT Placebo	49	Medium	+	Direct	Could not determine*
Nouri-Aria 2003[101]	Timothy	SCIT Placebo	44	Low	+	Direct	Strong
Dreborg 1986[111]	*Cladosporium*	SCIT Placebo	30	Low	+	Direct	Weak
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong

+ = positive; SCIT = subcutaneous immunotherapy

*Not enough data were provided in the article to calculate the magnitude of effect.

Combined Asthma Symptom and Medication Scores

In contrast to the larger number of studies reporting individual symptom scores or medication scores, only six asthma studies reported combined asthma symptom-medication scores[41,50,64,95,109,112] (Appendix D, Evidence Tables D7 and D8). The number of participants in each study ranged from 23 to 50. The duration of assessment ranged from 5 months to 3 years. Five were placebo-controlled studies, and all five studies demonstrated significant improvement in the immunotherapy group compared with placebo[50,64,95,109,112] These included two studies of *Alternaria,* one with low risk of bias[95] and the other with moderate risk of bias[112]; one study of cat allergen with moderate risk of bias;[109] and studies of *Cladosporium*[64] and dust mite allergen[50] with high risk of bias. One study, with high risk of bias, compared subcutaneous immunotherapy with dust mites to pharmacotherapy.[41] After a seven-month treatment, there was more reduction of the symptom-medication scores in the immunotherapy group than the pharmacotherapy group; however, this difference was not statistically significant.[41] Fifty percent of the studies did not report the magnitude of effect.

Overall, these six studies reporting asthma symptom-medication scores included 196 participants. The strength of evidence is low to support that subcutaneous immunotherapy improves asthma symptom-medication scores (Table 6).

Akmanlar et al. compared rush immunotherapy with conventional immunotherapy. They observed a significant reduction in symptom-medication scores in both study groups after 3 years of immunotherapy, but there was no significant difference in scores between the two groups.[97] This study was not included for grading the evidence because both treatment groups received immunotherapy.

Table 6. Body of evidence for subcutaneous immunotherapy affecting combined asthma symptom-medication scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Altintas 1999[50] **	Dust mite	SCIT-Adsorbed Al SCIT-Adsorbed Ca SCIT-aqueous Placebo	35	High	+	Direct	Strong
Garcia-Ortega 1993[41]	Dust mite	SCIT Pharmacotherapy	36	High	+	Direct	Strong
Horst 1989[95]	*Alternaria*	SCIT Placebo	24	Low	+	Direct	Could not determine*
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong
Alvarez-Cuesta 1994[109]	Cat	SCIT Placebo	28	Medium	+	Direct	Could not determine*
Malling 1986[64]	*Cladosporium*	SCIT Placebo	23	High	+	Direct	Could not determine*

+ = positive; Al = Aluminum; Ca = Calcium; SCIT = subcutaneous immunotherapy

*Not enough data were provided in the article to calculate the magnitude of effect.

**Altintas: 3 subcutaneous immunotherapy groups were treated with different types of extract (aluminum adsorbed, calcium adsorbed, and aqueous extracts). All subcutaneous immunotherapy groups demonstrated significant improvement over placebo. There was no significant difference when active subcutaneous immunotherapy groups were compared with each other. The group that received aluminum adsorbed extract demonstrated the greatest improvement in symptom-medication scores. For evidence grading, we used only the relevant comparison, i.e. subcutaneous immunotherapy versus placebo. When each subcutaneous immunotherapy arm was compared against placebo, there was a strong positive effect in favor of subcutaneous immunotherapy.

Pulmonary Function Testing

Thirteen asthma studies, including 1,024 participants, reported changes in pulmonary function test results; these included peak expiratory flow (PEF) or peak flow in 12 studies,[38,42,48,56,58,59,61,65,89,91,110,111] forced expiratory volume 1 (FEV1) in 2 studies,[52,56] and forced vital capacity (FVC) in 1 study[56] (Appendix D, Evidence Table D10). Risk of bias was low for 2 studies[65,111] and medium for 11 studies.[38,42,48,52,56,58,59,61,89,91,110] Study duration ranged from 3 months to 3 years.

Nine studies (82%) compared subcutaneous immunotherapy to placebo.[48,56,61,65,89,91,110,111] Only one, with a moderate risk of bias, demonstrated a statistically significant improvement in mean daily PEF in the immunotherapy group compared with the placebo group; the magnitude of this effect was small.[48] Another placebo-controlled trial with low risk of bias demonstrated a small treatment effect in favor of immunotherapy (with a mean difference of 3.8% points in the predicted value of PEF), and this approached statistical significance.[65] Three placebo controlled trials demonstrated significant improvement in PEF in the immunotherapy group comparing the post-treatment to pre-treatment measures.[56,59,110] However, two of these also demonstrated significant improvement in the placebo group after treatment.[56,110] One study compared subcutaneous immunotherapy to bronchodilators;[58] treatment significantly improved PEF only in the immunotherapy group. Another study comparing subcutaneous immunotherapy to nasal steroids found no difference between the two groups after six weeks of treatment.[42] Tabar et al. compared pre- and post-immunotherapy data for a group using a cluster schedule to a group using a conventional schedule; both groups demonstrated significant reduction in PEF variability after one year of immunotherapy.[38]

Among the studies that evaluated FEV_1 and or FVC, one trial which compared subcutaneous immunotherapy with a control group that did not receive immunotherapy, observed that immunotherapy produced a 20 percent increase in FEV1 when compared with the control group.[52] The other study found no significant change in FEV1 or FVC in either the immunotherapy or placebo group after treatment.[56] As described in the methods, we did not grade the strength of evidence for pulmonary function test results because it is an indirect outcome measure.

Bronchial Reactivity

Twenty-five asthma studies (76%) evaluated bronchial airway reactivity. Bronchial reactivity was evaluated by two methods: specific allergen bronchial provocation tests and nonspecific chemical bronchial provocation. The majority of the studies that performed nonspecific chemical bronchial provocation tests used methacholine and/or histamine, with the exception of one study which also used adenosine 5'-monophosphate (AMP)[94] (Appendix D, Evidence Table D11).

Specific allergen bronchoprovocation tests were reported in 17 studies, which included 514 participants. Of 15 studies that reported pre- versus post-treatment differences, 11 studies (73%) demonstrated significant decreases in bronchial sensitivity in favor of subcutaneous immunotherapy.[41,48,50,51,60,62,89,91,100,109,111] Four trials showed no statistically significant difference between the immunotherapy group and the comparison group.[54,61,63,97] Two studies reported only the pre- and post-treatment comparison.[55,58] Kohno et al. demonstrated a significant decrease in bronchial sensitivity in the immunotherapy group and not the comparison group.[58]

Nonspecific chemical bronchoprovocation tests were reported in 16 studies, which included 750 participants.[41,42,53,54,56,58,59,61,62,65,89,94,98,100,101,109] One study did not report relevant statistical comparisons.[89] Of 11 studies that reported comparisons with the comparison group,[41,42,53,54,56,62,65,94,98,100,101] only two demonstrated a significant decrease in bronchial sensitivity in favor of subcutaneous immunotherapy.[53,101] Nine studies found no significant difference between the immunotherapy group and the comparison group.[41,42,54,56,62,65,94,98,100] In the study by Hedlin et al, both groups were treated with some form of immunotherapy.[100]

Four studies reported only pre- versus post-treatment comparisons.[58,59,61,109] Only one of these studies demonstrated a significant improvement in bronchial sensitivity in the immunotherapy group after treatment; there was no significant change in the comparison group (which received bronchodilators).[58] We did not grade the strength of evidence for bronchial reactivity because it is an indirect outcome measure.

Summary of Evidence

Table 7 summarizes the studies and the strength of evidence for subcutaneous immunotherapy and asthma outcomes.

Table 7. Key Question 1: Summary of studies and strength of evidence for subcutaneous immunotherapy and asthma outcomes

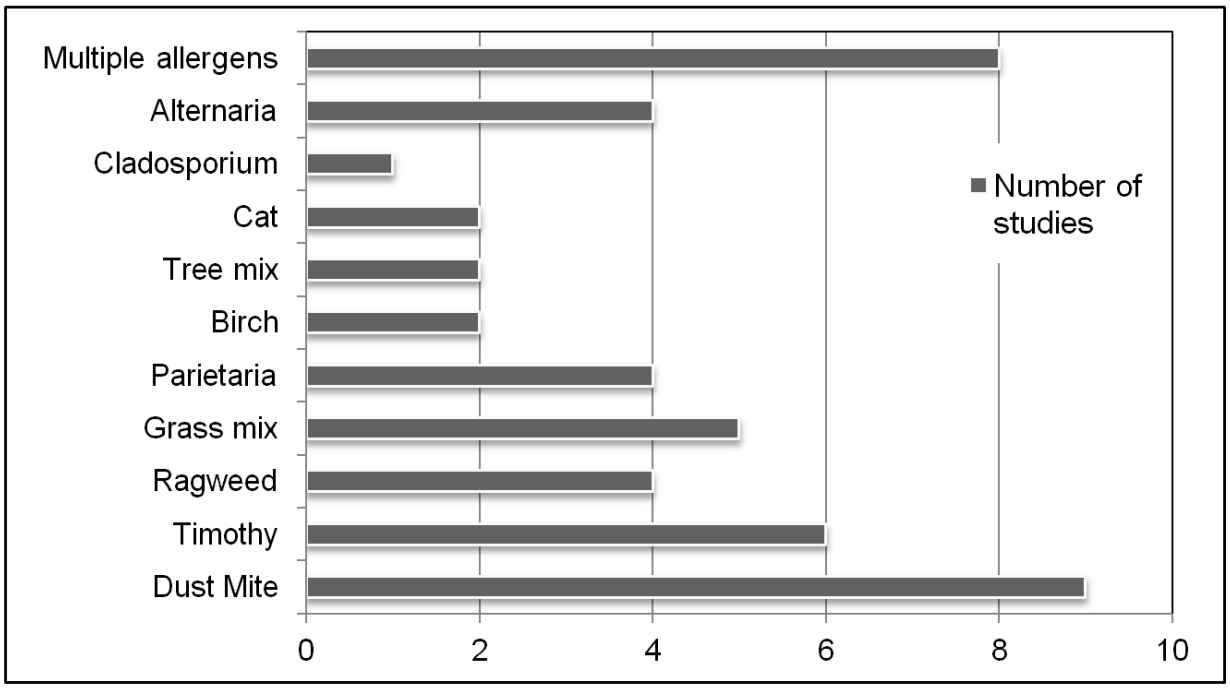
Outcome	Number of Studies/ Number of Participants	Risk of Bias	Direction of change	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Asthma Symptoms	16 / 1178	3 high 7 medium 6 low	14 positive 2 negative	Consistent	Direct	6 strong 6 moderate 1 weak 3 CND	2 studies with low RofB AND strong magnitude	High
Asthma plus Rhinitis/ Rhinoconjunctivitis Symptom Scores	5 / 175	1 high 2 medium 2 low	5 positive	Consistent	Direct	2 strong 1 moderate 2 CND	1 study with low RofB and moderate magnitude and 1 with medium RofB and strong magnitude	Moderate
Asthma Medication Scores	12 / 1062	3 high 6 medium 3 low	9 positive 1 negative 2 NR	Consistent	Direct	3 strong 3 moderate 3 weak 3 CND	3 studies with low RofB, 1 of which has strong magnitude	High
Asthma plus Rhinitis/ Rhinoconjunctivitis Medication Scores	5 / 203	1 high 2 medium 2 low	5 positive	Consistent	Direct	3 strong 1 weak 1 CND	2 studies with low RofB, 1 of which has strong magnitude	High
Asthma or Asthma plus Rhinitis Combined Symptom-Medication Scores	6 / 196	3 high 2 medium 1 low	5 positive 1 NR	Consistent	Direct	3 strong 3 CND	1 study with medium RofB AND strong magnitude 2 studies with high RofB AND strong magnitude 3 studies with insufficient data regarding magnitude of effect and/or direction of change	Low

CND = could not determine; NR = not reported; RofB = risk of bias

Evidence for the Efficacy and Effectiveness of Subcutaneous Immunotherapy in the Treatment of Rhinitis and Rhinoconjunctivitis

In this section we report findings from the 74 references that investigated the safety and efficacy of subcutaneous immunotherapy in the treatment of rhinitis and rhinoconjunctivitis. Figure 10 shows the distribution of allergens in the studies included.

Figure 10. Subcutaneous immunotherapy studies by type of allergen in rhinitis/rhinoconjunctivitis



Key Points

Relative to a control group:

- High grade evidence supports that subcutaneous immunotherapy improves rhinitis/rhinoconjunctivitis symptoms, based on 26 randomized controlled trials with 1764 subjects.
- High grade evidence supports that subcutaneous immunotherapy improves conjunctivitis symptoms, based on 14 randomized controlled trials with 1104 subjects.
- High grade evidence supports that subcutaneous immunotherapy improves control of combined nasal, ocular, and bronchial symptoms, based on six randomized controlled trials with 591 subjects.
- Moderate grade evidence supports that subcutaneous immunotherapy decreases rhinitis/rhinoconjunctivitis medication use, based on ten randomized controlled trials with 564 subjects
- High grade evidence supports that subcutaneous immunotherapy decreases combined medication use (rhinitis/rhinoconjunctivitis plus asthma medication use), based on 11 randomized controlled trials with 768 subjects.
- Low grade evidence supports that subcutaneous immunotherapy improves rhinitis/rhinoconjunctivitis (with or without asthma) combined symptom-medication scores, based on six randomized controlled trials with 400 subjects.

- High grade evidence supports that subcutaneous immunotherapy improves disease-specific quality of life, based on six randomized controlled trials with 889 subjects.

Rhinitis/Rhinoconjunctivitis Symptoms

Rhinitis/rhinoconjunctivitis symptom scores were reported in 30 studies.[32,37,42,48,61,66,69,70,72,73,75-77,81-86,96,98,99,101-103,106,108,111-113]

Rhinitis/rhinoconjunctivitis symptom scores were included from studies that enrolled patients with rhinitis/rhinoconjunctivitis with or without asthma. Thirteen studies exclusively examined patients with a primary diagnosis of rhinitis/rhinoconjunctivitis.[37,66,69,70,72,73,75,76,81-84,86] Five studies examined patients with rhinitis/rhinoconjunctivitis and asthma, although the studies did not meet criteria for inclusion with the asthma studies,[77,96,102,106,108] findings from these studies are reported in this section. An additional six studies that met our criteria for inclusion with the asthma studies enrolled patients with asthma and rhinitis/rhinoconjunctivitis.[42,98,99,101,111,112] Combined outcome data from these latter six studies were previously reported with other asthma studies. Lastly, two studies of patients with asthma also described their rhinitis/rhinoconjunctivitis symptom scores[48,61] (Appendix D, Evidence Table D12). Four included studies were not graded because all study groups received immunotherapy.[32,85,103,113]

Four studies reported combined nasal and ocular symptoms.[76,82,101,114] while two studies reported unspecified nasal symptom scores[69,108] The scales used to report nasal and ocular symptoms varied across studies. Two studies used visual analog scores,[84,112] one examined the time to increase in nasal symptoms after allergen exposure,[61] while the remainder used numeric systems to score the severity and presence or absence of nasal or nasal and ocular symptoms. The number of participants in each study ranged from 17 to 410 and the duration of follow-up ranged from 1 month to 3 years, with the majority of studies reporting symptoms at 12 months. While one study compared a group receiving subcutaneous immunotherapy to a group of patients receiving nasal steroids,[42] the remainder used a placebo control group.

Nineteen studies (73%) reporting rhinitis/rhinoconjunctivitis symptom scores demonstrated statistically significant improvement in rhinitis/rhinoconjunctivitis symptoms with subcutaneous immunotherapy. Eighteen of these studies compared subcutaneous immunotherapy with placebo while one compared subcutaneous immunotherapy with patients receiving only nasal steroids.[42] One of the studies[81] showed a difference only with the high dose of immunotherapy, while at the lowest dose it showed no statistical difference when compared with placebo. The remaining six studies did not show significant improvement in symptoms relative to placebo treated subjects.[61,70,72,83,102,114]

Majority of the studies used a single allergen for immunotherapy. The most common single allergens used in the rhinitis/rhinoconjunctivitis scores were Timothy grass in four studies,[70,77,81,101] and dust mite allergens in four studies.[72,73,98,99] Of these studies, three (75%) evaluating Timothy Grass[77,81,101] and two (50%) evaluating dust mites[98,99] demonstrated significant improvement in rhinitis/rhinoconjunctivitis symptom control.

Overall, 25 RCTs reported rhinitis/rhinoconjunctivitis symptom scores in 1734 participants. The overall strength of evidence is high to support that subcutaneous immunotherapy improves rhinitis/rhinoconjunctivitis symptoms (Table 8).

Table 8. Body of evidence for subcutaneous immunotherapy affecting rhinitis/rhinoconjunctivitis symptom scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Nouri-Aria 2003[101]	Timothy	SCIT Placebo	44	Low	+	Direct	Moderate
Varney 1991[77]	Timothy	SCIT Placebo	40	Medium	+	Direct	Strong
Frew 2006[81]	Timothy	SCIT high SCIT low Placebo	410	Low	+	Direct	Moderate
Durham 1999[70]	Timothy	SCIT continuous SCIT discontinuous No treatment	32	High	+	Direct	Strong
Pichler 1996[98]	Dust mites	SCIT Placebo	30	Medium	+	Direct	Strong
Varney 2003[99]	Dust mites	SCIT Placebo	36	Low	+	Direct	Strong
Junqueira de Queiros 2008[72]	Dust mite	SCIT Placebo	50	Medium	+	Direct	Weak
McHugh 1990[73]	Dust mite	SCIT- purified SCIT- crude Placebo	80	Medium	+	Direct	Strong
Bernstein 1976[76]	Short ragweed	SCIT Placebo	148	High	+	Direct	Moderate
Creticos 1996[48]	Short ragweed	SCIT Placebo	90	Medium	+	Direct	Moderate
Mirone 2004[102]	Short ragweed	SCIT Placebo	32	Low	+	Direct	Strong
Crimi 2004[75]	*Parietaria*	SCIT Placebo	30	Low	+	Direct	Strong
Polosa 2004[66]	*Parietaria*	SCIT Placebo	30	Low	+	Direct	Strong
Leynadier 2000[83]	Grass mix	SCIT Placebo	29	Medium	+	Direct	Weak
Zenner. 1996[86]	Grass mix	SCIT Placebo	86	Medium	+	Direct	Moderate
Rak 2001[42]	Birch	SCIT Nasal steroid	41	Medium	-	Direct	Weak
Tabar 2007[96]	*Alternaria*	SCIT Placebo	28	Low	-	Direct	Weak
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong
Ohman 1984[61]	Cat	SCIT Placebo	17	Medium	NR	Direct	Could not determine*
Möller 2002[84] Niggeman 2006[115]	Grass/ Birch	SCIT Placebo	205	Medium	+	Direct	Moderate
Ariano 1997[69]	Cypress/ Cedar	SCIT Placebo	20	Medium	+	Direct	Strong

Table 8. Body of evidence for subcutaneous immunotherapy affecting rhinitis/rhinoconjunctivitis symptom scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Klimek 1999[37]	Grass/ Tree mix	SCIT Pharmaco-therapy	48	Medium	+	Direct	Strong
Dolz 1996[108]	Timothy, Orchard, Ryegrass	SCIT Placebo	28	Medium	+	Direct	Strong
Bousquet 1991[106]	Orchard, Olive, *Parietaria*	SCIT grass Placebo grass SCIT multiple Placebo multiple	70	Medium	+	Direct	Strong
Frostad 1983[82]	Timothy/ Grass mix	SCIT- purified SCIT- crude SCIT mix Placebo	60	Medium	+	Direct	Strong

+ = positive; - = negative; NR = not reported; SCIT = subcutaneous immunotherapy
*Not enough data were provided in the article to calculate the magnitude of effect.

Conjunctivitis Symptoms

Fifteen subcutaneous immunotherapy studies reported conjunctivitis symptom scores (Appendix D, Evidence Table D13). The comparator in all studies reporting conjunctivitis scores was placebo, except for one study that was not included in grading because all study groups received immunotherapy.[103] Most studies used numeric scales to quantify symptoms, except for one study,[61] which evaluated the time to see an increase in ocular symptoms upon exposure to cat allergen, and two other studies, which used a visual analog score.[84,112]

Studies that used numeric scales were inconsistent across studies. The duration of assessment varied from 10 weeks to 5 years.

Six studies demonstrated significant improvement in conjunctivitis symptom scores when compared with placebo.[77,101,112,81,84,88] The remaining studies did not show significant improvement in conjunctivitis symptom scores. Again the most commonly evaluated allergen was Timothy Grass, and three out of five studies (60%) showed significant improvement in conjunctivitis symptoms.

Fourteen subcutaneous immunotherapy trials reported conjunctivitis scores and included 1104 subjects. The majority of the studies used a single allergen for immunotherapy. The overall strength of evidence is high to support that subcutaneous immunotherapy improves allergic conjunctivitis symptoms (Table 9).

Table 9. Body of evidence for subcutaneous immunotherapy affecting conjunctivitis symptoms

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Varney 1991[77]	Timothy	SCIT Placebo	40	Medium	+	Direct	Strong
Nouri-Aria 2003[101]	Timothy	SCIT Placebo	44	Low	+	Direct	Strong
Frew 2006[81]	Timothy	SCIT high SCIT low Placebo	410	Low	+	Direct	Moderate
Durham 1999[70]	Timothy	SCIT continuous SCIT discontinuous No treatment	32	High	+	Direct	Strong
Leynadier 2000[83]	Grass Mix	SCIT Placebo	29	Medium	+	Direct	Weak
Zenner. 1996[86]	Grass Mix	SCIT Placebo	86	Medium	+	Direct	Weak
Tabar 2007[96]	*Alternaria*	SCIT Placebo	28	Low	-	Direct	Weak
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong
Dreborg 1986[111]	*Cladosporium*	SCIT Placebo	30	Low	+	Direct	Moderate
Ferrer 2005[88]	*Parietaria*	SCIT Placebo	57	Medium	+	Direct	Moderate
Ohman 1984[61]	Cats	SCIT Placebo	17	Medium	+	Direct	Moderate
Klimek 1999[37]	Grass/ Tree mix	SCIT Pharmacotherapy	48	Medium	+	Direct	Strong
Möller 2002[84] Niggeman 2006[115]	Grass/ Birch	SCIT Placebo	205	Medium	+	Direct	Moderate
Dolz 1996[108]	Timothy, Orchard, Ryegrass	SCIT Placebo	28	Medium	+	Direct	Strong

+ = positive; - = negative; SCIT = subcutaneous immunotherapy

Control of Combined Symptom Scores (Nasal, Ocular, and Bronchial)

Eight rhinitis/rhinoconjunctivitis studies reported combined scores including nasal, ocular, and bronchial symptom scores (Appendix D, Evidence Table D12). Study size ranged from 28 to 410 subjects. Although many of these patients did not have an objective diagnosis of asthma, they did have bronchial symptoms at baseline. Combined symptom scores from primary asthma studies that met our criteria are reported in the subcutaneous immunotherapy asthma section. The total symptom scores used numeric scales that were not validated and varied between studies. All graded studies compared subcutaneous immunotherapy with placebo. Two studies were not graded because all study groups received immunotherapy.[87,92]

Three studies showed significant improvement in combined symptom scores for nasal, ocular, and bronchial symptoms when compared with placebo,[81,99,104] and one in the comparison of post-treatment symptoms to pre-treatment symptoms.[99]

Six trials reported symptoms in 591 individuals. The strength of evidence is high to support that subcutaneous immunotherapy improves combined (nasal, ocular, bronchial) symptoms scores (Table 10).

Table 10. Body of evidence for subcutaneous immunotherapy affecting bronchial, nasal and ocular combined symptoms scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Weyer 1981[105]	Grass mix	SCIT Placebo	33	High	+	Direct	Moderate
Walker 2001[79]	Grass mix	SCIT Placebo	44	Low	+	Direct	Strong
Frew 2006[81]	Timothy	SCIT high SCIT low Placebo	410	Low	+	Direct	Moderate
Pence 1975[104]	Mountain cedar	SCIT Placebo	40	Medium	+	Direct	Strong
Tabar 2007[96]	*Alternaria*	SCIT Placebo	28	Low	-	Direct	Weak
Varney 2003[99]	Dust mites	SCIT Placebo	36	Low	+	Direct	Strong

+ = positive; - = negative; SCIT = subcutaneous immunotherapy

Medication Scores (Including Combined Medication Scores)

Rhinitis/rhinoconjunctivitis medication scores were reported in 13 of the subcutaneous immunotherapy studies as were combined medication scores (including rhinitis/rhinoconjunctivitis and asthma medications) (Appendix D, Evidence Tables D15 and D16). Three of the included studies were not graded since because all study groups received immunotherapy.[32,73,82] The 10 graded studies used some type of numeric scoring scale for medication use, but these were inconsistent across studies. The duration of assessment of medication use ranged from 3 months to 3 years. Studies that reported only on rhinitis/rhinoconjunctivitis medications included oral antihistamines and intranasal corticosteroids, while those trials that described combined medication scores, included those used by patients with asthma and rhinitis/rhinoconjunctivitis, including inhaled beta agonists and oral corticosteroids.

Seven trials (70%) reporting rhinitis/rhinoconjunctivitis medication scores demonstrated significant improvement with subcutaneous immunotherapy.[37,73,76,77,82,83,88] In six of these, the comparator group was placebo; one study compared treatment with immunotherapy with pharmacotherapy treatment.[37] Of the two Timothy Grass allergen studies that reported medication scores,[70,77] only one study showed improvement with immunotherapy.[77] Similarly, of the three dust mite allergen trials,[72,73,113] two demonstrated significant improvement with subcutaneous immunotherapy compared with placebo.[73,113]

Ten RCTs reported medication scores in 564 participants. The overall strength of evidence is moderate to support that subcutaneous immunotherapy decreases medication use for rhinitis/rhinoconjunctivitis (Table 11).

Table 11. Body of evidence for subcutaneous immunotherapy affecting medication use (rhinitis/rhinoconjunctivitis medications)

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Junqueira de Queiros 2008[72]	Dust mite	SCIT Placebo	50	Medium	+	Direct	Moderate
McHugh 1990[73]	Dust mite	SCIT- purified SCIT- crude Placebo	80	Medium	+	Direct	Strong
Varney 1991[77]	Timothy	SCIT Placebo	40	Medium	+	Direct	Strong
Durham 1999[70]	Timothy	SCIT continuous SCITdiscontinuous No treatment	32	High	+	Direct	Strong
Bernstein 1976[76]	Short ragweed	SCIT Placebo	148	High	+	Direct	Moderate
Ferrer 2005[88]	*Parietaria*	SCIT Placebo	57	Medium	+	Direct	Strong
Leynadier 2000[83]	Grass Mix	SCIT Placebo	29	Medium	+	Direct	Strong
Ariano 1997[69]	Cypress/ Cedar	SCIT Placebo	20	Medium	+	Direct	Weak
Klimek 1999[37]	Grass/ Tree Mix	SCIT Pharmacotherapy	48	Medium	+	Direct	Strong
Frostad 1983[82]	Timothy/ Grass Mix	SCIT- purified SCIT- crude SCIT mix Placebo	60	Medium	+	Direct	Strong

+ = positive; - = negative; SCIT = subcutaneous immunotherapy

Twelve studies reported pooled asthma and rhinitis/rhinoconjunctivitis medication scores. Eleven studies were graded excluding one study where all arms received immunotherapy[92] Among the graded studies that reported pooled asthma and rhinitis/rhinoconjunctivitis medication scores, ten of the eleven studies demonstrated significant improvement from subcutaneous immunotherapy when compared with placebo or when comparing medication use after treatment to a pre-treatment period[66,75,77,79,81,88,96,102,105,108] (Appendix D, Evidence Table D17). Three *Parietaria* studies reported significant improvement in combined medication scores when compared with placebo.[66,75,88] Two Timothy Grass studies also reported significant improvement in combined medication scores when compared with placebo.[77,81]

Thus, eleven trials reported medication scores in 768 participants. The strength of evidence is high to support that subcutaneous immunotherapy decreases combined medication use (Table 12).

Table 12. Body of evidence for subcutaneous immunotherapy affecting asthma and rhinitis/rhinoconjunctivitis medication use

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Crimi 2004[75]	*Parietaria*	SCIT Placebo	30	Low	+	Direct	Strong
Polosa 2004[66]	*Parietaria*	SCIT Placebo	30	Low	+	Direct	Strong
Ferrer 2005[88]	*Parietaria*	SCIT Placebo	57	Medium	+	Direct	Strong
Mirone 2004[102]	Ragweed	SCIT Placebo	32	Low	+	Direct	Strong
Varney 1991[77]	Timothy	SCIT Placebo	40	Medium	+	Direct	Strong
Frew 2006[81]	Timothy	SCIT high SCIT low Placebo	410	Low	+	Direct	Moderate
Weyer 1981 [105]	Grass mix	SCIT Placebo	33	High	+	Direct	Strong
Varney 2003[99]	Dust mite	SCIT Placebo	36	Low	+	Direct	Weak
Tabar 2007[96]	*Alternaria*	SCIT Placebo	28	Low	-	Direct	Strong
Dolz 1996[108]	Timothy, Orchard, Ryegrass	SCIT Placebo	28	Medium	+	Direct	Strong
Walker 2001[79]	Grass mix	SCIT Placebo	44	Low	+	Direct	Strong

+ = positive; - = negative; SCIT = subcutaneous immunotherapy.

Combined Symptom-Medication Scores

Twelve studies reported combined rhinitis/rhinoconjunctivitis symptoms plus medication scores. The six studies where all study groups received immunotherapy were not graded.[32,38,71,78,93,103] All of the studies used some type of numeric scoring scale for the combination score, but these were inconsistent across studies. The duration of assessment of medication use ranged from one pollen season up to 3 years (Appendix D, Evidence Table D17).

In five studies, nasal, ocular, and bronchial symptoms were scored in addition to medication use, specifically beta agonist, oral and nasal steroid, and antihistamine use.[80,96,105,107,112] Only nasal and ocular symptoms were reported along with nasal corticosteroids and antihistamines in one study.[67]

Five of the six studies that reported a combination symptom plus medication score demonstrated significant improvement with subcutaneous immunotherapy. The remainder of studies compared subcutaneous immunotherapy with placebo.

Six trials reported combined symptom plus medication scores in 400 participants. The overall strength of evidence is low to support that subcutaneous immunotherapy improves combination symptoms plus medication scores (Table 13).

Table 13. Body of evidence for subcutaneous immunotherapy affecting combined rhinitis (with or without asthma) symptom-medication scores

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Van Metre 1980[67]	Ragweed	SCIT Placebo	39	Medium	+	Direct	Moderate
Van Metre 1981[68]	Ragweed	SCIT Placebo	44	High	-	Direct	Could not determine*
Weyer 1981[105]	Grass mix	SCIT Placebo	33	High	+	Direct	Strong
Shamji, 2012 [80]	Grass mix	SCIT 100,000 SCIT 10,000 Placebo	221	Medium	+	Direct	Moderate
Tabar 2007[96]	*Alternaria*	SCIT Placebo	28	Low	-	Direct	Weak
Chakraborty 2006[107]	Date trees	SCIT Placebo	35	Medium	+	Direct	Strong

+ = positive; - = negative; SCIT = subcutaneous immunotherapy
*Not enough data were provided in the article to calculate the magnitude of effect.

Quality of Life

Quality of life was reported in eight placebo-controlled trials.[40,79,81,88,96,112,113] The instruments used to assess quality of life were validated, disease-specific instruments: the Rhinoconjunctivitis Quality of Life questionnaire (RQLQ, Adult, Pediatric, Adolescent, and Japanese language version) and/or the Short Form 36 questionnaire (SF-36) (Appendix D, Evidence Table D18).

Four of the six studies reported significant improvement in disease-specific quality of life when compared with placebo.[79,81,96,112] The other two studies found no overall improvement.[40,88]

Six studies with 889 subjects included quality of life outcomes. Two studies were not graded because all study groups received immunotherapy. [93,113] The evidence is high to support that subcutaneous immunotherapy improves disease-specific quality of life among individuals with rhinitis/rhinoconjunctivitis (Table 14).

Table 14. Body of evidence for rhinitis/rhinoconjunctivitis (with or without asthma) quality-of-life scores after subcutaneous immunotherapy rhinitis

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Tabar 2007[96]	*Alternaria*	SCIT placebo	28	Low	+	Direct	Strong
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong
Frew 2006[81]	Timothy	SCIT high SCIT low Placebo	410	Low	+	Direct	Strong
Ferrer 2005[88]	*Parietaria*	SCIT placebo	57	Medium	+	Direct	Could not determine*
Cantani 1997[40]	Dust Mites, Grass, Weeds	SCIT Pharmacotherapy	300	High	+	Direct	Could not determine*
Walker 2001[79]	Grass Mix	SCIT Placebo	44	Low	+	Direct	Strong

+ = positive; SCIT = subcutaneous immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Nasal and Ocular Allergen Challenge (Provocation)

Seventeen subcutaneous immunotherapy studies challenged subjects to specific allergens in order to quantify nasal and ocular symptoms (Appendix D, Evidence Table D19). Seven studies used nasal provocation.[33,69,73,83,95,106,112] Ten studies used conjunctival provocation tests;[63,85,87,89,90,98,109-111,115] for two of these studies, both treatment groups received SCIT.[85,87] Four of the seven nasal challenge studies (57%) reported significant improvement in symptoms after subcutaneous immunotherapy compared with placebo or when comparing post-treatment to pre-treatment response.[73,95,106,112] Six of the conjunctival provocation studies (60%) demonstrated significant improvement in symptoms after subcutaneous immunotherapy compared with placebo or with comparison of post-treatment to pre-treatment response.[63,90,98,109,110,115]

Secondary Outcomes

Few studies evaluated secondary outcomes such as biomarkers or asthma prevention. There is insufficient data about the effect of subcutaneous immunotherapy on these secondary outcomes. (Appendix D, Evidence Tables D20 and D21).

Summary of Evidence

Table 15 summarizes the studies and the strength of evidence for subcutaneous immunotherapy and rhinitis/rhinoconjunctivitis outcomes.

Table 15. Key Question 1: Summary of studies and strength of evidence for subcutaneous immunotherapy and rhinitis/rhinoconjunctivitis outcomes

Outcome	Number of Studies/ Number of Participants	Risk of Bias	Direction of change	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Rhinitis/Rhino-conjunctivitis Symptoms	26 / 1764	2 high 16 medium 8 low	23 positive 2 negative 1 NR	Consistent	Direct	14 strong 6 moderate 5 weak 1 CND	5 studies with low RofB AND 4 of these with strong magnitude	High
Conjunctivitis Symptoms	14 / 1104	1 high 9 medium 4 low	13 positive 1 negative	Consistent	Direct	7 strong 4 moderate 3 weak	4 studies with low RofB AND 1 of these with strong magnitude 4 studies with medium RofB AND strong magnitude	High
Combined Symptom Score (Bronchial, Nasal, Ocular)	6 / 591	1 high 1 medium 4 low	5 positive 1 negative	Consistent	Direct	3 strong 2 moderate 1 weak	4 studies with low RofB AND 2 of these with strong magnitude	High
Rhinitis/Rhino-conjunctivitis Medication Use	10 / 564	2 high 8 medium	10 positive	Consistent	Direct	7 strong 2 moderate 1 weak	8 studies with medium RofB AND 6 of these with strong magnitude	Moderate
Asthma plus Rhinitis/Rhino-conjunctivitis Medication Use	11 / 768	1 high 3 medium 7 low	10 positive 1 negative	Consistent	Direct	9 strong 1 moderate 1 weak	7 studies with low RofB AND 4 of these with strong magnitude	High
Combined Rhinitis (with or without asthma) Symptom-Medication Scores	6 / 400	2 high 3 medium 1 low	4 positive 2 negative	Consistent	Direct	2 strong 2 moderate 1 weak 1 CND	3 positive studies with medium RofB AND only 1 has strong magnitude 2 studies with medium RofB AND moderate magnitude 1 negative study with low RofB AND weak magnitude	Low
Rhinitis/Rhino-conjunctivitis Quality of Life	6 / 889	1 high 2 medium 3 low	6 positive	Consistent	Direct	4 strong 2 CND	3 studies with low RofB AND strong magnitude	High

CND = could not determine; RofB = risk of bias

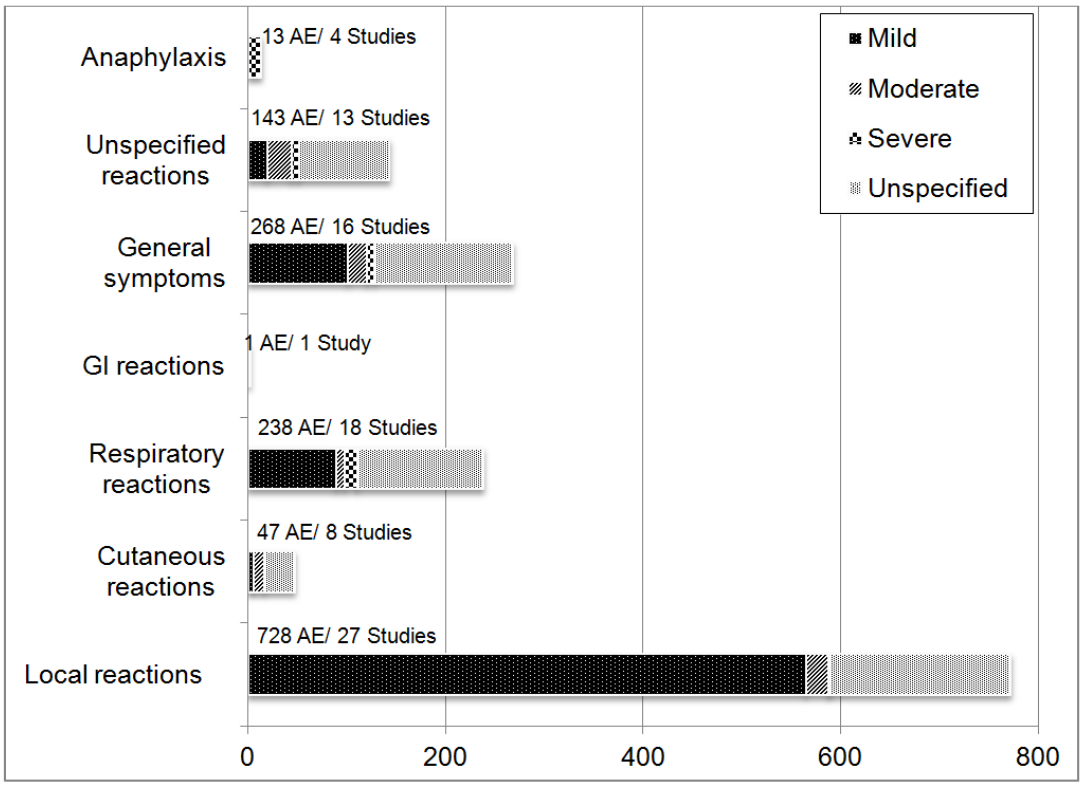
Key Question 2. What is the evidence for the safety of subcutaneous immunotherapy in patients with rhinitis/rhinoconjunctivitis and/or asthma?

Key Points

- Lack of a consistent reporting system and grading system for subcutaneous immunotherapy precluded pooling safety data across studies.
- Local reactions (occurring at the site of allergen administration) were most common but mild.
- Systemic reactions occurred less frequently. Of these, respiratory reactions were the most common and gastrointestinal symptoms were least frequent.
- Thirteen anaphylactic reactions were reported in four trials.
- No deaths were reported.

Figure 11 shows the distribution of adverse events by location and severity. The graph shows only adverse events reported in the Immunotherapy arms.

Figure 11. Subcutaneous immunotherapy safety data by location and severity



AE = adverse event; GI = gastrointestinal

Safety data reported in this systematic review includes only the randomized control trials that met the criteria for inclusion in the review. Not all studies reported safety data, and the lack of a consistent reporting system and grading system for the adverse outcomes made it impossible to pool safety data across studies.

Forty-five studies of subcutaneous immunotherapy reported safety data.[37,38,40,41,48,50,51,57,58,61-64,67,68,70-74,76,77,81,83,86,88,89,91,92,94-97,99-101,103,106-113] In this body of evidence, local reactions, reported in five percent to 58 percent of patients and 0.6 percent to 54 percent of injections, were more

common than systemic reactions. Most local reactions were mild. The most common systemic reactions were respiratory reactions, occurring in up to 46 percent of patients and up to 15 percent of injections. General symptoms (such as headache, fatigue, arthritis, anxiety) also occurred frequently and were reported to affect up to 44 percent of patients. Majority of the systemic reactions were either mild or unspecified. Gastrointestinal reactions, reported in only one study, were the least frequent reactions. Thirteen anaphylactic reactions were reported in four trials (Executive Summary, Table B; Appendix D, Evidence Table D 22).

Key Question 3. Is the safety and effectiveness of subcutaneous immunotherapy different in distinct subpopulations with rhinitis/rhinoconjunctivitis and/or asthma?

Key Points

- There is insufficient evidence to comment on safety and effectiveness in the following populations: the elderly, pregnant women, minorities, inner-city residents, rural residents, and patients with severe asthma.
- There is no consistent difference in efficacy of subcutaneous immunotherapy when comparing responses in mono-sensitized and poly-sensitized subjects.
- Although the evidence supports the use of subcutaneous immunotherapy to improve asthma and allergic rhinitis outcomes in children, we found that there are fewer pediatric studies, and as a result, the strength of evidence is weaker for the pediatric subpopulation than in the mixed adult and pediatric population.

The included articles did not present specific data on the following subgroups: the elderly, pregnant women, minorities, inner-city residents or rural residents. Insufficient data exist to comment on these subpopulations.

The majority of the studies excluded subjects with severe asthma. Few articles explicitly stated that patients with severe asthma were included, although Adkinson et al. specifically recruited children with moderate to severe perennial allergic asthma[65] This was a study with low risk of bias which investigated the benefit of subcutaneous immunotherapy with injections of multiple allergens in patients already receiving appropriate medical treatment. They demonstrated, after 2 years or more of immunotherapy, continuing immunotherapy provided no additional benefit in children with moderate to severe asthma. Subgroup analysis in this study suggested that a younger age ($\leq$8.5 years) and lower medication scores (indicating milder asthma) may be factors leading to a favorable response to subcutaneous immunotherapy.[65]

Seven studies were performed exclusively in monosensitized subjects.[41,48,51,53,91,95,97] There was no consistent difference in the efficacy of subcutaneous immunotherapy when considering these studies of monosensitized individuals relative to studies including polysensitized individuals.

Some studies performed subgroup analyses on monosensitized individuals and select age groups. One study by Bousquet et al. demonstrated that in the subgroup of patients allergic only to *D. pteronyssinus* who received immunotherapy, there was a significant decrease in mean asthma symptom scores, medication scores, and a significant improvement in FEV1 in comparison to the control group that did not receive immunotherapy.[52] In this study, the investigators observed that children and patients with mild asthma demonstrated the most improvement; they also observed that patients with an FEV1 less than 70 percent predicted before immunotherapy (indicating more severe asthma) did not improve after 12 months of

treatment. Another study, by Wang et al., demonstrated a reduction in asthma symptom scores in both pediatric (16 years of age or younger) and adult subgroups after 1 year of immunotherapy with a dust mite extract; however when compared with placebo, no significant difference was observed in either age group.[56] Similarly, there was no significant difference in treatment response in monosensitizedz or in polysensitized individuals.

Subcutaneous Immunotherapy in Pediatric Population

Thirteen articles on subcutaneous immunotherapy were eligible for inclusion in this review. Two additional articles provided long term followup outcomes. The 13 articles with 920 subjects were published between 1982 and 2011. The publications originated mostly from Europe with one each from North America and Australia. Thirty-eight percent of studies (n=5) had at least some industry support, although 7 studies had no identified funding source (Appendix G, Evidence Table G1). Four studies had a low risk of bias (31%); 4 studies were rated as having a medium risk of bias (31%), and 5 studies were considered to have a high risk of bias (38%). (Appendix G, Evidence Table G4)

The pediatric population ranged in age from 3 to 18 years. The number of participants in each study ranged from 18 to 300. The primary diagnoses of the subjects studied in the articles included asthma in 7 studies,[49,50,53,55,57,63,65] rhinitis in zero studies, rhinoconjunctivitis in one study,[84] asthma with rhinitis in 3 studies,[40,97,100] and asthma with rhinoconjunctivitis in two studies.[111,112] (Appendix G, Evidence Table G2)

Inclusion criteria required that all subjects have positive skin allergy testing and/or in vitro specific IgE allergy testing. Seven studies (54%) required that the study participants had not received prior immunotherapy. Two studies (17%) focused on monosensitized individuals only.[53,97]

The majority of studies evaluated perennial allergens (62%), followed by seasonal allergen (23%) and studies including both seasonal and perennial allergens (15%) (Appendix G, Evidence Table G1).

All studies allowed either conventional pharmacotherapy or rescue allergy medications during the study. The maintenance dosing interval varied from biweekly to every 6 week dosing, and the duration of treatment ranged from 4 months to 3 years. There was great heterogeneity in the reporting of the maintenance or cumulative dose delivered to the study participants, and the studies used various units to report dosing (Appendix G, Evidence Table G3).

Key Points Regarding Asthma Outcomes in the Pediatric Population

Relative to placebo or control treatment:

- Moderate evidence supports that subcutaneous immunotherapy improves asthma symptom control based on 6 randomized controlled trials with 550 subjects. Low grade evidence supports that subcutaneous immunotherapy reduces asthma medication use based on 4 randomized controlled trials with 470 subjects.
- Low grade evidence supports that subcutaneous immunotherapy reduces asthma plus rhinitis/rhinoconjunctivitis medication use based on 2 randomized controlled trials with 80 subjects.
- Low grade evidence supports that subcutaneous immunotherapy improves combined asthma/rhinitis/rhinoconjunctivitis symptom and medication scores use based on 2 randomized controlled trials with 85 subjects.

Asthma and Asthma/Rhinoconjunctivitis Symptoms

Asthma symptom scores were reported in 6 asthma studies[40,49,53,65,111,112] (Appendix G, Evidence Table G5). Six (46%) of 13 studies evaluated asthma symptom scores. The number of participants in each study ranged from 20 to 300. The duration of treatment ranged from 10 months to 3 years. Four studies compared subcutaneous immunotherapy to placebo, and two studies compared subcutaneous immunotherapy to pharmacotherapy. Various measures of asthma symptoms were used. Although the scoring system was not always described, some studies used self-reported symptoms using an ordinal scale. Other measures of asthma symptoms include mean percentage of days and nights with asthma,[40] and number of exacerbations per year.[53] The allergens used for SCIT included dust mite, *Cladosporium*, ryegrass, *Alternaria*, and multiple allergens.

Five studies reported statistical comparisons between subcutaneous immunotherapy and the comparison group.[40,53,65,111,112] Four of these studies demonstrated improvement in asthma symptoms from subcutaneous immunotherapy when compared with pharmacotherapy,[40,53] or to placebo;[111,112] however only three of these were reported as statistically significant.[40,53,112] One study demonstrated significant improvement in the subcutaneous immunotherapy group when symptom scores were compared before and after immunotherapy, although the placebo group also had a significant reduction in symptoms scores.[65]

One study did not report statistical comparisons between the immunotherapy and the comparison groups.[49] This study was a 2-year study in which patients were treated with preseasonal immunotherapy only in the first year of the study. Symptom scores were recorded before, during, and after the pollen season for both years; however the investigators did not report a direct comparison of the symptom scores between the first and second year.

Two of 6 studies reporting asthma symptom scores were large studies with 121 to 300 participants.[40,65] One of the large studies had low risk of bias,[65] and the other had a high risk of bias. Both studies investigated multiple allergens. One study showed no significant improvement.[65] The other study showed a decrease in the mean percentage of days and nights with asthma symptoms in children receiving SCIT for 3 years compared with controls, but baseline data were not reported, so we were unable to determine the magnitude of effect.[40] Two high quality studies, including one large study, reported no significant improvement in asthma symptoms following treatment with subcutaneous immunotherapy when the immunotherapy group was compared with the placebo group.[65,111] In fact, in the larger study by Adkinson et al., the placebo group had a greater reduction in symptoms than the immunotherapy group.[65] Allergen doses varied across studies with no clear association between dose and symptom response.

These 6 studies reporting asthma symptom scores include 550 participants. The overall strength of evidence is moderate that subcutaneous immunotherapy using a single allergen improves asthma symptoms. However, there is low grade evidence to support that subcutaneous immunotherapy using multiple allergens does not improve asthma symptoms. There were no studies that reported combined asthma and rhinoconjunctivitis symptom scores (Table 16).

Table 16. Body of evidence for subcutaneous immunotherapy and asthma symptom scores in children and adolescents

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pifferi 2002[53]	Dust mite	SCIT Pharmacotherapy	29	Medium	+	Direct	Strong
Dreborg 1986[111]	*Cladosporium*	SCIT Placebo	30	Low	+	Direct	Moderate
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Moderate
Hill 1982[49]	Rye	SCIT Placebo	20	High	+	Direct	Strong
Adkinson 1997[65]	Multiple	SCIT Placebo	121	Low	-	Direct	Moderate
Cantani 1997[40]	Multiple (Dust mite, Rye, *Parietaria*)	SCIT Pharmacotherapy	300	High	+	Direct	Could not determine*

+ = positive; - = negative; SCIT = subcutaneous immunotherapy
*Not enough data were provided in the article to calculate the magnitude of effect.

Asthma Medication Use and Asthma Plus Rhinitis/Rhinoconjunctivitis Medication Use

Asthma medication scores, or asthma plus rhinitis/rhinoconjunctivitis medication scores were reported in 6 (46%) asthma studies[40,49,53,65,111,112] (Appendix G, Evidence Tables G6 and G8). Methods of assessing medication consumption varied across studies. Some studies reported calculated medication scores, with scoring scales different across studies. Other measures of asthma medication consumption include number of days during which medications were used[53] and sum of daily medication doses.[111]

Four studies reported medication scores for asthma alone.[40,49,53,65] One study used dust mite as a single allergen[53] while another used rye grass.[49] Two studies used multiple allergens.[40,65] Two studies compared subcutaneous immunotherapy to placebo,[49,65] and two studies compared subcutaneous immunotherapy to pharmacotherapy.[40,53] One placebo controlled study of rye pollen allergy did not report results of relevant statistical analyses.[49]

Three studies reported results from direct comparison between the immunotherapy group and the comparison group.[40,53,65] Two of these studies reported a significant difference in medication consumption in favor of the immunotherapy group when compared with pharmacotherapy.[40,53] The allergens investigated by these studies include dust mite in both studies [40,53] as well as *Parietaria* and ryegrass pollen in one study.[40] The remaining one study found no significant difference in medication use between the immunotherapy group and the comparison groups. This placebo controlled study investigated multiple allergens[65] and demonstrated significant reduction in medication use in both the immunotherapy and placebo groups after treatment, with no difference between groups.[65]

Overall, 4 studies reported asthma medication consumption in 470 participants. The overall strength of evidence is low grade to support the use of subcutaneous immunotherapy to improve asthma medication use (Table 17).

Table 17. Body of evidence for subcutaneous immunotherapy affecting asthma medication scores in children and adolescents

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Direct-ness	Magnitude of Effect
Pifferi 2002[53]	Dust mite	SCIT Pharmacotherapy	29	Medium	+	Direct	Strong
Hill 1982[49]	Rye	SCIT Placebo	20	High	+	Direct	Moderate
Adkinson 1997[65]	Multiple	SCIT Placebo	121	Low	-	Direct	Weak
Cantani 1997[40]	Multiple (Dust mite, Rye, *Parietaria*)	SCIT Pharmacotherapy	300	High	+	Direct	Could not determine*

+ = positive; - = negative; SCIT = subcutaneous immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect

Two studies reported combined asthma and rhinoconjunctivitis medications scores and investigated molds, *Cladosporium*[111] and *Alternaria.*[112] These studies included 30 to 50 participants, compared immunotherapy to placebo, and had a low risk[111] and high risk[112] of bias. These studies demonstrated a reduction in asthma and rhinoconjunctivitis medication consumption in the immunotherapy group when compared with the comparison groups.

The overall strength of evidence is low grade to support the use of subcutaneous immunotherapy to reduce asthma and rhinoconjunctivitis medication consumption (Table 18).

Table 18. Body of evidence for subcutaneous immunotherapy affecting asthma plus rhinitis/rhinoconjunctivitis medication scores in children and adolescents

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Dreborg 1986[111]	*Cladosporium*	SCIT Placebo	30	Low	+	Direct	Weak
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong

+ = positive; SCIT = subcutaneous immunotherapy

Combined Asthma Symptoms and Medication Scores

Two asthma studies reported combined symptom-medication scores for asthma or asthma plus rhinoconjunctivitis[50,112] (Appendix G, Evidence Tables G7 and G8). These studies compared subcutaneous immunotherapy to placebo and investigated dust mite allergen[50] with high risk of bias and *Alternaria* mold allergen[112] with moderate risk of bias. Both studies demonstrated significant improvement in the immunotherapy group compared with placebo.[50,112] Kuna et al. reported a 63 percent reduction in combined symptom-medication score after 3 years of treatment, compared with 17 percent reduction in the placebo group.[112]

Another study by Akmanlar et al. compared rush immunotherapy to conventional immunotherapy and observed significant reduction in symptom-medication scores in both study groups after immunotherapy, but there was no significant difference in scores between the two groups. This study was graded as having a high risk of bias and was not included for evidence grading because both treatment groups received SIT.[97]

Overall, 2 studies reporting asthma symptom-medication scores included 85 participants. The strength of evidence is low grade to support that subcutaneous immunotherapy improves asthma symptom-medication scores (Table 19).

Table 19. Body of evidence for subcutaneous immunotherapy affecting combined symptom-medication scores in children and adolescents)

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Altintas 1999[50]	Dust mite	SCIT-Adsorbed Al SCIT-Adsorbed Ca SCIT-aqueous Placebo	35	High	+	Direct	Strong
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong

+ = positive; Al = aluminum; Ca = calcium; SCIT = subcutaneous immunotherapy

Pulmonary Function Testing

Two studies reported changes in pulmonary function test results with peak expiratory flow rates (PEF or PEFR)[65,111] (Appendix G, Evidence Table G9). Risk of bias was low for these 2 studies, comparing subcutaneous immunotherapy to placebo.[65,111] One study demonstrated a small treatment effect in favor of immunotherapy (with a mean difference of 3.8 percentage points in the predicted value of PEFR) and this approached statistical significance.[65] The other study found no significant difference in mean PEF between subcutaneous immunotherapy and placebo.[111]

Bronchial Reactivity

Eight asthma studies (67%) evaluated bronchial airway reactivity (Appendix G, Evidence Table G10). Bronchial reactivity was evaluated by two methods: specific allergen bronchial provocation tests and nonspecific chemical bronchial provocation. The majority of the studies that performed nonspecific chemical bronchial provocation tests used methacholine and/or histamine (Appendix G, Evidence Table G10).

Specific allergen bronchoprovocation studies were reported in 6 studies. Of 5 studies that reported pre- versus post-treatment differences, 3 studies (60%) demonstrated significant decreases in bronchial sensitivity in favor of subcutaneous immunotherapy.[50,100,111] Two trials showed no statistically significant difference between the immunotherapy group and the comparison group.[63,97] One study reported only the pre- and post-treatment comparison. [55] Nonspecific chemical bronchoprovocation tests were reported in 3 studies.[53,65,100] All 3 studies reported comparisons with a comparator group, although only one demonstrated a significant decrease in bronchial sensitivity in favor of subcutaneous immunotherapy.[53] Two studies demonstrated no significant difference between the immunotherapy group and the comparison group. [65,100] In the study by Hedlin et al, both groups were treated with some form of immunotherapy.[100]

Secondary Outcomes

Few studies evaluated secondary outcomes including quality of life, biomarkers, and prevention of asthma development. One study commented on asthma quality of life. Kuna et al. demonstrated a significant improvement of 38 percent in quality of life scores after 3 years of immunotherapy, compared with a 19 percent decrease in quality of life scores in the placebo group.[112] There is insufficient evidence to comment on the strength of the evidence about the effect of subcutaneous immunotherapy on these secondary outcomes.

Key Points Regarding Rhinitis/Rhinoconjunctivitis Outcomes in the Pediatric Population

Relative to a control group:

- Moderate grade evidence supports that subcutaneous immunotherapy improves rhinitis/rhinoconjunctivitis symptoms based on 3 randomized controlled trials with 285 subjects.
- Low grade evidence supports that subcutaneous immunotherapy improves conjunctivitis symptoms based on 3 randomized controlled trials with 285 subjects.
- Low grade evidence supports that subcutaneous immunotherapy improves disease specific quality of life based on 2 randomized controlled trials with 350 subjects.

There were no pediatrics studies that reported on subcutaneous immunotherapy outcomes of combined nasal, ocular, and bronchial symptoms, rhinitis/rhinoconjunctivitis medication use, combined medication use (both asthma and rhinitis/rhinoconjunctivitis medications), or combined symptom and medication use.

Rhinitis/Rhinoconjunctivitis Symptoms

Rhinitis/Rhinoconjunctivitis symptom scores were reported in 3 studies[84,111,112] (Appendix G, Evidence Table G11). Rhinitis/rhinoconjunctivitis symptom scores were included from studies that enrolled rhinitis/rhinoconjunctivitis and/or asthma patients. One study exclusively examined patients with a primary diagnosis of rhinoconjunctivitis,[84] while the other two studies enrolled patients with asthma and/or rhinitis/rhinoconjunctivitis, and met our criteria for inclusion with the asthma studies.[111,112]

Two studies used visual analog scores to measure nasal symptoms,[84,112] while the other study used an unspecified numeric system to score the severity and presence/absence of nasal symptoms.[111] Two studies reporting rhinitis/rhinoconjunctivitis symptom scores demonstrated statistically significant improvement in rhinitis/rhinoconjunctivitis symptoms with subcutaneous immunotherapy compared with placebo.[84,112] These studies had medium risk of bias, included 50 to 205 participants, and investigated grass/birch allergen mix and *Alternaria* respectively. The third study did not show significant improvement in symptoms relative to placebo treated subjects.[111] This study also had low risk of bias, included 30 patients, and investigated *Cladosporium* allergen.

Overall, three RCTs reported rhinitis/rhinoconjunctivitis symptom scores in 285 participants. The overall strength of evidence is moderate to support that subcutaneous immunotherapy improves rhinitis/rhinoconjunctivitis symptoms (Table 20).

Table 20. Body of evidence for subcutaneous immunotherapy affecting rhinitis/rhinoconjunctivitis symptom scores in children and adolescents

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Dreborg 1986[111]	*Cladosporium*	SCIT Placebo	30	Low	+	Direct	Weak
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Moderate
Möller 2002[84] Niggeman 2006[115]	Grass/ Birch	SCIT Placebo	205	Medium	+	Direct	Strong

+ = positive; SCIT = subcutaneous immunotherapy

Conjunctivitis Symptoms

Three subcutaneous immunotherapy studies reported conjunctivitis symptom scores (Appendix G, Evidence Table G12).[84,111,112] The comparator in these three studies was placebo. Two studies used a visual analog score for ocular symptoms,[84,112] and the other study did not describe the scale used.[111] The duration of assessment varied from 10 months to 5 years.

One study, with medium risk of bias and involving 205 participants, reported significant improvement in conjunctivitis symptom scores when compared with placebo, although actual scores were not reported to determine the magnitude of effect.[84] Kuna et al. also found significant improvement with a 47 percent absolute reduction in conjunctivitis symptoms after 3 years of subcutaneous immunotherapy compared with controls.[112] The third study, also with low risk of bias and involving 30 participants, did not show significant improvement in conjunctivitis symptom scores compared with placebo.[111]

Three subcutaneous immunotherapy trials reported conjunctivitis scores and included 285 subjects. The overall strength of evidence is low to support that subcutaneous immunotherapy improves allergic ocular symptoms in children (Table 21).

Table 21. Body of evidence for subcutaneous immunotherapy affecting conjunctivitis symptoms in children and adolescents

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Dreborg 1986[111]	*Cladosporium*	SCIT Placebo	30	Low	+	Direct	Weak
Möller 2002[84] Niggeman 2006[115]	Grass/ Birch	SCIT Placebo	205	Medium	+	Direct	Could not determine*
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong

+ = positive; SCIT = subcutaneous immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Quality of Life

Quality of life (QOL) was reported in 2 trials comparing subcutaneous immunotherapy to placebo with medication treatment.[40,112] One 3 year study compared the mean number and percentage of limitations of quality of life per year for the two groups. This study reported significant improvement in disease-specific quality of life when compared with placebo[40] (Appendix G, Evidence Tables G14 and G15). In Kuna, et al, a 38 percent increase in QOL in treated children was seen at 3 years, compared with a 18 percent decrease in QOL in the placebo group.[112] Kuna et al also described a significant increase in QOL in adolescents, compared with placebo.[112] A similar increase in QOL was also seen in the parents of children with symptoms.[112]

Overall, two studies with 350 subjects evaluated quality of life outcomes. There is low grade evidence to support that subcutaneous immunotherapy improves disease-specific quality of life among children and adolescents with rhinitis/rhinoconjunctivitis (Table 22).

Table 22. Body of evidence for rhinitis/rhinoconjunctivitis quality-of-life scores after subcutaneous immunotherapy (in children and adolescents)

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Cantani 1997[40]	Dust Mites, Grass, Weeds	SCIT Pharmaco-therapy	300	High	+	Direct	Could not determine*
Kuna 2011[112]	*Alternaria*	SCIT Placebo	50	Medium	+	Direct	Strong

+ = positive; SCIT = subcutaneous immunotherapy

*Data provided in the article was not enough to calculate the magnitude of effect.

Nasal and Ocular Allergen Challenge (Provocation)

Three subcutaneous immunotherapy studies challenged subjects to specific allergens in order to quantify symptoms (Appendix G, Evidence Table G11). None of the studies used nasal provocation. Three studies performed conjunctival provocation tests comparing subcutaneous immunotherapy to placebo.[63,84,111] Two of the 3 conjunctival provocation studies demonstrated significant improvement in symptoms comparing subcutaneous immunotherapy to placebo after 1 or 5 years.[63,84] One study demonstrated no significant difference between subcutaneous immunotherapy and placebo after 10 weeks during peak allergy season.[111] This study had low risk of bias, included 30 children, and investigated *Cladosporium* allergen.

Secondary Outcomes

Few studies evaluated secondary outcomes such as biomarkers. In general, there is insufficient evidence about the effect of subcutaneous immunotherapy on these secondary outcomes. Moller et al conducted a medium risk of bias study investigating asthma prevention as a primary outcome; they observed that among 151 children with allergic rhinoconjunctivitis without asthma, there was a 52 percent increased odds (OR 2.52 (1.3-5.1)) of preventing the development of asthma after 3 years of SCIT compared with placebo.[84,115] A 5-year followup study, by the same investigators, found a 68 percent increased odds (OR 2.68 (1.3-5.7)) of preventing the development of asthma in children receiving SCIT 2 years after stopping a 3-year course of SCIT.[84,115] In a 10-year followup study (7 years after completing a 3-year course of SCIT), there was a 50 percent increased odds (OR: 2.5 (1.1-5.9)) of preventing asthma in children that had received SCIT, compared with placebo[116] (Appendix G, Evidence Table G14 and G16).

Summary of Evidence for Efficacy and Effectiveness in the Pediatric Population

When considering the key evidence for the efficacy and effectiveness of subcutaneous immunotherapy in the treatment of asthma, the pertinent direct clinical outcomes include symptom scores and medication use. The strength of evidence regarding the effectiveness of subcutaneous immunotherapy is moderately supportive that this treatment improves asthma symptom scores but there is low evidence for improvement of asthma medication use and symptom medication scores (Table 23).

When considering the key evidence for the efficacy and effectiveness of subcutaneous immunotherapy in the treatment of rhinitis and rhinoconjunctivitis, the pertinent direct clinical outcomes include symptom scores, medication use, and quality of life. The strength of evidence

regarding the effectiveness of subcutaneous immunotherapy is moderately supportive that this treatment improves rhinoconjunctivitis, but there is low grade evidence to support the use of subcutaneous immunotherapy to improve conjunctivitis symptoms and quality of life in children with rhinitis/rhinoconjunctivitis (Table 24).

Table 23. Summary of studies and strength of evidence for subcutaneous immunotherapy and asthma outcomes in children and adolescents

Outcome	Number of Studies/ Number of Participants	Risk of Bias	Direction of change	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Asthma Symptoms	6 / 550	2 high 2 medium 2 low	5 positive 1 negative	Consistent	Direct	2 strong 3 moderate 1 CND	2 studies with low RofB AND moderate magnitude 1 study with medium RofB AND strong magnitude 1 study with medium RofB AND moderate magnitude	Moderate
Asthma plus Rhinitis/ Rhino-conjunctivitis Symptoms	0 / 0	NA	NA	NA	NA	NA		NA
Asthma Medication Scores	4 / 470	2 high 1 medium 1 low	3 positive 1 negative	Consistent	Direct	1 strong 1 moderate 1 weak 1 CND	1 study with medium RofB AND strong magnitude 1 study with low RofB and weak magnitude	Low
Asthma plus Rhinitis/Rhino-conjunctivitis Medication Scores	2 / 80	1 medium 1 low	2positive	Consistent	Direct	1 strong 1 weak	1 study with medium RofB AND strong magnitude 1 study with low RofB and weak magnitude	Low
Combined Symptom-Medication Scores	2 / 85	1 high 1 medium	2 positive	Consistent	Direct	2 strong	1 study with medium RofB AND strong magnitude 1 study with high RofB AND strong magnitude	Low

CND = could not determine; NA = not available; RofB = risk of bias

Table 24. Summary of studies and strength of evidence for subcutaneous immunotherapy and rhinitis/rhinoconjunctivitis outcomes in children and adolescents

Outcome	Number of Studies/ Number of Participants	Risk of Bias	Direction of Change	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Rhinitis/Rhino-conjunctivitis Symptoms	3 / 285	2 medium 1 low	3 positive	Consistent	Direct	1 Strong 1 Moderate 1 Weak	1 study with medium RofB AND strong magnitude 1 study with medium RofB AND moderate magnitude 1 study with low RofB AND weak magnitude	Moderate
Conjunctivitis Symptoms	3 / 285	2 medium 1 low	3 positive	Consistent	Direct	1 Strong 1 Weak 1 CND	1 study with medium RofB AND strong magnitude 1 study with low RofB AND weak magnitude	Low
Combined Symptom Score	0 / 0	NA	NA	NA	NA	NA	NA	NA
Rhinitis/Rhino-conjunctivitis Medication Use	0 / 0	NA	NA	NA	NA	NA	NA	NA
Asthma plus Rhinitis/Rhino-conjunctivitis Medication Use	0 / 0	NA	NA	NA	NA	NA	NA	NA
Combined RhinitisSymptom-Medication Score	0 / 0	NA	NA	NA	NA	NA	NA	NA
Rhinitis/Rhino-conjunctivitis Quality of Life	2 / 350	1 high 1 medium	2 positive	Consistent	Direct	1 Strong 1 CND	1 study with medium RofB AND strong magnitude	Low

CND = could not determine; NA = not available; RofB = risk of bias

Safety of Subcutaneous Immunotherapy in the Pediatric Trials

- Few studies reported adverse events.
- Lack of a consistent reporting system and grading system for subcutaneous immunotherapy precluded pooling safety data across studies.
- There were no reports of anaphylaxis or deaths

Adverse events were noted in 10 of the 13 studies for subcutaneous immunotherapy in children. The studies reported local and systemic reactions as either number of patients with reactions or the number of events per patient. Local reactions were reported in 7 studies. Four studies reported local swelling in 11 to 17 percent of patients.[50,54,97,111,112] Three studies, with 10-20 patients in each arm, reported local reactions including redness and swelling, as events with a frequency of 0.25 to 21 events per patient.[57,63,111] In one study there was a greater number of local reaction events per patient in the placebo group (20.9) than in the SCIT group (20.6).[63] One study reported local injection edema in 1.1 percent of all injections with 11 events occurring in 4 patients.[112]

Eight studies reported systemic reactions in children receiving subcutaneous immunotherapy. Respiratory reactions were observed in 1 percent to 33 percent of patients in 2 studies.[40,97] There were insufficient data to determine a difference in frequency of respiratory reactions between the active group and the comparator group. One study reported a respiratory reactions occurring with approximately 4 percent of all dust mite injections.[57] Cutaneous reactions with urticaria were reported in two studies in 2 to 19 percent of patients.[40,111] One study reported headache in 1 patient, 3 percent of 30 patients receiving subcutaneous immunotherapy, and mild facial flushing and redness in 2 patients with placebo injections.[112] Unspecified mild systemic reactions were reported in 33 percent (n=5) of patients in one study,[100] in 34 percent (n=21) of patients receiving SCIT and 7 percent of patients receiving placebo injections in another study,[65] and as 2.8 events per patient with 45 unspecified systemic reactions occurring in 16 patients receiving SCIT.[111] There were no reports of anaphylaxis (Appendix G, Evidence Table G18).

Conclusion: Summary of Evidence for Key Question 3 for Subcutaneous Immunotherapy

We did not observe any substantial difference in the efficacy of subcutaneous immunotherapy when considering monosensitized and polysensitized individuals. Little data exist about the following subpopulations: the elderly, pregnant women, minorities, inner-city residents, rural residents, and severe asthmatics, so the evidence is insufficient to comment on the effectiveness of this therapy in these subgroups. The limited available data suggest that subcutaneous immunotherapy is less beneficial in patients with severe asthma than in individuals with mild asthma. There are few studies that focused exclusively on children and adolescents. As a result, we found that the strength of evidence is weaker for the pediatric subpopulation than in the mixed adult and pediatric population. Tables 23 and 24 summarize the studies and the strength of evidence for subcutaneous immunotherapy affecting asthma and allergic rhinitis/rhinoconjunctivitis outcomes in the pediatric subpopulation.

Sublingual Immunotherapy

Study Characteristics

Sixty articles on sublingual immunotherapy were eligible for inclusion in this review. These 60 articles, with 4870 subjects, were published between 1993 and 2012. The publications originated from North America, Europe, and Asia. Sixty-one percent of studies had at least some industry support, although 8 studies had no identified funding source (Appendix E, Evidence Table E1). Twenty-two percent of the studies were rated as having a low risk of bias; 68 percent were rated as having a moderate risk of bias, and 14 percent were considered to have a high risk of bias (Appendix E, Evidence Table E4).

The primary diagnoses of the subjects studied in the articles included asthma in eight studies,[117-124] rhinitis in seven studies,[125-131] rhinoconjunctivitis in 14 studies,[43 132-144] asthma and rhinitis in 17 studies,[44,45,145-159] and asthma with rhinoconjunctivitis in 14 studies.[160-172,173]

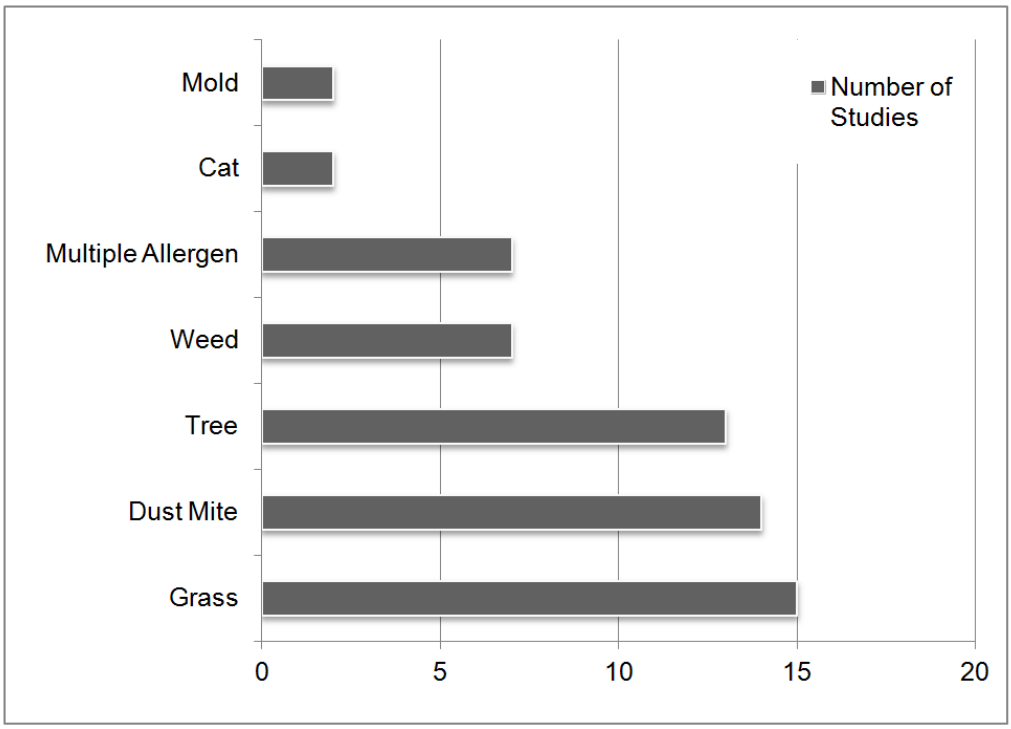
Most studies enrolled adults only, although sixteen RCTs included both adults and children,[122,124,129,132,140,142,145,149,153,159,167,169,170,172-174] and 18 exclusively studied children.[117,120,121,130,144 131,138,141,148,152,154,157,158,160,163,164,168,171] Seven studies did not report sex [45,132,147,149,155,165,170] and the remainder enrolled both males and females (Appendix E, Evidence Table E2).

By design, all studies required subjects to have positive skin allergy testing and/or in vitro specific IgE allergy testing. Thirty-two studies (54%) required that the subjects had not received previous immunotherapy.[44,45,117,120,124,126,128-130,132,133,135,138-140,145,148,149,152,154,157-159,161,162,164-166, 123,143,171,172] Eighteen studies (32%) focused on monosensitized individuals.[43,44,117,120,124,130,132,138,144,146,152,153,155,158,161,162,166,171] Nine studies specifically excluded pregnant individuals[43,123,126,128,129,143,149,165,169] (Appendix E, Evidence Table E1).

The majority of studies evaluated seasonal allergens (66 percent), followed by perennial allergens (31%); a small number of studies included both seasonal and perennial allergens (3%) (Appendix E, Evidence Table E1) The study allergens were grass/grass mix (in 15 studies),[44,119,125,137-142,152,164-167,174] dust mite (in 14 studies),[117,120,121,129-131,149,154-159,171] tree (in 13 studies),[45,126-128,134-136,143,146,150,162,163,168] weeds/weed mix (7 studies),[43,124,132,133,144,160,161] mixed or multiple allergens (7 studies),[122,145,147,148,151,153,172] cat (2 studies),[118,170] and mold (2 studies).[123,169] (Figure 12). Half of the studies used only one allergen in their study protocols, while the other half used multiple allergens in their studies.

The trials compared sublingual immunotherapy to placebo (71%), to another sublingual intervention without a placebo group (15%), or to a conventional treatment without placebo (pharmacotherapy or rescue medications) (14%) (Appendix E, Evidence Table E3). All studies allowed either conventional pharmacotherapy or rescue allergy medications in both the sublingual therapy arm and in the comparison arm. The maintenance dosing interval varied from daily to weekly, and the duration of treatment ranged from 3 months to 5 years. There was great heterogeneity in the reporting of the maintenance or cumulative dose delivered to the study participants, and the studies used a variety of units to report dosing.

Figure 12. Sublingual immunotherapy studies by type of allergen



Population Characteristics

The mean age range of subjects in the included studies was four to 74 years (Appendix E, Evidence Table E2). Forty-two percent of the studies reported the mean or minimum duration of disease among the enrolled participants. The range of mean duration of disease was one to 19 years. Race was not reported in any study.

Key Question 1. What is the evidence for the efficacy and effectiveness of sublingual immunotherapy in the treatment of allergic rhinitis/rhinoconjunctivitis and/or asthma?

Key Points

- High grade evidence supports that sublingual immunotherapy improves asthma symptoms based on 13 randomized controlled trials with 625 subjects.
- Moderate grade evidence supports that sublingual immunotherapy improves asthma or rhinitis/rhinoconjunctivitis (asthma combined scores) symptom control based on 5 randomized controlled trials with 308 subjects.
- Moderate grade evidence supports that sublingual immunotherapy improves rhinitis/rhinoconjunctivitis symptoms based on 35 randomized controlled trials with 2658 subjects.
- Moderate grade evidence supports that sublingual immunotherapy improves control of conjunctivitis symptoms based on 13 randomized controlled trials with 1074 subjects.
- Moderate grade evidence supports that sublingual immunotherapy decreases medication use based on 38 randomized controlled trials with 2724 subjects.

- Moderate grade evidence supports that sublingual immunotherapy improves allergy symptoms or decreases medication use based on 19 randomized controlled trials with 1462 subjects.
- Moderate grade evidence supports that sublingual immunotherapy improves disease-specific quality of life based on eight randomized controlled trials with 819 subjects.

Asthma Outcomes

Asthma symptom scores alone, or asthma with rhinitis/rhinoconjunctivitis symptom scores (asthma combined scores) were reported in 24 studies.[43-45,117,120,121,123,124,131,137,140,145-147,150,153,154,156,158,160,164,168,169,171] (Appendix E, Evidence Table E5). As described in the Methods, asthma scores and asthma combined symptom scores were included from studies only if objective measures of lung function were used to diagnose subjects with asthma.

Asthma symptoms scores were reported in 13 studies (22%) [44,117,120,121,123,150,154,157,158,160,168,169,171] (Appendix E, Evidence Table E6). The types of scales used to report asthma symptoms scores were not uniform. Two studies used visual analog scores,[117,160] one study counted number of days with asthma,[150] and the remainder used numeric systems to score presence/absence of asthma symptoms and severity. One study compared sublingual immunotherapy with inhaled corticosteroids,[44] another to montelukast,[45] while the remainder used a placebo control group. The number of participants across studies ranged from 15 to 110. The duration of assessment ranged from one pollen season to 5 years.

All of the studies reporting asthma symptom scores demonstrated significant improvement in asthma symptoms with sublingual immunotherapy. Ten studies with asthma symptom scores demonstrated significant improvement in asthma symptoms with sublingual immunotherapy when compared with placebo;[44,117,120,121,123,131,150,154,160,168] and eight studies demonstrated significant improvement in pre- versus post-treatment asthma scores in the sublingual immunotherapy arm.[44,45,117,120,123,157,158,171] The study comparing sublingual immunotherapy to inhaled corticosteroids demonstrated significant improvement from pre-treatment scores in both the sublingual and inhaled corticosteroid groups.[44] However, the participants receiving immunotherapy improved significantly more than those receiving inhaled corticosteroids. One study compared sublingual immunotherapy to montelukast,[45] and found a greater improvement in asthma scores in the immunotherapy group. The most common single allergen used in the asthma scores was dust mite, in seven studies.[117,120,121,154,157,158,171] All dust mite studies which reported asthma scores reported significant benefit with sublingual immunotherapy.

We conclude that there is high grade evidence that sublingual immunotherapy reduces asthma symptoms (Table 25).

Table 25. Body of evidence for sublingual immunotherapy affecting asthma symptoms

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pajno 2000[117]	Dust mite	SLIT Placebo	24	Low	Night + VAS +	Direct	Night Strong VAS Strong
Lue 2006[120]	Dust mite	SLIT Placebo	20	Medium	+	Direct	Strong
Niu, 2006 [121]	Dust mite	SLIT Placebo	110	Medium	+	Direct	Strong
Hirsch 1997[154]	Dust mite	SLIT Placebo	30	Low	+	Direct	Strong
Bahceciler 2001[158]	Dust mite	SLIT Placebo	15	Medium	+	Direct	Moderate
Ippoliti 2003[171]	Dust mite	SLIT Placebo	86	Medium	+	Direct	Strong
Tari, 1990[157]	Dust mite	SLIT Placebo	58	Low	+	Direct	Moderate
Pozzan 2010 [169]	*Alternaria*	SLIT Placebo	52	Medium	+	Direct	Could not determine*
Cortellini 2010[123]	*Alternaria*	SLIT Placebo	27	High	+	Direct	Strong
Pajno, 2004[160]	*Parietaria*	SLIT Placebo	30	Low	Sx + VAS +	Direct	Sx Could not determine* VAS Could not determine*
Voltolini, 2009[150]	Birch	SLIT Placebo	24	Medium	+	Direct	Strong
Valovirta 2006[168]	Tree mix	high dose low dose Placebo	98	Medium	High dose + Low dose +	Direct	High dose: Strong Low dose: Moderate
Marogna, 2009[44]	Grass mix	SLIT Budesonide	51	Medium	+	Direct	Strong

+ = positive; Night = nighttime symptom score; SLIT = sublingual immunotherapy; Sx = symptom score; VAS = visual analog scale score

*Not enough data were provided in the article to calculate the magnitude of effect.

Five trials of sublingual immunotherapy, involving 308 participants, reported asthma plus rhinitis or rhinoconjunctivitis symptoms scores in comparison to placebo or control.[146,147,156,168,169] Study size ranged from 31 to 98 subjects. All studies used numeric scoring systems, but the types of scales used were not validated and varied between studies. One study compared sublingual immunotherapy with pharmacotherapy,[147] while the remaining studies made comparisons to a placebo group. The duration of assessment ranged from one pollen season to 4 years.

Four studies reporting asthma plus rhinitis or rhinoconjunctivitis combined symptom scores demonstrated statistically significant positive effects on combined asthma plus rhinitis/rhinoconjunctivitis symptoms with sublingual immunotherapy;[146,147,168,169] one study did not.[156] Three studies demonstrated significant improvement in asthma symptoms when compared

with controls.[140,147,168] One study found significant improvement in total symptoms when compared with pharmacotherapy.[147]

Several studies reporting asthma plus rhinitis/rhinoconjunctivitis symptoms made comparisons with more than one sublingual group compared with placebo or medication. One study found no improvement with either high or low dose dust mite allergen therapy when compared with placebo.[156] A study comparing high dose tree allergen, low dose tree allergen, and placebo found only the high dose had a significant impact on asthma combined scores when compared with placebo.[168] A study of birch allergen alone, grass allergen alone, and birch plus grass allergens delivered sublingually compared with placebo found all groups to be significantly better then placebo in asthma combined scores.[147] Finally, one study identified in our search compared co-seasonal grass sublingual immunotherapy to continuous therapy, but did not include any non-immunotherapy comparators; this was not included in grading this body of evidence.[164] This study found continuous sublingual immunotherapy had a greater magnitude of effect in both asthma and combined asthma scores than co-seasonal sublingual immunotherapy.

We concluded that there is moderate evidence that sublingual immunotherapy reduces asthma and/or rhinitis or rhinoconjunctivitis symptoms (Table 26).

Table 26. Body of evidence for sublingual immunotherapy affecting asthma and/or rhinitis/ or rhinoconjunctivitis symptoms

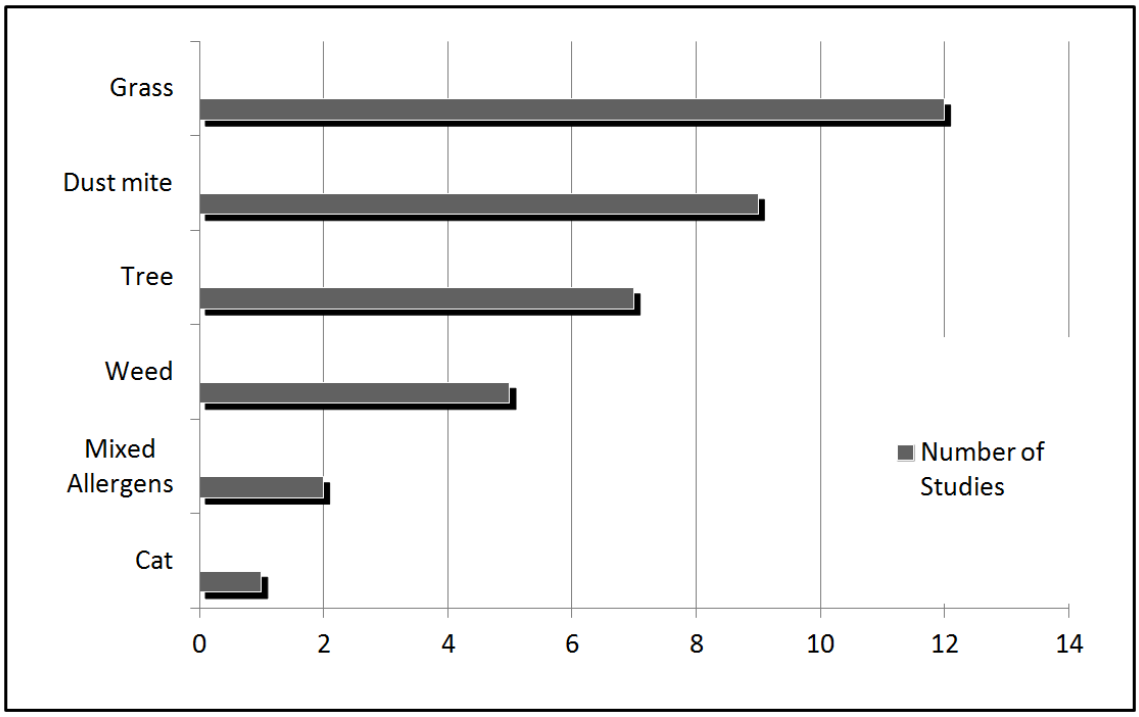
Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pozzan 2010[169]	*Alternaria*	SLIT Placebo	52	Medium	+	Direct	Could not determine*
Marogna 2005[146]	Birch	SLIT Placebo	79	Medium	+	Direct	Moderate
Bush 2011[156]	Dust mite	high dose low dose Placebo	31	Medium	NR	Direct	Could not determine*
Valovirta 2006[168] Savolainen 2006[175]	Tree mix	high dose low dose Placebo	98	Medium	High dose + Low dose +	Direct	High dose: Strong Low dose: Moderate
Marogna 2006[147]	Birch and Grass	SLIT birch SLIT grass SLIT birch+grass Pharmacotherapy	48	Medium	+	Direct	Strong

+ = positive; NR = not reported; SLIT = sublingual immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Rhinitis or Rhinoconjunctivitis Symptoms

Rhinitis or rhinitis plus conjunctivitis symptoms scores were reported in 36 of the sublingual immunotherapy articles included in this review (Appendix E, Evidence Table E5).[44,45,118,124-127,129-133,137-142,144,150,151,153-155,157-160,162,163,165,167,168,171,174] The types of scales used in the studies and the scoring systems were not uniform; the articles used numeric point systems to grade symptoms. The duration of assessment ranged from one pollen season to 6 years. In the studies reporting rhinitis/rhinoconjunctivitis scores, the most common allergen was grass or grass mix, followed by dust mite and tree/tree mix (Figure 13). The comparator group was placebo in all but three studies which compared immunotherapy to medication.[44,45,138]

Figure 13. Allergens used in studies of rhinitis/rhinoconjunctivitis symptoms (sublingual immunotherapy)



Fifty-six percent of sublingual immunotherapy studies reporting rhinoconjunctivitis symptoms demonstrated significant improvement in allergic rhinoconjunctivitis scores with sublingual immunotherapy. Two studies compared sublingual immunotherapy to medical treatment, one to inhaled budesonide[44] and one to montelukast.[45] Another study compared 2 years of immunotherapy to 3 years of immunotherapy without a control group[129] and was not included in the body of evidence grading. The remainder of studies reported rhinitis/rhinoconjunctivitis scores compared with a placebo group. Therefore 35 studies compared sublingual immunotherapy to either placebo or medication and were included in the grading this body of evidence (Table 27).

Nine studies reporting rhinitis/rhinoconjunctivitis scores found significant improvement in the sublingual immunotherapy study group when comparing pre-treatment to post-treatment rhinoconjunctivitis symptom scores.[44,45,118,124,140,153,155,159,171] Fourteen studies found significant improvement in rhinitis/rhinoconjunctivitis scores when compared with placebo.[44,45,118,125,126,132,133,139,140,144,150,157,165,168] The single study comparing 2 years to 3 years of sublingual immunotherapy found rhinitis symptoms at the 6 year evaluation to be significantly reduced in the 3-year treatment group compared with the 2-year treatment group.[129]

We conclude that there is moderate grade evidence that sublingual immunotherapy improves control of rhinitis or rhinoconjunctivitis symptoms, particularly with grass mix allergens (Table 27).

Table 27. Body of evidence for sublingual immunotherapy affecting rhinitis/rhinoconjunctivitis symptoms

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Hordijk 1998[125]	Grass Mix	SLIT Placebo	69	Medium	+	Direct	Strong
Roder, 2007[141]	Grass Mix	SLIT Placebo	204	Low	+	Direct	Weak
Sabbah 1994[142]	Grass Mix	SLIT Placebo	58	Medium	+	Direct	Could not determine*
Pradalier, 1999[167]	Grass Mix	SLIT Placebo	126	Medium	+	Direct	Could not determine*
de Blay, 2007[174]	Grass Mix	SLIT Placebo	118	Medium	+	Direct	Weak
Ott, 2008[139]	Grass Mix	SLIT Placebo	213	Medium	+	Direct	Strong
Feliziani, 1995[165]	Grass Mix	SLIT Placebo	34	Medium	+	Direct	Strong
Panzner 2008[140]	Grass Mix	SLIT Placebo-SLIT	35	Medium	+	Direct	Strong
Novembre 2004[138]	Grass Mix	SLIT Control	113	High	+	Direct	Could not determine*
Marogna 2009[44]	Grass Mix	SLIT Budesonide	51	Medium	+	Direct	Strong
Tseng, 2008[130]	Dust Mite	SLIT Placebo	63	Medium	-	Direct	Weak
Hirsch 1997[154]	Dust Mite	SLIT Placebo	30	Low	+	Direct	Could not determine*
O'Hehir, 2009[155]	Dust Mite	SLIT Placebo	30	High	+	Direct	Weak
Bahceciler 2001[158]	Dust Mite	SLIT Placebo	15	Medium	+	Direct	Moderate
Guez, 2000[159]	Dust Mite	SLIT Placebo	72	Medium	+	Direct	Moderate
Ippoliti 2003[171]	Dust Mite	SLIT Placebo	86	Medium	+	Direct	Strong
Tari, 1990[157]	Dust Mite	SLIT Placebo	58	Low	+	Direct	Moderate
deBot 2011[131]	Dust Mite	SLIT Placebo	257	High	-	Direct	Weak
D'Ambrosio 1999 [124]	*Parietaria*	SLIT Placebo	30	Medium	+	Direct	Could not determine*
La Rosa 1999[144]	*Parietaria*	SLIT Placebo	41	Low	+	Direct	Could not determine*
Pajno 2004[160]	*Parietaria*	SLIT Placebo	30	Low	+	Direct	Could not determine*
Lima 2002[137]	Timothy	SLIT Placebo	56	Low	+	Direct	Could not determine*
Amar 2009[151]	Timothy	monotherapy multiple Placebo	58	Low	+	Direct	Weak
Bowen 2004 [132]	Ragweed	SLIT Placebo	83	Medium	+	Direct	Could not determine*
Skoner 2010[133]	Ragweed	High dose Low dose Placebo	115	Low	+	Direct	Could not determine*

Table 27. Body of evidence for sublingual immunotherapy affecting rhinitis/rhinoconjunctivitis symptoms (continued)

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Horiguchi, 2007[126]	Japanese cedar	SLIT Placebo	67	Medium	+	Direct	Could not determine*
Okubo 2008[127]	Japanese cedar	SLIT Placebo	61	Medium	+	Direct	Could not determine*
Voltolini 2009[150]	Birch	SLIT Placebo	24	Medium	+	Direct	Moderate
Marogna 2010[45]	Birch	SLIT Montelukast	33	High	+	Direct	Strong
Vourdas 1998[163]	Olive	SLIT Placebo	70	Medium	+	Direct	Strong
Vervloet 2007[162]	Mountain cedar	SLIT Placebo	76	High	+	Direct	Could not determine*
Valovirta 2006[168] Savolainen 2006[175]	Tree mix	High dose Low dose Placebo	98	Medium	High dose + Low dose +	Direct	High dose Moderate Low dose Moderate
Moreno-Ancillo 2007[153]	Grass mix plus Olive	High dose Low dose Placebo	105	Low	+	Direct	Weak
Panzner 2008[140]	Grass mix plus Olive	SLIT Placebo-SLIT	35	Low	+	Direct	Strong
Nelson 1993[118]	Cat	SLIT Placebo	44	Medium	+	Direct	Weak

+ = positive; SLIT = sublingual immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Conjunctivitis Symptoms

Thirteen studies of sublingual immunotherapy reported conjunctivitis symptom scores (Appendix E, Evidence Table E7).[124,131,132,137,140,142,153,157,160,162,163,168,174] The comparator in all studies reporting conjunctivitis scores was placebo. All of the studies used a numeric scale when reporting the symptoms, but none of the scales appeared to be validated or consistent between studies. One study had separate scores reported for ocular redness and ocular pruritus.[142] The duration of assessment ranged from one pollen season up to 2 years.

Forty-six percent of the studies demonstrated significant improvement in conjunctivitis symptom scores when compared with placebo or to pre-treatment symptom levels in the sublingual immunotherapy arm. Three studies demonstrated improvement with sublingual immunotherapy when compared with placebo during peak season or the entire pollen season.[140,142,168] Two studies demonstrated significant improvement pre- versus post-treatment in the sublingual arms. [124,147]

We conclude that there is moderate grade evidence that sublingual immunotherapy reduces conjunctivitis symptoms based on 13 studies (Table 28).

Table 28. Body of evidence for sublingual immunotherapy affecting conjunctivitis symptoms

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Sabbah 1994[142]	Grass mix	SLIT Placebo	58	Medium	+	Direct	Could not determine*
de Blay, 2007[174]	Grass mIx	SLIT Placebo	118	Medium	+	Direct	Could not determine*
Panzner 2008[140]	Grass mix	SLIT Placebo-SLIT	35	Low	+	Direct	Strong
Moreno-Ancillo, 2007[153]	Grass mix and Olive	SLIT Placebo	105	Low	+	Direct	Moderate
Tari 1990[157]	Dust mite	SLIT Placebo	58	Low	+	Direct	Weak
deBot 2011[131]	Dust mite	SLIT Placebo	257	High	+	Direct	Could not determine*
Lima 2002[137]	Timothy	SLIT Placebo	56	Low	+	Direct	Could not determine*
Bowen 2004[132]	Ragweed	SLIT Placebo	83	Medium	-	Direct	Could not determine*
D'Ambrosio 1999[124]	*Parietaria*	SLIT Placebo	30	Medium	+	Direct	Could not determine*
Pajno 2004[160]	*Parietaria*	SLIT Placebo	30	Low	NR	Direct	Could not determine*
Vervloet, 2007[162]	Mountain Cedar	SLIT Placebo	76	High	+	Direct	Weak
Vourdas, 1998[163]	Olive	SLIT Placebo	70	Medium	+	Direct	Strong
Valovirta, 2006[168] Savolainen, 2006[175]	Tree Mix	High dose Low dose Placebo	98	Medium	High dose + Low dose +	Direct	High dose: Strong Low dose: Moderate

+ = positive; SLIT = sublingual immunotherapy

*Data provided in the article was not enough to calculate the magnitude of effect.

Medication Use

Medications scores were reported in 40 of the sublingual immunotherapy trials included in this review (Appendix E, Evidence Table E8).[44,45,117,120,121,127,130-133,135,137-142,146,147,149,151,154,156,159-165,167,168, 123,124,143,144,153,158,169,174] However, two studies were not included in the grading of the body of evidence due to the lack of a control group not receiving sublingual immunotherapy.[149,164] Therefore, 38 studies were included in grading this body of evidence (Table 29). All of the studies used some type of numeric scoring scale for medication use, but none of the scales or scoring appeared to be validated or consistent between studies. The duration of assessment of medication scores ranged from one pollen season up to 5 years. The medication use that was scored varied from study to study and included such medications as inhaled beta-agonists and corticosteroids for control of pulmonary symptoms as well as oral antihistamines and intranasal corticosteroids.

Forty-seven percent of the studies reporting medication scores in the body of evidence demonstrated significant improvement in this domain with sublingual immunotherapy. Fifteen of the 38 studies with medication scores reported significant improvement in medication scores when compared with controls. [44,45,117,123,133,138,140,143,146,147,158,162,165,168,176] In four of these studies the comparator group was pharmacotherapy or conventional treatment,[45,138,143,147] and in the remaining 11 studies the comparator was placebo. Five studies demonstrated significant

improvement in pre-treatment versus post-treatment medication scores in the sublingual immunotherapy arms.[44,120,124,143,161]

Grass mix was the most frequently studied allergen, with 9 studies reporting medication scores; five showed benefit from sublingual immunotherapy,[44,138,140,142,165] but four studies demonstrated no improvement.[139,141,167,174] Medication scores were reported in 8 studies with dust mite; of these, two studies found statistically significant improvement in medications scores,[117,120] while six did not show significant benefit in medication use.[121,130,131,154,156,159] Five trials of *Parietaria* immunotherapy studies reported medication scores; three showed significant improvement,[124,161,176] while two found no improvement.[144,160]

The two studies that did not include a non-sublingual control group were not included in the body of evidence. One compared co-seasonal to continuous grass sublingual immunotherapy and found no significant difference in medication scores.[164] The second study compared 3, 4, and 5 years of dust mite sublingual immunotherapy.[149] After 20 years, the longest treatment group had a stronger magnitude of effect when compared with the shortest treatment group.

We conclude that there is moderate grade evidence that sublingual immunotherapy reduces medication use based on 38 studies with 2724 subjects (Table 29).

Table 29. Body of evidence for sublingual immunotherapy affecting medication use

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pajno 2000[117]	Dust mite	SLIT Placebo	27	Low	+	Direct	Strong
Lue 2006[120]	Dust mite	SLIT Placebo	20	Medium	+	Direct	Moderate
Niu 2006[121]	Dust mite	SLIT Placebo	110	High	ICS + BA + AH+ OC +	Direct	ICS: Weak BA: Strong AH: Strong OC: Strong
Tseng, 2008[130]	Dust mite	SLIT Placebo	63	Medium	BA – AH +	Direct	BA: Moderate AH: Moderate
Guez, 2000[159]	Dust mite	SLIT Placebo	72	Medium	+	Direct	Weak
Hirsch 1997[154]	Dust mite	SLIT Placebo	30	Medium	BA/TH + AH/INS -	Direct	Could not determine*
deBot 2011[131]	Dust mite	SLIT Placebo	257	High	+	Direct	Could not determine*
Bush 2011[156]	Dust mite	High dose Low dose Placebo	31	Medium	+	Direct	Weak
Ott, 2008[139]	Grass mix	SLIT Placebo	213	Medium	+	Direct	Weak
Roder 2007[141]	Grass mix	SLIT Placebo	204	Low	-	Direct	Could not determine*
Feliziani, 1995[165]	Grass mix	SLIT Placebo	34	Medium	+	Direct	Could not determine*
Pradalier 1999[167]	Grass mix	SLIT Placebo	126	Medium	+	Direct	Could not determine*
de Blay 2007[174]	Grass mix	SLIT Placebo	118	Medium	+	Direct	Moderate
Sabbah 1994[142]	Grass Mix	SLIT Placebo	58	Medium	+	Direct	Strong
Panzner 2008[140]	Grass mix	SLIT Placebo-SLIT	35	Low	+	Direct	Strong
Marogna 2009[44]	Grass Mix	SLIT Budesonide	51	Medium	+	Direct	Strong

Table 29. Body of evidence for sublingual immunotherapy affecting medication use (continued)

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Novembre 2004[138]	Grass Mix	SLIT Control	113	High	+	Direct	Could not determine*
D'Ambrosio 1999[124]	*Parietaria*	SLIT Placebo	30	Medium	+	Direct	Strong
La Rosa, 1999[144]	*Parietaria*	SLIT Placebo	41	Low	NR	Direct	Could not determine*
Pajno 2004[160]	*Parietaria*	SLIT Placebo	30	Low	+	Direct	Could not determine*
Passalacqua 1999[161]	*Parietaria*	SLIT Placebo	30	Low	+	Direct	Moderate
Lima 2002[137]	Timothy	SLIT Placebo	56	Low	+	Direct	Could not determine*
Amar, 2009[151]	Timothy	SLIT Monotherapy SLIT Multiple Placebo	58	Low	+	Direct	Weak
Makino 2010[135]	Japanese Cedar	SLIT Placebo	25	Medium	+	Direct	Weak
Okubo 2008[127]	Japanese Cedar	SLIT Placebo	61	Medium	+	Direct	Weak
Vervloet, 2007[162]	Mountain cedar	SLIT Placebo	76	High	+	Direct	Strong
Bowen 2004[132]	Ragweed	SLIT Placebo	83	Medium	+	Direct	Weak
Skoner 2010[133]	Short ragweed	High dose Low dose Placebo	115	Low	+	Direct	High Dose Strong Low dose Moderate
Marogna 2005[146]	White birch	SLIT Placebo	79	Medium	+	Direct	Strong
Marogna 2010[45]	Birch	SLIT Montelukast	33	High	+	Direct	Strong
Vourdas, 1998[163]	Olive	SLIT Placebo	70	Medium	OC+ NR for other medications	Direct	Could not determine*
Pozzan 2010 [169]	*Alternaria*	SLIT Placebo	52	Medium	+	Direct	Strong
Cortellini 2010[143]	*Alternaria*	SLIT Placebo	27	High	+	Direct	Strong
Valovirta 2006 [168] Savolainen 2006[175]	Tree mix	High dose Low dose Placebo	98	Medium	High dose + Low dose +	Direct	High dose: Moderate Low dose: Weak
Voltolini 2001[143]	Tree mix	SLIT medication	30	Medium	+	Direct	Strong

Table 29. Body of evidence for sublingual immunotherapy affecting medication use (continued)

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Marogna 2006 [147]	Birch and Grass	SLIT - birch SLIT - grass SLIT Birch/grass Pharmaco-therapy	48	Medium	+	Direct	Strong
Moreno-Ancillo, 2007[153]	Grass mix Olive tree	SLIT Placebo	105	Low	+	Direct	Weak
Bahceciler 2001[158]	Grass mix and Olive	SLIT Placebo	15	Medium	BA + INS + ICS +	Direct	BA: Moderate INS: Strong ICS: Strong

+ = positive; - = negative; AH = antihistamine; BA = beta agonist; ICS = inhaled corticosteroid; INS = intranasal steroid; NR = not reported; OC = oral corticosteroids; SLIT = sublingual immunotherapy; TH = theophylline
*Data provided in the article was not enough to calculate the direction of change or magnitude of effect.

Combined Symptom and Medication Scores

Combined symptom plus medication scores were reported in 21 of the sublingual immunotherapy studies included in this review and involved 1312 subjects (Appendix E, Evidence Table E9).[43,126-128,134,135,138,139,159,161,164,166 122-124,133,143,144,147,149,153] However, 2 studies did not include a non-sublingual comparator group and were not included in the body of evidence grading.[149,164] Therefore, 19 studies were included in the body of evidence grading (Table 30).

All of the studies used some type of numeric scoring scale for the combination score, but none of the scales or scoring appeared to be validated or consistent between studies. The duration of assessment of medication scores ranged from one pollen season up to 4 years. The symptoms scored as part of the studies were combined nasal, eye, and bronchial in the majority of studies; exceptions were five studies that included only nasal symptoms.[126-128,135,159] The medications scored varied from study to study and included such medications as inhaled beta-agonists and corticosteroids for control of pulmonary symptoms as well as oral antihistamines and intranasal corticosteroids.

Thirteen (68%) of the studies reporting a combination symptom plus medication score demonstrated significant improvement in scores with sublingual immunotherapy. Ten of the 13 studies with combination symptom plus medication scores reported significant improvement in medication scores when compared with controls.[43,122,123,126,128,133,143,148,159,166] In three of these studies, the comparator groups was pharmacotherapy/conventional treatment,[43,122,143] and in the remaining seven studies the comparator was placebo. Five studies demonstrated significant improvement in pre-treatment versus post-treatment medication scores in the sublingual immunotherapy arms.[122,124,147,159,161] Three studies of *Parietaria* allergen reported combination symptom plus medications scores: all three found significant improvement in scores.[43,124,161] Four studies of Japanese cedar allergen[126-128,135] produced mixed results, as did three grass mix studies.[138,139,166]

The two studies not included in the body of evidence compared different sublingual groups.[149,164] One compared differing lengths of dust mite sublingual immunotherapy, but p-values were not reported and magnitude of effect was unable to be determined. The second study

compared co-seasonal to continuous sublingual immunotherapy and found no difference in reported medication plus symptom score.

We conclude that there is moderate grade evidence that sublingual immunotherapy reduces medication use and improves symptom control (Table 30).

Table 30. Body of evidence that sublingual immunotherapy affects combined medication use and symptoms

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Horiguchi, 2007[126]	Japanese cedar	SLIT Placebo	67	Medium	+	Direct	Could not determine*
Okubo 2008[127]	Japanese cedar	SLIT Placebo	61	Medium	+	Direct	Could not determine*
Makino 2010[135]	Japanese cedar	SLIT Placebo	25	Medium	+	Direct	Could not determine*
Fujimura 2011[128]	Japanese cedar	SLIT Placebo	103	Low	NR	Direct	Could not determine*
D'Ambrosio 1999[124]	*Parietaria*	SLIT Placebo	30	Medium	+	Direct	Strong
Passalacqua 1999[161]	*Parietaria*	SLIT Placebo	30	Low	+	Direct	Weak
D'Ambrosio 1996[43]	*Parietaria*	SLIT Pharmaco-therapy	40	High	+	Direct	Could not determine*
Novembre 2004[138]	Grass Mix	SLIT Control	113	High	+	Direct	Could not determine*
Ott, 2008[139]	Grass mix	SLIT Placebo	113	Medium	+	Direct	Weak
Pfaar, 2007[166]	Grass mix	SLIT Placebo	185	Medium	+	Direct	Strong
Guez, 2000[159]	Dust mite	SLIT Placebo	72	Medium	+	Direct	Weak
Cortellini 2010[123]	*Alternaria*	SLIT Placebo	27	High	+	Direct	Could not determine*
Di Rienz, 2006[134]	Mountain cedar	SLIT Placebo	34	High	+	Direct	Weak
Voltolini 2001[143]	Tree Mix	SLIT Medications	20	Medium	+	Direct	Could not determine*
Skoner 2010[133]	Ragweed	High dose Low dose Placebo	115	Low	+	Direct	Strong
Moreno-Ancillo 2007[153]	Grass Mix and Olive	SLIT Placebo	105	Low	+	Direct	Weak
Sambugaro 2003[122]	Dust mite, grass mix, ragweed, *Parietaria*	8-day induction 15-day induction 20-day induction Untreated	58	Medium	+	Direct	Strong
Marogna 2008[148]	Dust mite, birch, grass mix, *Parietaria*	SLIT Control	216	Medium	+	Direct	Strong
Marogna, 2006[147]	Birch, grass, birch plus grass	SLIT - birch SLIT - grass SLIT Birch/grass Pharmaco-therapy	48	Medium	+	Direct	Strong

+ = positive; NR = not reported; SLIT = sublingual immunotherapy

*Data provided in the article was not enough to calculate the magnitude of effect.

Quality of Life

Quality of life was reported in eight studies involving 819subjects.[127,128,131,134,135,141,153,155] The instrument used to assess quality of life was a validated, disease-specific instrument: The Rhinoconjunctivitis Quality of Life questionnaire (Adult, Pediatric, Adolescent, and Japanese language versions). Four of the eight studies reported significant improvement in disease-specific quality of life when compared with placebo.[127,128,134,135] (Appendix E, Evidence Table E11). Two studies reported significant improvement in the sublingual immunotherapy group when comparing initial to final quality of life scores.[153,155] One study found no improvement in quality of life either compared with control group or with pre-treatment quality of life scores.[141]

We concluded that there is moderate grade evidence that sublingual immunotherapy improves disease-specific quality of life (Table 31).

Table 31. Body of evidence that sublingual immunotherapy affects disease-specific quality of life

Study	Quality of Life Measure	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Okubo 2008[127]	Japanese RQLQ[1]	Japanese cedar	SLIT Placebo	61	Medium	+	Direct	Strong
Makino 2010[135]	Japanese RQLQ[1]	Japanese cedar	SLIT Placebo	25	Medium	+	Direct	Could not determine*
Fujimura 2011[128]	Japanese RQLQ[1]	Japanese cedar	SLIT Placebo	103	Low	+	Direct	Could not determine*
O'Hehir 2009[155]	RQLQ[1]	Dust mite	SLIT Placebo	30	High	+	Direct	Could not determine*
Di Rienz 2006[134]	RQLQ[1]	Mountain cedar	SLIT Placebo	34	Medium	+	Direct	Strong
Moreno-Ancillo 2007[153]	RQLQ[1]	Grass mix and Olive	SLIT Placebo	105	Medium	+	Direct	Moderate
deBot 2011[131]	Pediatric RQLQ[1] Adolescent RQLQ[1]	Dust mite	SLIT Placebo	257	High	- -	Direct	Could not determine* Could not determine*
Roder 2007[141]	Pediatric RQLQ[1] Adolescent RQLQ[1]	Grass mix	SLIT Placebo	204	Low	- +	Direct	Could not determine* Could not determine*

+ = positive; - = negative; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SLIT = sublingual immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Pulmonary Function Testing and Chemical Bronchial Provocation

Pulmonary function testing results were reported in 14 studies involving 1375 subjects (Appendix E, Evidence Table E10). Pulmonary function results described here are from studies where subjects had a diagnosis of asthma that was objectively confirmed with methods other than clinical impression. As pulmonary function tests are not a direct clinical outcome, this evidence was not graded as a body of evidence. The studies reported measures of pulmonary function, but were heterogeneous in terms of which measures were reported: FEV1 was most commonly reported, but other measures included percent of patients with a positive

methacholine challenge, peak expiratory flow rate (PEF), forced vital capacity (FVC), and PD20, the dose a substance administered by aerosol, which causes the FEV1 to fall by 20 percent.

All studies reported either significant improvement compared with controls or when considering pre- versus post-treatment pulmonary function. Six of ten studies reported a significant improvement when comparing pre-treatment to post-treatment FEV1 in groups treated with sublingual immunotherapy,[120-122,147,157,171] and two reported a significant improvement in the FEV1 of the sublingual immunotherapy group when compared with controls.[45,122] Two trials reported a significant decrease in the number of participants with a positive methacholine challenge in the sublingual immunotherapy group when compared with controls.[145,148] Four studies reported a significant decrease in PD20 compared with controls,[44,45,147,149], and three also demonstrated significant improvement when comparing post-treatment to pre-treatment scores.[44,45,147] We did not grade the evidence for indirect outcomes such as pulmonary function test results. However, we observed that sublingual immunotherapy consistently improves measure of pulmonary function in the allergic asthmatic population.

Allergen Challenge (Provocation)

Ten studies of sublingual immunotherapy studies challenged subjects to specific allergen after treatment in order to quantify symptoms (Appendix E, Evidence Table E11). Six studies used nasal provocation.[129,143,151,154,157,161] Three studies performed conjunctival provocation tests.[123,137,144] One study provoked cat-allergic subjects by having them remain in a "cat allergen" room.[170] Seventy percent of the studies using a specific ocular or nasal allergen challenge reported a significant improvement in symptoms in the sublingual immunotherapy groups. Two studies used bronchial challenges.[156,157] Both studies found significant improvement in pulmonary function testing with the dust mite bronchial challenge after sublingual immunotherapy.

Long-Term Outcomes: Disease Modification, Disease Prevention

In our review, we sought information regarding long-term outcomes in allergic rhinitis and asthma (Appendix E, Evidence Table E12). Disease modification in asthma was addressed in two studies included in this review.[121,148] A study by Niu et al found that sublingual immunotherapy with dust mite in children (ages 6 to 12 years) decreased the severity of asthma over 6 months of treatment when compared with controls ($p=0.043$).[121] Severity in this study was determined by a global assessment by physicians unfamiliar with the patient who reviewed the asthma scores, medication consumption, and pulmonary function tests. In a study of 216 children undergoing sublingual immunotherapy with dust mite, tree, and grass, Marogna found a significantly lower percentage of children with mild persistent asthma at the conclusion of the study.[148]

Asthma prevention was reported in one of the sublingual immunotherapy studies,[138] and in one 8-year followup to a prior study. [144] Novembre et al. found that grass pollen sublingual immunotherapy in children significantly decreased the development of asthma over 3 years;[138] controls in this study developed asthma 3.8 times more frequently. However, in the 8-year follow-up study, 2 years of sublingual immunotherapy had no asthma preventative effect.[144]

Prevention of new allergy sensitivities was discussed in three studies. Marogna found that treatment with multi-antigen sublingual immunotherapy (dust mite, birch, weeds, and grass mix) decreased the development of new skin sensitizations significantly ($p=0.01$);[145] he reported in a second study that the proportion of children with new allergen skin sensitivities was significantly

decreased after 3 years.[148] However, in a different study with 8-year follow-up, there was no preventative effect on the development of new sensitivities 2 years after *Parietaria* sublingual immunotherapy. [144] In a 2010 study by Marogna comparing 3, 4, and 5 years of sublingual immunotherapy; in the 5 year group, 11.7 percent developed new sensitivities compared with 21.4 percent in the 3 year group.

Other Outcomes

Adherence

Adherence and compliance were discussed infrequently in the articles, but were discussed by Marogna.[145] Adherence was determined by measuring the amount of remaining extract in returned vials compared with expected consumption as prescribed: poor adherence was less than 40 percent consumption, insufficient was less than 60 percent consumption, good was 60 to 80 percent consumption, and excellent was more than 80 percent consumption. Adherence was found to be excellent in 76 percent of subjects and good in 18 percent of subjects. In a second study by the same author, adherence was found to be excellent in 74 percent of subjects.[148] Another study reported that 14 percent of subjects had poor compliance, and 48 percent of subjects forgot to take their medications from time to time.200 In a 2010 study of 15 patients, adherence was greater than 80 percent in 10 subjects, and greater than 60 percent in five subjects.[45] Another 2010 study found adherence 85-95 percent determined by the residual volume of extract in returned vials[123] (Appendix E, Evidence Table E11).

Single Versus Multiple Antigen Sublingual Immunotherapy

Two sublingual studies included in this review examined single versus multi-antigen immunotherapy.[147,151] The first of these articles, by Amar, compared Timothy Grass monotherapy to Timothy Grass multi-antigen therapy, consisting of Timothy Grass plus 9 other allergens.[151] This study included one outcome of interest to the current review, nasal allergen challenge. While nasal challenge with Timothy Grass yielded significantly better results when comparing timothy monotherapy to placebo, there was no difference in Timothy Grass multi-antigen versus placebo. In Marogna's paper, 3 groups were compared: sublingual birch, sublingual birch plus grass, and pharmacotherapy.[147] Marogna found that the multi-antigen treatment group had significantly greater improvement in clinical symptoms when compared with the single antigen group. The data is insufficient to comment on effectiveness of single versus multiple antigen sublingual immunotherapy.

Biomarkers

During the course of the review, the number of studies reporting select biomarkers was recorded: IgG total, IgG4, and IgE. Eleven studies reported changes in specific IgG, 28 study-specific IgG4, and 32 IgE (total and/or specific IgE (Appendix E, Evidence Table E13).

Conclusion: Summary of Evidence for Key Question 1

When considering the key evidence for the efficacy and effectiveness of sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma, the pertinent clinical outcomes include symptom scores, medication use, and quality of life. Pulmonary function testing is a useful, objective, indirect measure of asthma that can be measured by clinicians in the office.

The strength of evidence regarding the effectiveness of sublingual immunotherapy is moderately supportive that this treatment improves clinical outcomes (Table 32).

Table 32. Summary of strength of evidence regarding the effectiveness of sublingual immunotherapy

Outcome	Number of Studies/ Number of Participants	Overall Risk of Bias	Direction of Change	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Asthma Symptoms	13 / 625	1 high 8 medium 4 low	13 positive	Consistent	Direct	10 strong 1 moderate 1 weak 1 CND	2 studies with low RofB AND strong magnitude	High
Rhinitis or Rhino-conjunctivitis Symptoms	35 / 2658	5 high 20 medium 10 low	35 positive	Consistent	Direct	9 strong 5 moderate 8 weak 13 CND	1 study with low RofB AND strong magnitude 6 studies with medium RofB AND strong magnitude	Moderate
Asthma plus Rhinitis or Rhino-conjunctivitis Combined symptoms	5 / 308	5 medium	4 positive 1 NR 1 +/- *	Consistent	Direct	2 strong 1 moderate 2 CND	2 studies with medium RofB AND strong magnitude 1 study with medium RofB and moderate magnitude 2 studies with medium RofB and magnitude not determinable	Moderate
Conjunctivitis Symptoms	13 / 1074	2 high 6 medium 5 low	11 positive 1 negative 1 NR	Consistent	Direct	3 strong 2 moderate 2 weak 7 CND	5 studies with low RofB AND 1 of these with strong magnitude 6 studies with medium RofB AND 1 of these with strong magnitude 7 studies with insufficient data to determine magnitude of effect	Moderate

Table 32. Summary of strength of evidence regarding the effectiveness of sublingual immunotherapy (continued)

Outcome	Number of Studies/ Number of Participants	Overall Risk of Bias	Direction of Change	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Medication Use	38 / 2724	6 high 22 medium 10 low	33 positive 1 negative 1 NR 3 +/- *	Consistent	Direct	13 strong 4 moderate 8 weak 10 CND 3 s/m/w*	10 studies with low RofB; 2 of these with strong magnitude; 2 with low magnitude of effect and 4 of these with magnitude not determinable 22 studies with medium RofB ;7 of these with strong magnitude, 6 of these with low magnitude of effect 6 studies with high RofB AND 3 of these with strong magnitude 9 studies with insufficient data to determine magnitude of effect	Moderate
Combined Medication plus Symptoms	19 / 1462	4 high 11 medium 4 low	18 positive 1 NR	Consistent	Direct	6 strong 5 weak 8 CND	4 studies with low RofB: 1 of these with strong magnitude and 2 with low magnitude 11 studies with medium RofB AND 5 of these with strong magnitude 8 studies with insufficient data to determine magnitude of effect 4 studies with high RofB, 3 of these insufficient data to determine magnitude of effect	Moderate
Disease-Specific Quality of Life	8 / 819	2 high 4 medium 2 low	6 positive 1 negative 1 +/-*	Consistent	Direct	2 strong 1 moderate 5 CND	4 studies with medium RofB AND 2 of these with strong magnitude 2 studies with low RofB AND insufficient data to determine magnitude of effect 5 studies with insufficient data to determine magnitude of effect	Moderate

+ = positive; - = negative; s: strong, m moderate, w weakCND = could not determine; NR = not reported; RofB = risk of bias
*Different direction or magnitude depending on comparators.

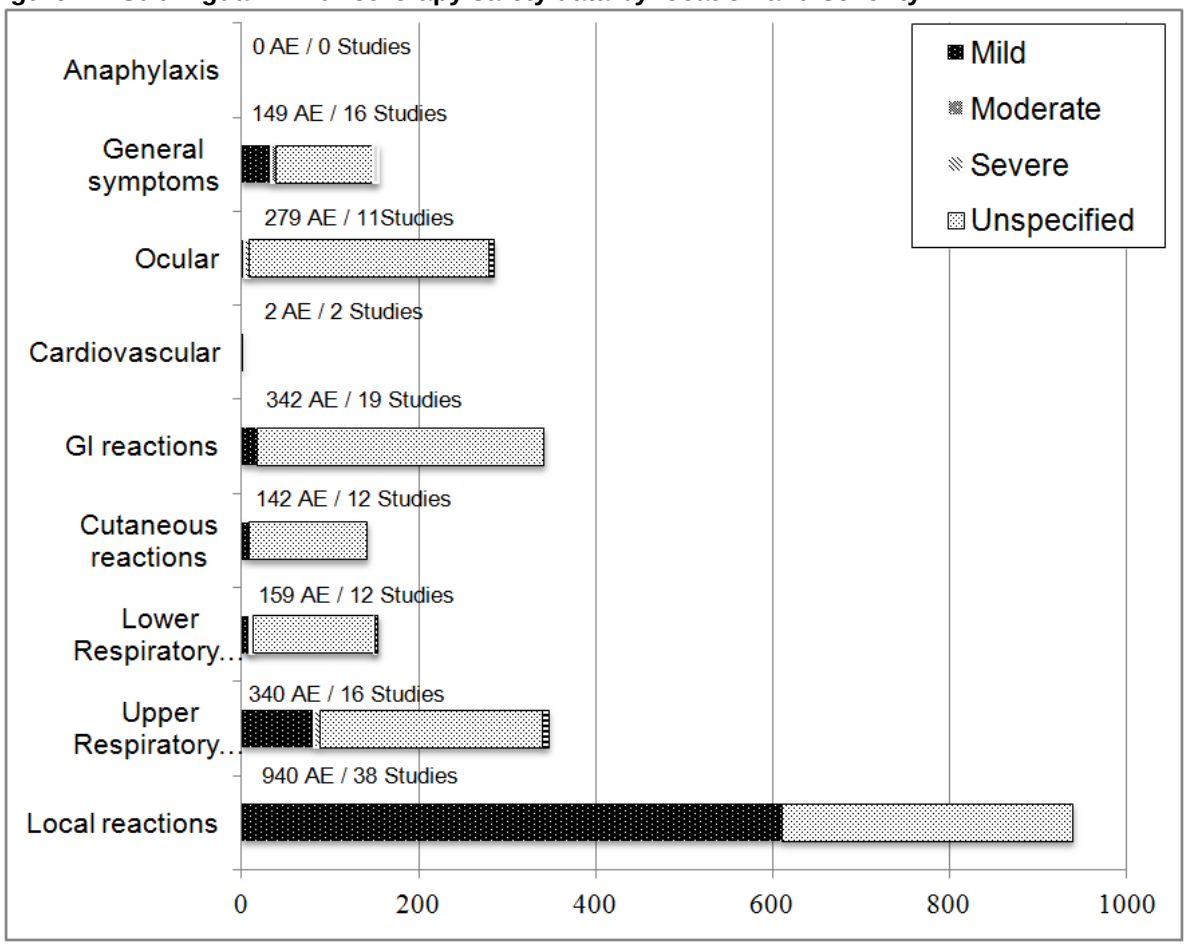
Key Question 2. What is the evidence for the safety of sublingual immunotherapy in patients with allergic rhinitis/rhinoconjunctivitis and/or asthma?

Key Points

- Local reactions (occurring at the site of allergen administration) were common across trials
- Systemic reactions were uncommon
- No life threatening systemic reactions or anaphylaxis were reported in these trials
- No deaths were reported

Figure 14 shows the distribution of events by location and severity. The graph shows only adverse events reported in the immunotherapy arms.

Figure 14. Sublingual immunotherapy safety data by location and severity



AE = adverse event; GI = gastrointestinal

We evaluated the safety of sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma by assessing the harms or adverse events reported in the included studies.

All 60 sublingual articles were analyzed for safety data. The studies did not uniformly report safety information, although 73 percent commented on safety.[117,118,121,122,125-127,129-132,134,136-142,144-149,151-157,159,160,162,163,166-169,172-175,177] The safety data were not reported in any consistent manner between studies, as there is no standard system for grading adverse events associated with sublingual immunotherapy. Because of the lack of a standard grading system and the heterogeneous reporting systems used by the different studies, the safety outcomes are presented descriptively and we conclude that the evidence is insufficient to comment about safety.

Local reactions were much more frequent in the groups receiving sublingual immunotherapy than in the comparator groups. In those studies in which local reactions occurred and were reported by percent of patients affected, the percent of subjects receiving immunotherapy with local reactions ranged from 0.2 to 97 percent. The placebo groups in which local reactions were reported ranged from 3 to 38.5 percent (Appendix E, Evidence Table E14). The local reactions were mild or unspecified in severity

Systemic reactions were more common in the groups receiving sublingual immunotherapy than in comparator groups. The reactions ranged from ocular, rhinitis/nasal, respiratory/asthma, cutaneous, gastrointestinal and cardiovascular Overall, there were few severe systemic reactions with a small number of exceptions: in one study, severe rhinitis was reported in subjects that exceeded their maximum dose of immunotherapy; in this same study, severe asthma symptoms were reported in subjects that exceeded their maximum dose.[157] These adverse events resolved when these subjects returned to a lower dose. There were no reported episodes of anaphylaxis, life threatening reactions, or death in any of the treated subjects across studies.

Key Points: Pediatric Studies

- Local reactions (occurring at the site of allergen administration) were more common across trials
- Systemic reactions were less common
- No life threatening systemic reactions or anaphylaxis were reported in these trials
- No deaths were reported

Evidence Synthesis

All eighteen articles about sublingual immunotherapy in children were analyzed for safety data. The studies did not uniformly report safety information, and 15 studies (83%) commented on safety.[117,131,138,144,148,152,154,157,163,168,121,130,164,178] The safety data was not reported in any consistent manner between studies, as there is no standard system for grading adverse events associated with sublingual immunotherapy. Because of the lack of a standard grading system and the heterogeneous reporting systems used by the different studies, the safety outcomes are presented descriptively and we concluded that the evidence is insufficient to comment about safety.

Local reactions were reported in 12 studies and were more frequent in the groups receiving sublingual immunotherapy than in the comparator groups. The local reactions were mild or unspecified. Three small studies reported local adverse reactions by number of events, and the average number of episodes of local reactions per participant in the sublingual arm ranged from 25 to 40 per 100 participants.[144,154,163] Local reactions were also reported in the placebo arms, ranging from seven to 19 per 100 participants (Appendix G, Evidence Table G31). Seven studies reported local reactions by percent of patients affected, and the percent of sublingual subjects with local reactions ranged from 0.7 to 50 percent.[117,131,138,148,152,163,168] Three studies reported

local reactions in the placebo group ranging from 14 to 25 percent[131,152,168] (Appendix G, Evidence Table G31).

Overall, there were few systemic reactions reported in eight studies. The reactions ranged from (in order of greatest to least number of studies reporting event): gastrointestinal, cutaneous, respiratory/asthma, cardiovascular, and rhinitis/nasal. Eight studies compared the occurrence of reactions in the sublingual and placebo arms.[117,131,138,144,152,154,163,168] In one of these studies, cutaneous systemic reactions were noted in 1.9 percent of 54 patients receiving sublingual immunotherapy, comparable to or less than the two placebo arms of 1.7 percent and 9.8 percent.[138] The other comparative study described a greater number of gastrointestinal events (nausea, abdominal pain, diarrhea) and reported 95 events per 100 patients receiving sublingual immunotherapy (20 patients in SLIT arm) compared with 5 events per 100 patients in the placebo arm (21 patients in placebo arm).[144] Another study had greater numbers of patients with 65 percent experiencing respiratory reactions in the placebo group compared with 57 percent of patients in the sublingual immunotherapy group.[131] Three studies reported cutaneous systemic reactions (rash, urticaria, angioedema) as percentage of patients, ranging from 0.7 percent in a study with 144 patients to 10 percent of patients in a study with 30 patients[138,148,157] Four studies reported gastrointestinal events as percent of patients with reactions, ranging from 0.7 to 11.4 percent. [138,148,157,168] One study reported rhinitis/nasal reactions with 0.7 events per 100 patients (1 asthma event/144 patients in SLIT arm).[148] Two studies reported lower respiratory reactions as percent of patients, ranging from 7 percent in a study with 15 patients per arm to 34 percent in a study with 32 patients per arm.[154,157] While few severe systemic reactions were reported, in one of these studies, severe rhinitis and severe asthma symptoms were reported in subjects that exceeded their maximum dose.[157] These adverse events resolved when these subjects returned to a lower dose. There were no reported episodes of anaphylaxis, life threatening reactions, or death in any of the treated subjects across studies.

Conclusion: Summary of Evidence for Key Question 2

The lack of consistent reporting and grading systems for sublingual immunotherapy made it impossible to pool safety data across studies. Furthermore, not all studies reported safety data. However, it appears that local reactions are common but mild. Systemic reactions can occur but are infrequent; no life-threatening reactions, anaphylaxis, or deaths were reported. The evidence is insufficient to comment on the safety of sublingual immunotherapy, both in adult and pediatric studies.

Key Question 3. Is the safety and effectiveness of sublingual immunotherapy different in distinct subpopulations with allergic rhinitis/rhinoconjunctivitis and/or asthma?

Key Points

- The evidence is insufficient to comment on the effectiveness of sublingual immunotherapy in the following subpopulations: the elderly, pregnant women, minorities, inner-city, and rural residents, and severe asthmatics.
- There is low evidence to support that there is difference in the effectiveness of sublingual immunotherapy for treating mono-sensitized individuals and poly-sensitized individuals.

Our review sought information on particular subgroups of patient populations of interest, including pediatric, the elderly, pregnant, minorities, and inner-city versus rural subjects. The reviewed articles did not present specific data on the following subgroups: elderly, pregnant women, minorities, inner-city, and rural residents. The articles in general excluded subjects with severe asthma. Insufficient data exist to comment on these subpopulations. However, 32 percent of the studies were performed on mono-sensitized subjects (Table 26-General summary table SLIT). There appears to be no consistent difference in effectiveness when considering mono-sensitized compared with poly-sensitized subjects and the effect of sublingual immunotherapy. Eighteen pediatric studies of sublingual immunotherapy were reviewed as a distinct subpopulation.

Sublingual Immunotherapy in the Pediatric Population

Eighteen studies focused exclusively on children[117,120,121,130,131,138,141,144,148,152,154,157,158,160,163,164,168,171] and four studies included both children and adults[145,165,170,174] The subgroup analysis for the pediatric population evaluates the 18 studies that only include children 18 years of age or younger. All articles included were randomized controlled trials which reported clinical outcomes. These 18 articles with a total of 1583 subjects comprised the evidence base to answer the Key Questions regarding sublingual immunotherapy for inhalant allergens in the pediatric population. The publication dates of the included studies ranged from 1990 through 2011. The publications originated from Europe and Asia. The primary diagnoses of the subjects studied in the articles included: asthma in three studies;[117,120,121] rhinitis in two studies;[130,131] rhinoconjunctivitis in four studies;[138,141,144,152] asthma and rhinitis in four studies;[148,154,157,158] and asthma with rhinoconjunctivitis in five studies[160,163,164,168,171] (Appendix G, Evidence Table G18).

Studies included perennial and/or seasonal allergens. There were nine studies each evaluating perennial and seasonal allergens for sublingual immunotherapy (Appendix G, Evidence Table G18). When considering the specific types of allergens used in the studies, these allergens were used from greatest to least frequency: dust mite (9 studies) [117,120,121,130,131,154,157,158,171] grass (4 studies),[138,141,152,164] tree (2 studies),[163,168] weeds (2 studies)[144,160] and mixed or multiple allergens (1 study).[148] (Figure 4, SLIT Studies by Allergen) The majority of the studies used multiple allergens (60%), with the remaining studies using only one allergen (40%) in their study protocols. Eleven studies (61%) required no prior history of immunotherapy.[117,120,130,138,148,152,154,157,158,164,171] Eight studies (44%) focused on monosensitized individuals.[117,120,130,138,144,152,158,171]

The funding sources for the studies included the following, from most common to least common: industry, not stated, government, nonprofit, and other. Eleven studies (61%) had industry support, either partial or complete funding or received supplies from industry. Four studies did not identify the funding source for their study. One study was funded by academia. [152]

All included sublingual immunotherapy studies had at least one comparator group. The comparator group(s) included the following (Appendix G, Evidence Table G20): placebo (15 studies), other sublingual comparator group (3 studies), conventional treatment (pharmacotherapy) or symptomatic therapy comparator group (2 studies, 20%). All studies allowed either conventional pharmacotherapy (12 studies) or only rescue allergy medications (6 studies) during the study. Maintenance dosing interval varied from daily to twice a week. Duration of treatment of the included studies ranged from 6 months to 3 years. Studies used various units to report dosing, and many studies did not include a cumulative dose. Subjects

ranged from 4 to18 years of age. All studies that reported sex included both boys and girls. The range of means for duration of disease was 1 to 5.2 years.

Key Points

- The efficacy and effectiveness of sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma were evaluated in these categories of treatment effect: clinical endpoints, long-term outcomes, biomarker endpoints, convenience of therapy, and adherence to therapy.
- Pertinent clinical outcomes evaluated include symptom scores, medication use, and quality of life.
- High strength of evidence exists for the benefit of sublingual immunotherapy in asthma symptom control versus control groups, based on nine randomized controlled trials with 471 subjects.
- Moderate strength of evidence exists for the benefit of sublingual immunotherapy in asthma plus rhinitis/rhinoconjunctivitis (asthma combined scores) symptom control versus control groups, based on one randomized controlled trial with 98 subjects.
- Moderate strength of evidence exists for the benefit of sublingual immunotherapy in rhinitis/rhinoconjunctivitis symptom control versus control groups based on 12 randomized controlled trials with 1065 subjects.
- Moderate strength of evidence exists for the benefit of sublingual immunotherapy in control of conjunctivitis symptoms versus control groups, based on five randomized controlled trials with 513 subjects.
- Moderate strength of evidence exists for the benefit of sublingual immunotherapy versus control on decreasing medication use, based on 13 randomized controlled trials with 1078 subjects.
- Low strength of evidence exists for the benefit of sublingual immunotherapy versus control on improving allergy symptoms plus decreasing medication use based on two randomized controlled trials with 329 subjects.
- Insufficient evidence exists for the benefit of sublingual immunotherapy versus control on improving disease-specific quality of life, based on two randomized controlled trial with 461 subjects.
- The overall strength of evidence for use of sublingual immunotherapy in children and adolescents when considering all domains with pertinent clinical outcomes together is moderate.

We evaluated the efficacy and effectiveness of sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma by using the following evaluable categories of treatment effect: clinical endpoints, long-term outcomes, biomarker endpoints, convenience of therapy, and adherence to therapy.

Asthma Symptom Control

Asthma symptom scores alone, or asthma with rhinitis/rhinoconjunctivitis symptom scores (asthma combined scores), were reported in 11 studies (61%) [117,120,121,131,154,157,158,160,164,168,171] (Appendix G, Evidence Table G22). Asthma scores and asthma combined symptom scores were included from studies only if objective measure of lung function were used to diagnose subjects with asthma; studies using clinical symptoms only for the diagnosis of asthma were not included in the asthma symptom scores analyzed.[152,163]

The types of scales used to report asthma symptoms scores were not validated or uniform. Two studies used visual analog scores,[117,160] and the remainder used purely numeric systems to score the presence/absence of asthma symptoms and severity. [120,121,154,157,158,160,168,171,157, 164] The number of participants in each study ranged from 15 to 257. The duration of assessment ranged from one pollen season to 5 years. All of the studies used a placebo control group, except for one study that compared SLIT given continuously versus co-seasonally,[164] therefore its results are not included in the evidence grading table. One study additionally reported rhinitis symptoms scores and is also categorized as asthma combined symptom scores.[168] Asthma combined symptom scores include asthma plus rhinitis or rhinoconjunctivitis symptoms.

All the studies reporting asthma symptoms scores demonstrated significant improvement in asthma symptoms with sublingual immunotherapy. Six studies with asthma symptom scores demonstrated significant improvement in asthma symptoms with sublingual immunotherapy when compared with placebo;[117,120,121,131,154,160] six studies demonstrated significant improvement in pre- versus post-treatment asthma scores in the sublingual immunotherapy arm.[117,120,157,158,164,171]

In seven studies, the most common single allergen used in the asthma scores was dust mite.[117,120,121,131,154,157,158,171] All dust mite studies with asthma scores reported significant improvement in asthma scores with sublingual immunotherapy.

Nine studies fulfilling asthma diagnosis criteria reported on asthma symptom scores and included 471 participants. All included studies are randomized controlled trials. The overall strength of evidence is high to support sublingual immunotherapy use to improve asthma symptoms scores (Table 33).

Table 33. Body of evidence for sublingual immunotherapy affecting asthma symptoms in children and adolescents

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change*	Directness	Magnitude of Effect
Pajno 2000[117]	Dust mite	SLIT Placebo	24	Low	Night: + VAS: +	Direct	Night: Strong VAS: Strong
Lue 2006[120]	Dust mite	SLIT Placebo	20	Medium	+	Direct	Strong
Niu 2006[121]	Dust mite	SLIT Placebo	110	Medium	+	Direct	Strong
Hirsch 1997[154]	Dust mite	SLIT Placebo	30	Low	+	Direct	Strong
Bahceciler 2001[158]	Dust mite	SLIT Placebo	15	Medium	+	Direct	Moderate
Ippoliti 2003[171]	Dust mite	SLIT Placebo	86	Medium	+	Direct	Strong
Tari, 1990[157]	Dust mite	SLIT Placebo	58	Low	+	Direct	Moderate

Table 33. Body of evidence for sublingual immunotherapy affecting asthma symptoms in children and adolescents (continued)

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change*	Directness	Magnitude of Effect
Pajno 2003[160]	*Parietaria*	SLIT Placebo	30	Medium	Sx: + VAS: +	Direct	Sx: Could not determine VAS: Could not determine*
Valovirta 2006 [168] Savolainen 2006[175]	Tree mix	High dose Low dose Placebo	98	Medium	High dose: + Low dose: +	Direct	High dose: Strong Low dose: Moderate

+ = positive; Night = nighttime symptom score; SLIT = sublingual immunotherapy; Sx = asthma symptom score; VAS = visual analogue scale score

*Data provided in the article was not enough to calculate the magnitude of effect.

Asthma Plus Rhinoconjunctivitis Symptom Scores

Two trials of sublingual immunotherapy, involving 98 and 80 participants, reported combined symptoms scores.[164,168] In the first study by Valovirta et al, the "Asthma combined symptom score" included asthma plus rhinoconjunctivitis symptoms and used numeric scoring systems. This study, with medium risk of bias and comparing sublingual immunotherapy to placebo over the whole pollen season, demonstrated statistically significant positive effects on combined asthma plus rhinoconjunctivitis symptoms with sublingual immunotherapy. The second study by Pajno et al, was a medium risk of bias trial and compared SLIT coseasonal to SLIT continuous, with a weak magnitude of effect. Because this study does not have a placebo comparator, it was not included in the evidence grading.

We conclude that there is moderate evidence that sublingual immunotherapy reduces asthma and/or rhinitis or rhinoconjunctivitis symptoms (Table 34).

Table 34. Body of evidence for sublingual immunotherapy affecting asthma plus rhinitis/rhinoconjunctivitis symptoms in children and adolescents

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Valovirta, 2006 [168] Savolainen, 2006[175]	Tree mix	High dose Low dose Placebo	98	Medium	High dose: + Low dose: +	Direct	High dose: Strong Low dose: Moderate

+ = positive

Rhinitis or Rhinoconjunctivitis Symptoms

Rhinitis or combined rhinitis plus conjunctivitis symptom scores were reported in 12 (67%) of the sublingual immunotherapy articles included in this review (Appendix G, Evidence Table G23). The types of scale used in the studies and the scoring systems were not uniform; the articles utilized numeric point systems to grade symptoms or the mean daily total of all rhinitis symptoms. The duration of assessment ranged from 6 months up to three years. In the studies reporting rhinitis/rhinoconjunctivitis scores, the most common allergen used was dust mite, used in six studies, followed by grass mix and *Parietaria* in two studies each , and olive or tree mix in

one study each. The comparator group was placebo in all studies. One study also compared high and low dose sublingual immunotherapy.[168]

Overall, five of the 12 (42%) sublingual immunotherapy studies reporting rhinoconjunctivitis symptoms demonstrated significant improvement in allergic rhinoconjunctivitis scores with sublingual immunotherapy. Eleven studies compared sublingual immunotherapy to placebo, and two of these eleven studies (18%) found significant improvement in rhinitis/rhinoconjunctivitis scores with sublingual immunotherapy. [144,168] Four studies compared pretreatment to post-treatment rhinoconjunctivitis symptom scores in the sublingual immunotherapy study group,[130,157,158,171] and significant improvement was found in three of the four studies.[157,158,171]

We conclude that there is moderate grade evidence that sublingual immunotherapy improves control of rhinitis or rhinoconjunctivitis symptoms (Table 35).

Table 35. Body of evidence for sublingual immunotherapy for rhinitis/rhinoconjunctivitis symptoms in children and adolescents

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Roder, 2007[141]	Grass mix	SLIT Placebo	204	Low	+	Direct	Weak
Novembre 2004 [138]	Grass mix	SLIT Control	113	High	+	Direct	Could not determine*
Tseng, 2008[130]	Dust mite	SLIT Placebo	63	Medium	-	Direct	Weak
Hirsch 1997[154]	Dust mite	SLIT Placebo	30	Low	+	Direct	Weak
Bahceciler 2001[158]	Dust mite	SLIT Placebo	15	Medium	+	Direct	Moderate
Ippoliti 2003[171]	Dust mite	SLIT Placebo	86	Medium	+	Direct	Strong
Tari, 1990[157]	Dust mite	SLIT Placebo	58	Low	+	Direct	Moderate
deBot 2011[131]	Dust mite	SLIT Placebo	257	High	+	Direct	Weak
La Rosa 1999[144]	*Parietaria*	SLIT Placebo	41	Low	+	Direct	Could not determine*
Pajno 2004[160]	*Parietaria*	SLIT Placebo	30	Medium	+	Direct	Could not determine*
Vourdas, 1998[163]	Olive	SLIT Placebo	70	Medium	+	Direct	Strong
Valovirta 2006[168] Savolainen, 2006[175]	Tree mix	High dose Low dose Placebo	98	Medium	High dose: + Low dose: +	Direct	High dose: Moderate Low dose: Moderate

+ = positive; - = negative; SLIT = sublingual immunotherapy

*Data provided in the article was not enough to calculate the magnitude of effect.

Conjunctivitis Symptoms

Twenty-eight percent of the sublingual immunotherapy studies reported conjunctivitis symptom scores (Appendix G, Evidence Table G24). There were 5 trials involving 513 subjects.[131,157,163,168] The comparator in all studies reporting conjunctivitis scores was placebo. All of the studies used a numeric scale when reporting the symptoms, but none of the scales appeared to be validated or consistent between studies. The duration of assessment ranged from one pollen season up to 18 months.

Two of the 4 studies demonstrated significant improvement in conjunctivitis symptom scores when compared with placebo or to pre-treatment symptom levels in the sublingual immunotherapy arm.

We conclude that there is moderate grade evidence that sublingual immunotherapy reduces conjunctivitis symptoms (Table 36).

Table 36. Body of evidence for sublingual immunotherapy for conjunctivitis symptoms in children and adolescents

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Tari, 1990[157]	Dust mite	SLIT Placebo	58	Low	+	Direct	Weak
deBot 2011[131]	Dust mite	SLIT Placebo	257	High	+	Direct	Could not determine*
Vourdas 1998[163]	Olive	SLIT Placebo	70	Medium	+	Direct	Strong
Valovirta 2006[168] Savolainen 2006[175]	Tree Mix	High dose Low dose Placebo	98	Medium	High dose: + Low dose: +	Direct	High dose: Strong Low dose: Moderate
Pajno 2004[160]	*Parietaria*	SLIT Placebo	30	Low	NR	Direct	Could not determine*

+ = positive; NR = not reported; SLIT = sublingual immunotherapy

*Data provided in the article was not enough to calculate the magnitude of effect.

Medication Use

Medications scores were reported in 14 (77%) of the pediatric sublingual immunotherapy trials included in this review (Appendix G, Evidence Table G25). All of the studies used a placebo or control group, except for one study that compared SLIT given continuously versus coseasonally;[164] therefore its results are not included in the evidence grading table. These 13 studies included 1078 participants. All of the studies used some type of numeric scoring scale for medication use, but none of the scales or scoring appeared to be validated or consistent between studies. The duration of assessment of medication scores ranged from 6 months or one pollen season up to three years. The medications scored varied from study to study and included such medications as inhaled beta agonists and corticosteroids for control of pulmonary symptoms as well as oral antihistamines and intranasal and oral corticosteroids.

Four of the 13 (42%) studies reporting medication scores demonstrated significant improvement in this domain with sublingual immunotherapy. Four of the 13 studies with medication scores reported significant improvement in medication scores when compared with controls.[117,138,158,168] In one of these 4 studies, the comparator group was pharmacotherapy or conventional treatment;[138] in the remaining studies the comparator was placebo. One study demonstrated significant improvement in pre-treatment versus post-treatment medication scores in the sublingual immunotherapy arms.[120]

Six studies of dust mite allergen reported medications scores: two low-medium risk of bias studies found significant improvement in medications scores[117,120] while four medium-high risk of bias studies did not show significant benefit in medication use.[121,130,131,154] Two trials of Parietaria immunotherapy studies reported medication scores and found no improvement.[144,160] Two grass mix studies reported medication scores: one large, high risk of bias study showed a strong benefit from sublingual immunotherapy,[138] and the other large, low risk of bias study demonstrated no improvement.[141]

We conclude that there is moderate grade evidence that sublingual immunotherapy reduces medication use (Table 37).

Table 37. Body of evidence for sublingual immunotherapy for medication scores in children and adolescents

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pajno 2000[117]	Dust mite	SLIT Placebo	27	Low	+	Direct	Strong
Lue 2006[120]	Dust mite	SLIT Placebo	20	Medium	+	Direct	Moderate
Niu, 2006[121]	Dust mite	SLIT Placebo	110	High	AH: + BA: + ICS: + OC: +	Direct	AH: Strong BA: Strong ICS: Weak OC: Strong
Tseng, 2008[130]	Dust mite	SLIT Placebo	63	Medium	AH: + BA: -	Direct	AH: Moderate BA: Moderate
Hirsch 1997[154]	Dust mite	SLIT Placebo	30	Low	AH/INS: - BA/Th: +	Direct	Could not determine*
deBot 2011[131]	Dust mite	SLIT Placebo	257	High	+	Direct	Could not determine*
Roder 2007[141]	Grass mix	SLIT Placebo	204	Low	-	Direct	Could not determine*
Novembre 2004 [138]	Grass mix	SLIT Control	113	High	+	Direct	Could not determine*
La Rosa 1999[144] Leonardi 2009[179]	*Parietaria*	SLIT Placebo	41	Low	Could not determine*	Direct	Could not determine*
Pajno 2004[160]	*Parietaria*	SLIT Placebo	30	Low	+	Direct	Could not determine*
Vourdas 1998[163]	Olive	SLIT Placebo	70	Medium	OC: + NR for other medications	Direct	Could not determine*
Valovirta 2006 [168] Savolainen 2006[175]	Tree mix	High dose Low dose Placebo	98	Medium	High dose: + Low dose: +	Direct	High dose: Moderate Low dose: Weak
Bahceciler 2001[158]	Grass mix and Olive	SLIT Placebo	15	Medium	BA: + ICS: + INS: +	Direct	BA: Moderate ICS: Strong INS: Strong

+ = positive; - = negative; AH = antihistamine; BA = beta agonist; ICS = inhaled corticosteroid; INS = intranasal steroid; NR = not reported; OC = oral corticosteroids, Th = theophylline

*Data provided in the article was not enough to calculate the magnitude of effect.

Combined Symptoms Plus Medication Scores

Combined symptom plus medication scores were reported in two of the sublingual immunotherapy studies included in this review and involved 329 subjects[138,148] (Appendix G, Evidence Table G26). The duration of assessment of medication scores was three years for both studies, and symptom scores included nasal, eye, and bronchial symptoms. The medications scored varied from study to study. Medications in one study included nasal mast cell inhibitors, oral antihistamines, intranasal corticosteroids,[148] inhaled beta agonists and corticosteroids for control of pulmonary symptoms as well as oral antihistamines and intranasal corticosteroids. Medications allowed in the other study included oral antihistamines, nasal corticosteroids, bronchodilators, and ocular corticosteroids.[138]

One study reporting a combination symptom plus medication score demonstrated significant improvement with sublingual immunotherapy when compared with controls.[148] One study of grass mix allergen showed no significant difference between sublingual immunotherapy and conventional therapy.[138]

We conclude that there is low evidence that sublingual immunotherapy reduces combined medication use and symptom scores (Table 38).

Table 38. Body of evidence for sublingual immunotherapy for combined symptom plus medication scores in children and adolescents

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Marogna 2008[148]	Dust mite, birch, grass mix, *Parietaria*	SLIT Control	216	Medium	+	Direct	Strong
Novembre 2004[138]	Grass mix	SLIT Control	113	High	+	Direct	Could not determine*

+ = positive; SLIT = sublingual immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Quality of Life

Quality of life was reported in two studies involving 461 subjects.[131,141] The instruments used to assess quality of life in both studies were validated, disease specific instrument: The Pediatric and Adolescent Rhinoconjunctivitis Quality of Life questionnaires. One study found no improvement in quality of life.[141] The other study found no difference between SLIT and placebo groups in both children and adolescents after 2 years[131] (Table 39). (Appendix G, Evidence Table G27).

We conclude that there is insufficient evidence that sublingual immunotherapy affects disease-specific quality of life in children and adolescents.

Table 39. Body of evidence that sublingual immunotherapy affects disease-specific quality of life in children and adolescents

Study	Quality of Life Measure	Allergen	Comparators	Number of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
deBot 2011[131]	Pediatric RQLQ[1]	Dust mite	SLIT Placebo	257	High	-	Direct	Could not determine*
	Adolescent RQLQ[1]					-		Could not determine*
Roder, 2007[141]	Pediatric RQLQ[1]	Grass mix	SLIT Placebo	204	Low	-	Direct	Could not determine*
	Adolescent RQLQ[1]					+		Could not determine*

+ = positive; - = negative; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SLIT = sublingual immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Pulmonary Function

Pulmonary function testing results were reported in five studies involving 490 subjects. (Appendix G, Evidence Table G28). Pulmonary function results described here are from studies where subjects had a diagnosis of asthma that was objectively confirmed with methods other

than clinical impression. The studies reported measures of pulmonary function, but were heterogeneous in terms of which measures were reported: FEV1 was most commonly reported, but other measures included percent of patients with a positive methacholine challenge, PEF, and FVC.

All studies reported either significant improvement compared with controls or when considering pre- versus post-treatment pulmonary function. Four of five studies reported a significant improvement when comparing pre-treatment to post-treatment FEV1 in groups treated with sublingual immunotherapy.[120,121,157,171] One trial reported a significant decrease in the number of participants with a positive methacholine challenge in the sublingual immunotherapy group when compared with controls.[148]

Allergen and Nonspecific-Chemical Challenge (Provocation)

Three of the sublingual immunotherapy studies challenged subjects to a specific allergen after treatment in order to quantify symptoms (Appendix G, Evidence Table G28). Two studies used nasal provocation.[154,157] One of the nasal provocation studies found significant improvement in the sublingual immunotherapy arm before and after treatment after 1 year, although no difference was noted between the sublingual and placebo arms.[154] The other nasal provocation study also found a significant improvement in the sublingual immunotherapy arm before and after treatment,[157] but did not compare between the sublingual and placebo arms. One study performed conjunctival provocation tests and found significant improvement in response with sublingual immunotherapy compared with placebo.[144] Two of the three studies using a specific allergen challenge reported a significant improvement in symptoms in the sublingual immunotherapy groups. One study also used bronchial challenges and found significant improvement in FEV1 with the dust mite bronchial challenge after sublingual immunotherapy.[157]

Long-Term Outcomes: Disease Modification, Disease Prevention

In our review, we sought information regarding long-term outcomes in allergic rhinitis and asthma (Appendix G, Evidence Table G29). Disease modification in asthma was addressed in three studies included in this review.[121,148] Niu et al[121] found a significant effect on the number of patients with a decrease in asthma classification from mild/moderate persistent asthma to mild intermittent asthma, after 6 months of SLIT with dust mite allergen compared with placebo. Severity in this study was determined by a global assessment by physicians who reviewed the asthma scores, medication consumption, and pulmonary function tests and were not familiar with the patient. Marogna et al found no significant difference in the percentage of children with mild intermittent asthma after 3 years of SLIT compared with placebo.[148] LaRosa et al found similar reports of rhinitis symptoms during Parietaria pollen season after 8 years of followup in the SLIT and placebo groups.[151]

Asthma prevention was reported in two of the sublingual immunotherapy studies, and in one eight-year followup to a prior study.[138,144,179] Novembre et al found that fewer children developed asthma after 3 years of grass pollen SLIT vs conventional therapy; controls in this study developed asthma 3.8 times more frequently (RR, 3.8; 95% CI,1.5-10).[138] Marogna et al found a lower occurrence of the development of mild persistent asthma in SLIT patients versus pharmacotherapy group after 3 years. However, in an eight year follow-up of the LaRosa study of *Parietaria*, sublingual immunotherapy treatment for two years showed no asthma preventative effect.[144,179]

Prevention of new allergy sensitivities was discussed in one article and one followup report.[148,179] Marogna found that treatment with multi-antigen sublingual immunotherapy (dust mite, birch, weeds, and grass mix) significantly decreased the development of new allergen skin sensitizations after three years (OR, 0.6; 95% CI, 0.02-0.17).[148] However, in an eight year follow-up report of the LaRosa study, there was no preventative effect on the development of new sensitivities after receiving *Parietaria* sublingual immunotherapy for two years.[144,179]

Other Outcomes

Adherence and compliance were discussed infrequently in the articles. In a followup study by Marogna et al., adherence was found to be excellent in 74 percent of subjects.[148] Another study reported 53 percent compliance in the SLIT arm and 67 percent compliance in the placebo arm.[154]

During the course of the review, the number of studies reporting select biomarkers was recorded: IgG total, IgG4, and IgE. Three studies reported changes in specific IgG, eight study-specific IgG4, and 10 IgE (total and/or specific IgE). (Appendix G, Evidence Table G31).

Conclusion: Summary of Pediatric Evidence for Key Question 1

When considering the key evidence for the efficacy and effectiveness of sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma in children, the pertinent clinical outcomes include symptom scores, medication use, and quality of life (Table 40). The overall strength of evidence for use of sublingual immunotherapy in children and adolescents when considering all domains with pertinent clinical outcomes together is moderate.

Table 40. Summary of strength of evidence regarding the effectiveness of sublingual immunotherapy in children and adolescents

Outcome	Number of Studies/ Number of Participants	Risk of Bias	Direction of change	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Asthma Symptoms	9 / 471	6 medium 3 low	9 positive	Consistent	Direct	5 strong 2 moderate 1 CND 1 strong/ moderate*	3 studies with low RofB AND 2 of these with strong magnitude 6 studies with medium RofB AND 3 of these with strong magnitude	High
Asthma plus Rhinitis/ Rhino-conjunctivitis Symptoms	1 / 98	1 medium	1 positive	Consistent	Direct	1 strong/ moderate*	1 study with medium RofB and mod/strong magnitude	Moderate
Rhinitis/Rhino-conjunctivitis Symptoms	12 / 1065	2 high 6 medium 4 low	11 positive 1 negative	Consistent	Direct	2 strong 3 moderate 4 weak 3 cnd	2 studies with medium RofB AND moderate magnitude	Moderate
Conjunctivitis Symptoms	5 / 513	1 high 2 medium 2 low	4 positive 1 CND	Consistent	Direct	1 strong 1 weak 2 CND 1 strong/ moderate*	2 studies with medium RofB; 1 with strong magnitude and 1 with strong/moderate magnitude 1 study with low RofB AND weak magnitude	Moderate
Medication Use	12 / 998	3 high 6 medium 4 low	11 positive 1 negative 1 CND	Consistent	Direct	2 strong 2 moderate 6 CND 3 mix*	1 study with low RofB AND strong magnitude 1 study with medium RofB AND moderate magnitude	Moderate
Outcome	Number of Studies/ Number of Participants	Risk of Bias	Direction of change	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Combined Medication Plus Symptoms	2 / 329	1 high 1 medium	2 positive	Consistent	Direct	1 strong 1 CND	1 study with medium RofB AND strong magnitude	Low
Quality of Life	2 / 461	1 high 1 low	1 negative 1 +/-*	Consistent	Direct	2 CND	2 studies where magnitude could not be determined	Insufficient

+ = positive; - = negative; CND = could not determine; RofB = risk of bias
*Different direction depending on comparators.

Sublingual Versus Subcutaneous Immunotherapy

Eight studies published between 1989 and 2010 reported on the efficacy and safety of sublingual versus subcutaneous immunotherapy. Two studies originated from Italy,[177,180] five from Turkey,[35,36,46,181,182] and one from Denmark.[34] Rhinitis was the primary diagnosis of the subjects in three studies,[177,180,181] rhinoconjunctivitis in one study,[34] and asthma with rhinitis in four studies.[35,36,46,182] Three studies included only adults;[34,35,180] two included both adults and children,[177,181] and three studied children exclusively.[36,46,182] All but one study required that the subjects had received no prior immunotherapy[46] (Appendix F, Evidence Tables F1 and F2)

Two studies focused on tree pollen immunotherapy,[34,180] and the remaining six studied dust mite immunotherapy.[35,36,46,177,181,182] Each study allowed the participants to take either conventional or rescue medications during the study in addition to the immunotherapy or placebo. The maintenance dosing interval for subcutaneous immunotherapy ranged from once every three weeks to once every eight weeks. In the sublingual treatment group the maintenance dosing interval varied from daily to three times a week. The treatment duration across studies was between one and three years (Appendix F, Evidence Table F3).

Most of the studies had biases arising due to improper concealment of the allocation of interventions, unmasked interventions and incomplete reporting of missing data. Only one study was considered to be at low risk of bias[34] (Appendix F, Evidence Table F4).

Key Question 1. What is the evidence for the efficacy and effectiveness of sit in the treatment of allergic rhinoconjunctivitis and/or asthma?

Key Points

- Low grade evidence favors subcutaneous immunotherapy over sublingual for allergic asthma symptom control.
- Moderate grade evidence favors subcutaneous immunotherapy over sublingual for allergic nasal and/or eye symptom control.
- Low grade evidence exists to suggest little difference between routes of therapy for reducing medication use.
- Low grade evidence exists to favor subcutaneous immunotherapy over sublingual immunotherapy for reducing symptoms and medication use in dust mite allergic patients.

Asthma Symptom Control

Four trials of dust mite allergen immunotherapy reported improvement in asthma symptom scores.[35,36,46,182] Two studies reported changes in subcutaneous and sublingual immunotherapy groups compared with placebo[35,36] and two compared with pharmacotherapy.[46,182] Both the studies with a placebo comparison group reported significant changes in asthma symptom scores in subcutaneous treatment group after treatment relative to before treatment;[35,36] one reported significant changes in the sublingual immunotherapy group after treatment.[36] In the latter study, the group treated with subcutaneous immunotherapy showed a significantly greater reduction in reducing asthma symptom scores compared with the group treated with sublingual immunotherapy.[36] The other two studies demonstrated the effectiveness of subcutaneous and sublingual immunotherapy groups in reducing asthma symptom scores compared with pharmacotherapy.[46,182] Both studies reported that subcutaneous immunotherapy significantly reduced asthma symptoms compared with pharmacotherapy. One study reported that sublingual

immunotherapy also reduced asthma symptoms significantly,[182] while the other study reported that subcutaneous and sublingual treatment, when combined, reduced symptoms significantly compared with pharmacotherapy (Appendix F, Evidence Table F5).

The strength of evidence is low (4 studies, N=171) to support subcutaneous immunotherapy over sublingual immunotherapy for allergic asthma symptom control (Table 41).

Table 41. Body of evidence for sublingual immunotherapy versus subcutaneous immunotherapy affecting asthma symptoms

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Treatment favored	Directness	Magnitude of Effect
Mungan 1999[35]	Dust mite	SLIT SCIT Placebo	36	Medium	SCIT	Direct	Moderate
Eifan 2010[182]	Dust mite	SLIT SCIT Pharmacotherapy	48	Medium	SLIT	Direct	Moderate
Yuksel en 2011[36]	Dust mite	SLIT+ placebo injections SCIT+ placebo drops Placebo injections + drops	31	Medium	SCIT	Direct	Moderate
Keles 2011[46]	Dust mite	SLIT SCIT SLIT + SCIT Pharmacotherapy	56	Medium	SCIT	Direct	Weak

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Rhinitis/Rhinoconjunctivitis Symptoms

Six studies reported rhinitis or rhinoconjunctivitis symptom scores in their study participants.[34-36,46,181,182] There was no uniformity in reporting of these scores and none of the scales were validated. The duration of assessment varied from one to six years. Three dust mite immunotherapy trials reported significant improvement in rhinitis/rhinoconjunctivitis symptom scores in both sublingual and subcutaneous study groups post-treatment compared with pre-treatment.[35,36,181] One birch immunotherapy trial [34] and two dust mite trial[36,182] demonstrated that both sublingual and subcutaneous immunotherapy reduced symptoms significantly compared with placebo or pharmacotherapy. Four studies directly compared the difference between sublingual immunotherapy and subcutaneous immunotherapy.[34,36,181,182] One dust mite allergen study demonstrated that subcutaneous immunotherapy resulted in a significantly greater reduction in symptom scores compared with sublingual immunotherapy;[181] two dust mite studies,[36,182] and a birch study[34] showed no significant difference between sublingual and subcutaneous immunotherapy for reducing rhinitis/rhinoconjunctivitis symptoms. One dust mite study reported a significant difference in rhinitis symptoms in participants receiving combined subcutaneous and sublingual immunotherapy compared with pharmacotherapy[46] (Appendix F, Evidence Table F6).

These six randomized controlled trials included 412 participants with rhinitis alone or with conjunctivitis or asthma. The strength of evidence is moderate that subcutaneous immunotherapy is more effective than sublingual immunotherapy for reducing allergic nasal and/or eye symptoms (Table 42).

Table 42. Body of evidence for sublingual immunotherapy versus subcutaneous immunotherapy affecting rhinitis/rhinoconjunctivitis symptoms

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Treatment favored	Directness	Magnitude of Effect
Mungan 1999[35]	Dust mite	SLIT SCIT Placebo	36	Medium	None favored	Direct	Weak
Yukselen 2011[36]	Dust mite	SLIT+ placebo injections SCIT+placebo drops Placebo injections+drops	31	Medium	SCIT	Direct	Moderate
Eifan 2010[182]	Dust mite	SLIT SCIT Pharmacotherapy	48	Medium	SCIT	Direct	Strong
Keles 2011[46]	Dust mite	SLIT SCIT SLIT + SCIT Pharmacotherapy	56	Medium	SCIT	Direct	Weak
Tahamile 2006[181]	Dust mite	SLIT SCIT	193	High	SCIT	Direct	Moderate
Khinchi 2004[34]	Birch	SLIT SCIT Placebo	48	Medium	SCIT	Direct	Moderate

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Medication Use

Medication scores were reported in five studies. Studies used various numerical scoring scales to evaluate the medications used. The duration of assessment of the scores ranged from one to two years. The medications that the study participants were allowed to use varied between studies, some allowed only rescue medications while some allowed conventional therapies including corticosteroids, beta-2 agonists and antihistamines.

One dust mite allergen trial demonstrated significant reductions in medication scores post-treatment compared with pre-treatment in both sublingual and subcutaneous immunotherapy groups.[35] Four studies compared changes in scores between the immunotherapy and placebo or pharmacotherapy groups.[34,36,46,182] In a birch immunotherapy trial, both sublingual immunotherapy and subcutaneous immunotherapy demonstrated significant reductions in scores compared with placebo, but the differences between sublingual and subcutaneous treatment groups were not significant.[34] In a dust mite study, only sublingual immunotherapy significantly reduced scores compared with pharmacotherapy; subcutaneous immunotherapy did not.[182] In another dust mite trial, there was significant reduction in rhinitis medication use in both subcutaneous and sublingual immunotherapy groups comparing pre-treatment to post treatment, but in the same trial there was significant reduction in asthma medication use only in subcutaneous immunotherapy group. Also there was no significant difference between the sublingual and subcutaneous immunotherapy groups.[36] Another dust mite trial reported changes in medication score for subcutaneous, sublingual and combined subcutaneous and sublingual immunotherapy compared with pharmacotherapy. It was demonstrated that sublingual immunotherapy significantly reduced asthma medication use compared with pharmacotherapy, while subcutaneous immunotherapy significantly reduced asthma medication, rhinitis medication and total medication scores compared with pharmacotherapy. The same was true in the combined subcutaneous-sublingual immunotherapy group.[46] (Appendix F, Evidence Table F6)

The strength of evidence is low (5 studies, N= 219). Given the inconsistency of the evidence, these studies support that there may not be a difference between these routes of administration for reducing medication use (Table 43).

Table 43. Body of evidence for sublingual immunotherapy versus subcutaneous immunotherapy affecting medication use

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Treatment Favored	Directness	Magnitude of Effect
Mungan 1999[35]	Dust mite	SLIT SCIT Placebo	36	Medium	SLIT	Direct	Moderate
Yukselen 2011[36]	Dust mite	SLIT +placebo injections SCIT +placebo drops Placebo injections + drops	31	Medium	SCIT	Direct	Moderate
Eifan 2010[182]	Dust mite	SLIT SCIT Pharmacotherapy	48	Medium	SLIT	Direct	Moderate
Keles 2011[46]	Dust mite	SLIT SCIT SLIT + SCIT Pharmacotherapy	56	Medium	SCIT	Direct	Strong
Khinchi 2004[34]	Birch	SLIT SCIT Placebo	48	Medium	SLIT	Direct	Moderate

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Combined Medication and Symptoms Scores

Two studies reported improvement in symptoms and medication scores.[177,180] A dust mite trial reported significant improvement post-treatment compared with pre-treatment in the subcutaneous immunotherapy group.[177] The sublingual immunotherapy group showed significant improvement during early treatment, but the effect was not sustained at two years. Another study in tree pollen allergic patients reported no significant differences in symptoms and medication scores between the sublingual and subcutaneous immunotherapy groups.[180] None of the studies reported between-group differences. The evidence is low to support subcutaneous immunotherapy over sublingual immunotherapy for improving combined medication and symptom scores for dust mite allergic patients (Table 44).

Table 44. Body of evidence that sublingual immunotherapy versus subcutaneous immunotherapy affects combined medication use and symptoms

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Treatment Favored	Directness	Magnitude of Effect
Piazza 1993[177]	Dust mite	SLIT SCIT	31	Medium	SCIT	Direct	Moderate
Mauroa 2007[180]	Tree pollen	SLIT SCIT	34	Medium	Could not determine*	Direct	Could not determine*

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy
*Data provided in the article was not enough to calculate the magnitude of effect.

Quality of Life

Quality of life was assessed in one study using the Danish version of SF-36 Health status Questionnaire.[34] Although definitive scores at baseline and after treatment are not provided, the study reports no statistically significant differences in quality of life scores in the groups receiving sublingual immunotherapy, subcutaneous immunotherapy or placebo.

Limited data (1 study, N= 48) precludes grading of strength of evidence for quality of life assessment.

Allergen or Chemical Challenge (Provocation)

Four dust mite studies evaluated nasal symptoms after exposure to allergen after immunotherapy.[36,46,181,182] All studies showed statistically significant increases in the tolerated allergen dose in the sublingual immunotherapy and subcutaneous immunotherapy groups. Two studies reported changes in bronchial symptoms to methacholine challenge.[35,46] Neither the sublingual or subcutaneous immunotherapy groups showed a statistically significant reduction in the dose of methacholine required for provocation. Another dust mite study evaluated allergen induced bronchial changes.[36] Significant changes in allergen dose were seen in the subcutaneous immunotherapy group only.

Biomarkers

Changes in biomarkers following immunotherapy were reported in six studies.[35,36,46,177,180,182] Allergen specific IgE was described in six studies, IgG4 in five studies and IgG in one study.

Conclusion: Summary of Evidence for Key Question 1

The evidence for efficacy and effectiveness of sublingual immunotherapy versus subcutaneous in the treatment of allergic rhinoconjunctivitis and/or asthma is drawn from clinically important outcomes such as symptom scores, medication use, and quality of life. The data is inadequate to comment on reduction of medication use, symptom and medication reduction, and quality of life. The strength of evidence lowly favors subcutaneous immunotherapy for reducing asthma symptoms and for control of nasal and eye symptoms. (Table 45).

Table 45. Summary of strength of evidence regarding the effectiveness of sublingual immunotherapy versus subcutaneous immunotherapy

Outcome	Number of Studies/ Number of Participants	Risk of Bias	Treatment Favored	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Asthma Symptoms	4 / 171	4 medium	3 SCIT 1 SLIT	Consistent	Direct	3 moderate 1 weak	3 studies with medium RofB AND moderate magnitude	Low favoring subcutaneous
Rhinitis or Rhino-conjunctivitis Symptoms	6 / 412	1 high 5 medium	5 SCIT 1 None	Consistent	Direct	1 strong 3 moderate 2 weak	1 study with medium RofB AND moderate magnitude 2 studies with medium RofB AND moderate magnitude	Moderate favoring subcutaneous
Medication Scores	5 / 219	5 medium	2 SCIT 3 SLIT	Consistent	Direct	1 strong 4 moderate	3 studies with medium RofB AND moderate magnitude	Low minimal difference-
Combined symptom and medication scores	2 / 65	2 medium	1 SCIT 1 CND	Consistent	Direct	1 moderate 1 CND	1 study with medium RofB AND moderate magnitude	Low favoring subcutaneous

CND = could not define; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Key Question 2. What is the evidence for safety of SIT in patients with allergic rhinitis/rhinoconjunctivitis and/or asthma?

The safety of sublingual immunotherapy and subcutaneous immunotherapy was assessed in all eight of the included articles. The recording and reporting of the adverse events was neither uniform nor comparable across studies. Adverse events were divided into local reactions and systemic reactions.

The local reactions consisted of oral cavity/oropharynx itching in the sublingual immunotherapy group and injection site reactions in the subcutaneous immunotherapy group. Four studies reported local reactions in sublingual immunotherapy treated patients ranging from seven to 56 percent of patients.[34-36,181] One study reported 0.2 local reactions per patient in the sublingual immunotherapy group.[180] In the subcutaneous immunotherapy treated group, local reaction frequency ranged from 6 to 18 per 100 patients across four studies.[177,180-182] Two studies reported that 20 percent of patients developed reactions at injection site.[35,36] All reactions were mild or moderate.

Systemic reactions were reported in seven of the trials.[34,35,46,177,180-182] Gastrointestinal events such as nausea, pain, and diarrhea were the most frequent systemic reaction reported in sublingual immunotherapy groups. In the subcutaneous immunotherapy group, three studies, the occurrence of respiratory events such as rhinitis/asthma were reported in five patients of which two were severe reactions that required hospitalization.[35,46,182]

Safety in the Pediatric Population

The safety of sublingual immunotherapy versus subcutaneous immunotherapy was assessed in the three studies with a total of 135 patients.[36,46,182]

In the Eifan study, side effects were only reported in the subcutaneous immunotherapy group. Two patients (12.5%) receiving subcutaneous immunotherapy experienced severe systemic reactions. A grade 3 reaction occurred in a 5 year old girl who experienced severe asthma symptoms after every injection given in the induction phase. The grade 4 reaction occurred in a 10 year old girl with flushing, wheezing, and dyspnea after the ninth injection during the induction phase and required adrenaline. One local event occurred in the subcutaneous group with swelling at the injection site (0.06 events per patient). No systemic or local reactions were reported in the sublingual or pharmacotherapy groups.

In the Yukselen study, 3 patients (30%) receiving SLIT experienced local oral cavity/oropharynx itching and 2 patients (20%) receiving SCIT experienced a local injection site reaction.[36] No systemic reactions were observed in either group.

In the Keles study, 2 patients (18.2%) experienced moderate respiratory reactions after receiving SCIT, while no systemic reactions were noted in the SLIT group.[46] No local reactions were reported in either group.

Among these three studies with a total of 135 patients, local injection site reactions were reported in three patients receiving subcutaneous immunotherapy, and local reactions (oral itching) were reported in three patients receiving sublingual immunotherapy. No systemic reactions were reported in patients receiving sublingual immunotherapy. Among patients receiving subcutaneous immunotherapy, four experienced systemic reactions, including 1 anaphylaxis event and 3 patients with moderate – severe respiratory symptoms.

These studies suggest that sublingual immunotherapy may be safer than subcutaneous immunotherapy (Appendix G, Evidence Table G42).

Key Question 3. Is the safety and effectiveness of allergen-specific immunotherapy different in distinct subpopulations with allergic rhinitis/rhinoconjunctivitis and/or asthma?

Key Points

- The evidence is insufficient to comment on the effectiveness and safety of sublingual immunotherapy compared with subcutaneous immunotherapy in subpopulations of the elderly, pregnant women, ethnic minorities, inner-city residents, rural residents, and patients with severe asthma.
- There is no apparent difference in efficacy of sublingual immunotherapy and subcutaneous immunotherapy in mono-sensitized versus poly-sensitized subjects.

The eight included studies did not report effectiveness and safety of sublingual compared with subcutaneous immunotherapy in subpopulations of the elderly, pregnant women, ethnic minorities, inner-city residents, rural residents, or patients with severe asthma. Four studies included only mono-sensitized subjects.[35,36,180,182] The results of these studies did not differ significantly from the results of the three studies that enrolled polysensitized patients.

Pediatric Population: Key Points

- Inadequate evidence exists to support sublingual immunotherapy over subcutaneous or vice versa for improvement of asthma or rhinitis symptoms or medication use.
- Low grade evidence favors subcutaneous immunotherapy over sublingual for allergic asthma symptom control, based on 3 randomized controlled trials with 135 subjects.
- Low grade evidence favors subcutaneous immunotherapy over sublingual for allergic nasal and/or eye symptom control, based on 3 randomized controlled trials with 135 subjects.
- Low grade evidence exists to suggest little difference between routes of therapy for reducing medication use, based on 3 randomized controlled trials with 135 subjects.

Only three RCTs, published in 2010 and 2011 and originating from Turkey, reported on the efficacy and safety of sublingual versus subcutaneous immunotherapy exclusively in children.[36,46,182] The primary diagnosis of the subjects in all 3 studies was asthma with rhinitis. All studies focused on dust mite immunotherapy. Two of the studies required that the subjects had received no prior immunotherapy and only included monosensitized individuals.[36,182] The ages of patients included in the study ranged from about 5 to 14 years of age. Two of the studies were funded by industry.[36,46] (Appendix G, Evidence Tables G32 and G33)

One study allowed the participants to take conventional medications[36] and two studies only allowed rescue medications during the study in addition to the immunotherapy.[46,182] The maintenance dosing interval for subcutaneous immunotherapy ranged from three times a week to monthly, while in the sublingual treatment group, the maintenance dosing interval was three times a week in all 3 studies.[36,46,182] The treatment duration across studies was for 1 year. Comparison groups in the study included sublingual immunotherapy, subcutaneous immunotherapy, and placebo/pharmacotherapy arms (Appendix G, Evidence Table G34). The three studies were considered to have a medium risk of bias (Appendix G, Evidence Table G35).

Asthma Symptom Control

All three trials of dust mite allergen immunotherapy reported improvement in asthma symptom scores.[36,46,182] One study reported changes in subcutaneous and sublingual immunotherapy groups compared with placebo with conventional therapy,[36] and two reported these changes compared with pharmacotherapy.[46,182] The study with the placebo comparison group reported significant changes in asthma symptom scores in the subcutaneous and sublingual treatment groups after treatment relative to before treatment;[36] The group treated with subcutaneous immunotherapy showed a significantly greater reduction asthma symptom scores compared with the group treated with sublingual immunotherapy.[36] The other two studies demonstrated the effectiveness of subcutaneous and sublingual immunotherapy groups in reducing asthma symptom scores compared with pharmacotherapy.[46,182] Both studies reported that subcutaneous immunotherapy significantly reduced asthma symptoms compared with pharmacotherapy. One study reported that sublingual immunotherapy also reduced asthma symptoms significantly,[182] while the other study reported that subcutaneous and sublingual treatment, when combined, reduced symptoms significantly compared with pharmacotherapy. (Appendix G, Evidence Table G36)

The strength of evidence is low (3 studies, N=135) to support subcutaneous immunotherapy over sublingual immunotherapy for allergic asthma symptom control (Table 46).

Table 46. Strength of evidence for sublingual immunotherapy versus subcutaneous immunotherapy affecting asthma symptoms in children and adolescents

Study	Allergen	Comparator	Number of Participants	Risk of Bias	Treatment Favored	Directness	Magnitude of Effect
Yukselen 2011[36]	Dust mite	SLIT + placebo injections SCIT + placebo drops Placebo injections + drops	31	Medium	SCIT	Direct	Moderate
Eifan 2010[182]	Dust mite	SLIT SCIT Pharmacotherapy	48	Medium	SLIT	Direct	Moderate
Keles 2011[46]	Dust mite	SLIT SCIT SLIT + SCIT Pharmacotherapy	56	Medium	SCIT	Direct	Weak

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy
Note: Positive direction of change indicates greater improvement with sublingual immunotherapy relative to subcutaneous immunotherapy, negative direction indicates greater improvement with subcutaneous immunotherapy.

Rhinitis/Rhinoconjunctivitis Symptoms

Three studies reported rhinitis or rhinoconjunctivitis symptom scores in their study participants.[36,46,182] There was no uniformity in reporting of these scores and none of the scales were validated. The duration of assessment was over one year. One trial reported significant improvement in rhinitis/rhinoconjunctivitis symptom scores in both sublingual and subcutaneous study groups post-treatment compared with pre-treatment.[36] Two other dust mite trials[36,182] demonstrated that both sublingual and subcutaneous immunotherapy reduced symptoms significantly compared with placebo or pharmacotherapy. Two studies directly compared the difference between sublingual immunotherapy and subcutaneous immunotherapy.[36,182] They showed no significant difference between sublingual and subcutaneous immunotherapy for reducing rhinitis/rhinoconjunctivitis symptoms. One dust mite study reported a significant

difference in rhinitis symptoms in participants receiving combined subcutaneous and sublingual immunotherapy compared with pharmacotherapy[46] (Appendix G, Evidence Table G37)

These three randomized controlled trials included 135 participants with rhinitis alone or with conjunctivitis or asthma. The strength of evidence is low that subcutaneous immunotherapy is more effective than sublingual immunotherapy for reducing allergic nasal and/or eye symptoms (Table 47).

Table 47. Body of evidence for sublingual immunotherapy versus subcutaneous immunotherapy affecting rhinitis/rhinoconjunctivitis symptoms in children and adolescents

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Treatment favored	Directness	Magnitude of Effect
Yukselen 2011[36]	Dust mite	SLIT + placebo injections SCIT + placebo drops Placebo injections + drops	31	Medium	SCIT	Direct	Moderate
Eifan 2010[182]	Dust mite	SLIT SCIT Pharmacotherapy	48	Medium	SCIT	Direct	Strong
Keles 2011[46]	Dust mite	SLIT SCIT SLIT + SCIT Pharmacotherapy	56	Medium	SCIT	Direct	Weak

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Note: Positive direction of change indicates greater improvement with sublingual immunotherapy relative to subcutaneous immunotherapy, negative direction indicates greater improvement with subcutaneous immunotherapy.

Medication Use

Medication scores were reported in the three studies. Studies used various numerical scoring scales to evaluate the medications used. The duration of assessment of the scores was one year. The medications that the study participants were allowed to use varied between studies, some allowed only rescue medications while some allowed conventional therapies including corticosteroids, beta-2 agonists and antihistamines.

The three studies compared changes in scores between the immunotherapy and placebo or pharmacotherapy groups.[36,46,182] In one of the dust mite studies, only sublingual immunotherapy significantly reduced scores compared with pharmacotherapy; subcutaneous immunotherapy did not.[182] In another dust mite trial, there was significant reduction in rhinitis medication use in both subcutaneous and sublingual immunotherapy groups comparing pre-treatment to post treatment, but in the same trial there was significant reduction in asthma medication use only in subcutaneous immunotherapy group. Also there was no significant difference between the sublingual and subcutaneous immunotherapy groups. Another dust mite trial reported changes in medication score for subcutaneous, sublingual and combined subcutaneous, and sublingual immunotherapy compared with pharmacotherapy. It was demonstrated that sublingual immunotherapy significantly reduced asthma medication use compared with pharmacotherapy, while subcutaneous immunotherapy significantly reduced asthma medication, rhinitis medication and total medication scores compared with pharmacotherapy. The same was true in the combined subcutaneous-sublingual immunotherapy group.[46] (Appendix G, Evidence Table G39)

With the inconsistent direction of change and risk of bias, the strength of evidence is low (3 studies, N= 135) to support improved medication use with sublingual immunotherapy compared with subcutaneous immunotherapy (Table 48).

Table 48. Body of evidence for sublingual immunotherapy versus subcutaneous immunotherapy affecting medication use in children and adolescents

Study	Allergen	Comparators	Number of Participants	Risk of Bias	Treatment Favored	Directness	Magnitude of Effect
Yukselen 2011[36]	Dust mite	SLIT + placebo injections SCIT + placebo drops Placebo injections + drops	31	Medium	SCIT	Direct	Moderate
Eifan 2010[182]	Dust mite	SLIT SCIT Pharmacotherapy	48	Medium	SLIT	Direct	Moderate
Keles 2011[46]	Dust mite	SLIT SCIT SLIT + SCIT Pharmacotherapy	56	Medium	SCIT	Direct	Strong

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy
Note: Positive direction of change indicates greater improvement with sublingual immunotherapy relative to subcutaneous immunotherapy, negative direction indicates greater improvement with subcutaneous immunotherapy.

Combined Medication and Symptoms Scores

None of the pediatric studies reported combined medication and symptom scores.

Quality of Life

None of the pediatric studies evaluated quality of life outcomes.

Allergen or Chemical Challenge (Provocation)

Three dust mite studies evaluated nasal symptoms after exposure to allergen after immunotherapy.[36,46,182] All studies showed statistically significant increases in the tolerated allergen dose in the sublingual immunotherapy and subcutaneous immunotherapy groups. One study reported changes in bronchial symptoms to methacholine challenge.[46] Neither the sublingual or subcutaneous immunotherapy groups showed a statistically significant reduction in the dose of methacholine required for provocation. Another dust mite study evaluated allergen induced bronchial changes.[36] Significant changes in allergen dose were seen in subcutaneous immunotherapy group only. (Appendix G, Evidence Table G40)

Biomarkers

Changes in biomarkers following immunotherapy were reported in three studies.[36,46,182] Allergen specific IgE was described in three studies and IgG4 in two studies.

Conclusion: Summary of Evidence for Key Question 3

The evidence for efficacy and effectiveness of sublingual immunotherapy versus subcutaneous in the treatment of allergic rhinoconjunctivitis and/or asthma in the pediatric population is drawn from clinically important outcomes such a symptom scores and medication use. The data is inadequate to comment on reduction of combined symptom and medication use

and quality of life. The strength of evidence is low for favoring subcutaneous immunotherapy for reducing asthma symptoms and for control of nasal and eye symptoms (Table 49).

Fewer pediatric specific studies have been performed, compared with SCIT versus placebo studies in adults. The strength of evidence for almost all clinically relevant asthma outcomes have been downgraded from high strength of evidence to low strength of evidence, when evaluating only studies with participants less than or equal to 18 years of age. The strength of evidence for asthma symptom-medication scores increased from low to moderate strength of evidence.

Table 49. Summary of strength of evidence regarding the effectiveness of sublingual immunotherapy versus subcutaneous immunotherapy in the pediatric population

Outcome	Number of Studies/ Number of Participants	Risk of Bias	Treatment Favored	Consistency	Directness	Magnitude of Effect	Studies	Strength of Evidence
Asthma Symptoms	3 / 135	3 medium	2 SCIT 1 SLIT	Consistent	Direct	2 moderate 1 weak	3 studies with medium RofB AND 2 of these with moderate magnitude	Low favoring subcutaneous
Rhinitis or Rhino-conjunctivitis Symptoms	3 / 135	3 medium	3 SCIT	Consistent	Direct	1 strong 1 moderate 1 weak	3 studies with medium RofB ; 1 with strong magnitude, 1 with moderate magnitude and 1 with low magnitude	Low favoring subcutaneous
Medication Scores	3 / 135	3 medium	2 SCIT 1 SLIT	Consistent	Direct	1 strong 2 moderate	3 studies with medium RofB 1 with strong magnitude, 2 with moderate magnitude	Low minimal difference

RofB = risk of bias; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Discussion

Our Comparative Effectiveness Review describes the efficacy and safety of specific immunotherapy, subcutaneous and sublingual, in the treatment of allergic rhinitis and asthma. Presently, in the United States, patients with allergies receive immunotherapy via increasing subcutaneous injections of allergen-containing extracts to suppress or eliminate allergic symptomatology. Over the last two decades, interest has grown in using sublingual immunotherapy as an alternate treatment approach. In 1996, a Task Force assembled by the World Allergy Organization on Immunotherapy cited the emerging clinical data on sublingual immunotherapy, recognizing its potential as an alternative to subcutaneous therapy, and encouraged continued clinical investigation to characterize optimal techniques. Sublingual forms of immunotherapy have gained favor in Europe; however, there are no FDA approved sublingual forms of immunotherapy. The aqueous materials developed for subcutaneous immunotherapy can be delivered sublingually, and U.S. physicians are exploring this alternate desensitization approach, off-label, in the treatment of allergic respiratory conditions; however due to differing standardization of potency in the Europe and United States, doses have been extremely hard to translate between countries.

To inform clinicians' use of these therapies, we reviewed the comparative efficacy and safety of these approaches to immunotherapy in the treatment of allergic rhinitis and asthma. We included studies that enrolled participants with confirmed environmental allergies, and symptoms of allergic rhinitis and/or asthma. The studies were limited to those in which the specific immunotherapy formulations used (or close substitutes) are presently available to clinicians in the United States, even if they were being used off-label. The literature search yielded 5646 citations. After the necessary exclusions, we had 142 English language randomized controlled trials for this review.

Summary of Key Findings

Subcutaneous Immunotherapy

Key Question 1. What is the evidence for the efficacy and effectiveness of subcutaneous immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma?

We included 74 randomized controlled studies using subcutaneous immunotherapy. We found high grade evidence to support that subcutaneous immunotherapy improves the following asthma outcomes: symptoms, medication use, and combined asthma plus rhinoconjunctivitis medication use. We found moderate grade evidence to support the use of subcutaneous immunotherapy to improve asthma and rhinitis/rhinoconjunctivitis symptoms and low grade evidence to support the use of subcutaneous immunotherapy to improve combined asthma (with or without rhinitis) symptom-medication scores. The majority of the studies used a single allergen; therefore, our findings primarily reflect the strength of the evidence when a single allergen is used for immunotherapy. In the United States, it is common practice to include multiple allergens in subcutaneous immunotherapy extracts. However, there are much fewer studies investigating subcutaneous immunotherapy using multiple allergens.

We did not grade the evidence for indirect outcomes such as pulmonary function test results and bronchial reactivity. However, we observed that subcutaneous immunotherapy provided

consistent improvement in specific bronchial reactivity to allergen challenge. No consistent benefit was observed for pulmonary function test results and nonspecific bronchial reactivity.

When evaluating allergic rhinoconjunctivitis outcomes, we found high grade evidence to support the use of subcutaneous immunotherapy to improve rhinitis/rhinoconjunctivitis symptoms, conjunctivitis symptoms, combined nasal, ocular, and bronchial symptoms, combined asthma plus rhinitis/rhinoconjunctivitis medication use, and disease-specific quality of life. Moderate grade evidence supports the use of subcutaneous immunotherapy to reduce rhinitis/rhinoconjunctivitis medication use. Low grade evidence supports the use of subcutaneous immunotherapy to reduce combined symptom-medication scores. Although we did not grade the evidence for indirect outcomes, we observed that subcutaneous immunotherapy provided consistent improvement in reactivity to nasal provocation testing and conjunctival provocation testing. Similarly to our observation with the asthma studies, majority of the rhinitis/rhinoconjunctivitis studies used a single allergen; therefore our findings primarily reflect the strength of the evidence when a single allergen is used for immunotherapy. We observed that much fewer studies used combined symptom-medication score as an outcome measure. This is probably the reason why the strength of evidence for improving symptom-medication scores is lower than the strength of evidence for improving the individual scores, i.e. symptom scores alone or medication scores alone.

Key Question 2. What is the evidence for safety of subcutaneous immunotherapy in patients with allergic rhinoconjunctivitis and/or asthma?

The lack of a consistent reporting system and grading system for subcutaneous immunotherapy made it impossible to pool safety data across studies. Furthermore, not all studies reported safety data. Fifty-four studies reported safety data. Local reactions are more common than systemic reactions, and anaphylaxis was infrequently reported. The evidence suggests that systemic reactions occurred more commonly in the active immunotherapy arms than in the comparators. No deaths were reported in any of the studies we reviewed.

Key Question 3. Is the safety and effectiveness of subcutaneous immunotherapy different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma?

We examined the evidence regarding the use of SCIT in subpopulations of interest. Insufficient data exists in the following subpopulations so that strength of evidence regarding efficacy or safety cannot be reported in these subpopulations: the elderly, pregnant women, minorities, inner-city versus rural residents, and severe asthmatics. However, findings from a few studies support that subcutaneous immunotherapy is more beneficial in patients with mild asthma than with severe asthma. There is no apparent difference in efficacy when considering mono-sensitized subjects or poly-sensitized subjects receiving subcutaneous immunotherapy. There were sufficient studies to report on the efficacy and safety in children.

Subcutaneous Immunotherapy in Children

We included 13 randomized controlled pediatric subcutaneous immunotherapy studies with 920 children. We found moderate strength of evidence to support that subcutaneous immunotherapy improves asthma symptoms. As observed in the general population, the majority of the pediatric studies used a single allergen. There is moderate strength of evidence that

subcutaneous immunotherapy improves rhinitis/rhinoconjunctivitis symptoms. There is low grade evidence to support the use of subcutaneous immunotherapy to improve asthma medication use, combined asthma plus rhinoconjunctivitis medication use, asthma symptom-medication scores, conjunctivitis symptoms, and rhinitis/rhinoconjunctivitis disease-specific quality of life. When compared with the mixed adult and pediatric population, the strength of the evidence is lower in the pediatric subpopulation; this is likely due to the fact that there are many fewer studies of subcutaneous immunotherapy in children and adolescents.

Inconsistent reporting of adverse events made it impossible to pool safety data across studies. However, local reactions were the most common adverse reactions in children and adolescents receiving subcutaneous immunotherapy. There were no reports of death.

Sublingual Immunotherapy

Key Question 1. What is the evidence for the efficacy and effectiveness of sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma?

Sixty RCTs of sublingual immunotherapy were included. The overall strength of evidence is moderate that sublingual immunotherapy improves allergic rhinitis and asthma outcomes. The evidence is high grade in the following individual clinical outcome: asthma symptoms.,. The evidence is moderate to support that sublingual immunotherapy improves each of the clinical outcomes: rhinitis/rhinoconjunctivitis symptoms, combined asthma plus rhinitis/rhinoconjunctivitis symptoms, combination medication plus symptom scores, quality of life, conjunctivitis symptoms, and medication use.

While the majority of sublingual studies included in this review utilized single allergens, this may not reflect the current off label practice of sublingual immunotherapy in the United States. Practitioners of sublingual immunotherapy in the United States are likely to use multi-allergen specific immunotherapy in treatment. Seven of the included studies utilized mixed or multiple allergens.[122,145,147,148,151,153,172] The number of multiple allergen studies combined with the heterogeneity of outcomes reported in these seven studies makes it difficult to comment on the efficacy of single allergen sublingual immunotherapy in comparison to multi-allergen.

Key Question 2. What is the evidence for the safety of sublingual immunotherapy in patients with allergic rhinoconjunctivitis and/or asthma?

The lack of a consistent reporting system and grading system for subcutaneous or sublingual immunotherapy made it impossible to pool safety data across studies. Furthermore, not all studies reported safety data.

Forty-three sublingual immunotherapy studies reported safety data. In these studies, local reactions (reactions at the site of allergen introduction such as oral itching and swelling) were common but mild. Systemic reactions were infrequent and no life-threatening reactions, anaphylaxis, or deaths were reported in these studies.

Key Question 3. Is the safety and effectiveness of sublingual immunotherapy different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma?

We examined the evidence regarding the use of SLIT in subpopulations of interest. Insufficient data exists in the following subpopulations so that the strength of evidence regarding efficacy or safety cannot be reported in these subpopulations: the elderly, pregnant women, minorities, inner-city versus rural residents, and severe asthmatics.

Sublingual Immunotherapy in Children

We included 18 studies of sublingual immunotherapy in 1579 children in this analysis. We found moderate strength of evidence to support the use of sublingual immunotherapy to reduce rhinitis/rhinoconjunctivitis symptoms, combined asthma plus rhinitis/rhinoconjunctivitis symptoms, conjunctivitis symptoms, and medication use. The strength of evidence is high that sublingual immunotherapy reduces asthma symptoms, conversely, the strength of evidence is low that sublingual immunotherapy reduces combined medication plus symptoms scores. There is insufficient evidence to determine the impact of sublingual immunotherapy on disease specific quality of life.

Inconsistent reporting of adverse events made it impossible to pool safety data across studies. Furthermore, not all studies reported safety data. However, it appears that local reactions are common but are mild. Systemic reactions were described in both sublingual and placebo arms. No life-threatening reactions, anaphylaxis, or deaths were reported

Subcutaneous Versus Sublingual Immunotherapy

Key Question 1. What is the evidence for the efficacy and effectiveness of subcutaneous versus sublingual immunotherapy in the treatment of allergic rhinoconjunctivitis and/or asthma?

Eight RCTs comparing sublingual immunotherapy versus subcutaneous immunotherapy were included. The overall strength of evidence is low grade to support subcutaneous immunotherapy over sublingual for control of asthma symptoms and combined symptom-medication scores, and moderate grade for control of rhinitis and/or conjunctivitis symptoms. However there is insufficient evidence from head to head comparisons to determine the overall superiority of one form of specific immunotherapy over the other.

Key Question 2. What is the evidence for safety of subcutaneous versus sublingual immunotherapy in patients with allergic rhinoconjunctivitis and/or asthma?

Eight RCTs reported on the efficacy and safety of sublingual versus subcutaneous immunotherapy. In comparing the two therapies, there is insufficient evidence from head to head comparisons to conclude that one route of administration is safer than the other.

Key Question 3. Is the safety and effectiveness of subcutaneous versus sublingual immunotherapy different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma?

We examined the evidence regarding the use of SCIT versus SLIT in subpopulations of interest. Insufficient data exists in the following subpopulations so that strength of evidence regarding efficacy or safety cannot be reported in these subpopulations: the elderly, pregnant women, minorities, inner-city versus rural residents, and severe asthmatics.

Subcutaneous Versus Sublingual Immunotherapy in Children

We included three studies with 135 subjects in this analysis comparing subcutaneous versus sublingual immunotherapy in children. There is low strength of evidence to support subcutaneous over sublingual immunotherapy in children and adolescents across clinical outcomes, including asthma symptoms and rhinitis/rhinoconjunctivitis symptoms. The strength of evidence is low to support comparable improvement of medication use between sublingual immunotherapy and subcutaneous immunotherapy.

There were few local reactions reported for both the subcutaneous immunotherapy and sublingual immunotherapy groups. No systemic reactions were reported in patients receiving sublingual immunotherapy. However, four patients receiving subcutaneous immunotherapy experienced systemic reactions, including one anaphylaxis event and three patients with moderate to severe respiratory symptoms.

Applicability

The results of this systematic review are applicable to patients with allergic rhinoconjunctivitis and/or asthma. We included only studies that confirmed the diagnosis of allergy, either by skin or in-vitro testing. Furthermore, asthma studies were included only if the studies used objective measures to confirm asthma diagnosis. We included only studies in which the specific immunotherapy formulations used (or close substitutes) are available to clinicians in the United States; hence these results should be applicable to practitioners in the United States.

The reviewed outcomes reflect important clinical outcomes for patients with environmental allergies. The majority of outcomes were direct measures of disease symptomatology, which should make the findings of our review meaningful to clinicians and to patients. Some surrogate measures such as pulmonary function testing were also included. While pulmonary function testing is an indirect measure of asthma outcomes, it is used frequently by clinicians in the United States.

However, the following should be considered regarding the applicability of the evidence described in this report. The majority of the included trials used a single allergen for immunotherapy; hence, it is difficult to determine the extent to which this evidence applies to U.S. practitioners using multiple allergen regimens. Based on the findings from a few studies which support that subcutaneous immunotherapy is more beneficial in patients with mild asthma than with severe asthma, the use of subcutaneous immunotherapy to treat asthma is probably most applicable to mild asthmatics. The majority of SLIT studies in this review included subjects with allergic rhinitis/rhinoconjunctivitis and/or mild asthma. Hence, although it may appear from this review that sublingual immunotherapy may be safer than subcutaneous immunotherapy, the safety data from these subgroups of patients must not be extrapolated to the

more severely affected patients. There is little evidence supporting the use of immunotherapy in patients with severe asthma.

While a separate sub-analysis of pediatric studies was performed in this review, several studies reported outcomes on a mixed population of adults and children without stratifying the outcomes by age group, so we could not say definitively to which population the results apply. Furthermore, the dosing regimens and durations of treatment reported in these studies varied widely. Therefore, this body of evidence is insufficient to comment specifically on target maintenance dose or the duration of sublingual therapy. This may, however, be interpreted as supporting the effectiveness of immunotherapy across a broad range of doses.

Our findings add to current knowledge on the strength of evidence for the efficacy and safety of allergen immunotherapy for treatment of asthma and allergic rhinoconjunctivitis. These findings are relevant to clinicians who provide care for patients affected by these medical conditions. The findings are also relevant to patients making decisions regarding therapy and can help inform them on the efficacy and safety of allergen immunotherapy. Guideline developers may also find our study useful for making recommendations about the use of allergen immunotherapy in adults and children.

Study Limitations

We included only RCTs in this review; hence, our findings primarily reflect the efficacy, rather than real world effectiveness, of subcutaneous and sublingual immunotherapy. The studies varied substantially in their risk of bias. While all studies used randomization, 90 studies (72%) were double blind, but the majority of studies did not specify explicitly from whom the intervention was concealed. The majority of studies of subcutaneous and sublingual immunotherapy received industry support financially or in the form of supplies. The studies rarely stated clearly the role or extent of involvement of their sponsors. For these reasons, several studies were considered to have a moderate or high risk of bias. The potential risk of bias played an important role in determining the strength of the evidence for each direct outcome.

The body of literature had much heterogeneity. The clinical outcomes reported varied from study to study, and there were no consistent scoring or grading systems for reporting pertinent primary outcomes such as symptoms or medication use. The heterogeneity of the data on symptoms and medication use precluded pooling the data for further analysis. The studies used varying criteria for diagnosing asthma and assessing asthma severity and control. It is possible that some of these asthma criteria may overestimate, while others may underestimate, the degree of asthma control. Some studies that reported combined asthma and rhinoconjunctivitis scores demonstrated significant improvement in individual disease outcomes. It is possible that a preferential effect of immunotherapy on one of these disease processes may have highly influenced the combined scores. Hence, such combined scores may not accurately reflect the degree of control of both disease processes, and yet may be relevant to patients.

Studies with multiple allergens presented a similar dilemma; response to one allergen may have determined the overall clinical score, and the true effect of desensitization with each allergen remains unclear. Another significant limitation of the study is in regards to single and multiple antigen therapy; the majority of studies included in this review were single allergen studies and therefore caution needs to be exercised in applying these conclusions to multiple allergen immunotherapy regimens.

One significant limitation of the current review is the difficulty in comparing European allergens to United States allergens.[183] While in the United States the FDA establishes for each

standardized allergen an in vitro potency test which all manufacturers must use to compare their extracts, this is not the case in Europe. In Europe, each allergen manufacturer has its own in-house reference standards rather than a European standard. Another difference is that the *in vivo* potency in the United States is quantified by intradermal testing methods, while in Europe, prick testing is utilized. In order to address this problem, the current review attempted to express where possible sublingual dosing in micrograms of major allergen (Appendix E, Table E14). However, it must be emphasized that due to the above differences in United States versus Europe allergen standardization and potency, caution must be exercised when attempting to translate European dosing to the United States.

Most challenging to this review, there was extreme variability in the dosing and treatment schedules from study to study. The doses were reported in varying units (BU, IR, SQ-U, micrograms, BAU, STU, etc), which made it very hard to compare outcomes across studies. In several studies, major allergen content was not reported. To illustrate, dust mite was the most widely used sublingual allergen (14 studies). When considering the dosing for dust mite in micrograms per month, the highest dose used was over 50 times greater than the lowest dose, yet clinical efficacy was reported at both ends of the spectrum. Treatment schedules varied widely as well; in the sublingual studies, dosing ranged from once a day to once a week, and the duration of treatment used varied from one pollen season to several years. The extreme variability in sublingual doses and treatment schedules makes it impossible to comment on the strength of the evidence regarding dosing and treatment schedule. However, this may also be interpreted as evidence of broad effectiveness of this therapy regardless of dose and schedule.

The same issues of heterogeneity existed with the safety data reported by these studies; the adverse events were reported with different denominators from study to study. The lack of a consistent reporting and grading system made it impossible to pool data. Furthermore, our study reports only the safety data from randomized controlled trials, and is therefore not a comprehensive review of the incidence of adverse events encountered in observational studies or clinical practice. A more inclusive study of randomized, non-randomized, and observational studies would be more applicable to the general population.

There were also deficiencies in the statistical reporting provided in the included studies. We observed that several studies did not report intergroup comparisons. Instead, the studies reported the statistical significance of the pre/post comparisons for each treatment arm. The absence of such comparisons makes it difficult to determine whether the intervention provided a true treatment effect. Relevant statistical information on the outcomes reported as scores was frequently unavailable (such as standard deviation, standard error, or confidence intervals); therefore, precision of the point estimates could not be assessed and these outcomes could not be pooled. As a result, precision was not used for grading the evidence for each outcome; magnitude of effect was used as a proxy for precision. In those few studies that compared subcutaneous and sublingual immunotherapy head-to-head, only three of the eight reported direct statistical comparisons between groups for the clinical outcomes of interest.

Due to the large number of articles identified and limited resources available for language translation, we included only studies published in English. We requested information from the pharmaceutical companies identified, but did not receive any information. We also searched Clinicaltrials.gov seeking for the literature resulted from finalized or ongoing clinical trials. However, all the references we identified from this search were already included in our database. As a result, we could not include any unpublished literature. This raises some concern for publication bias.

Comparison of Results With Prior Systematic Reviews

Most previous systematic reviews evaluating the efficacy, effectiveness, and safety of specific immunotherapy quantitatively pooled the data (meta-analyses). We did not pool data in this review because of the heterogeneity in the interventions across studies including types of allergen extracts, sources of extracts, allergen doses, and treatment duration, as well as heterogeneity in outcome scoring systems. Due to such heterogeneity, a recent review by Calderon et al. advised that results of meta-analyses be examined cautiously.[184] In the absence of meta-analyses, our review focused on grading the strength of the evidence for the efficacy and effectiveness of specific immunotherapy.

Subcutaneous Immunotherapy

Traditionally, subcutaneous allergen immunotherapy for allergic rhinitis has been considered a "second line" or slow acting disease modifying treatment. In many cases, subcutaneous immunotherapy is reserved for those who do not respond to conventional therapy or do not wish to remain on medications. In a comparison of four meta-analyses, Matricardi et al. concluded that subcutaneous immunotherapy is at least as potent as pharmacotherapy in controlling symptoms as early as the first season of treatment.[185] This study, however, did not conclude that subcutaneous immunotherapy is superior to pharmacotherapy. Another systematic review by Calderon et al., in the Cochrane database, reported that subcutaneous immunotherapy for seasonal allergic rhinitis results in a significant reduction in symptom scores and medication use with a low risk of adverse events.[186] Our review parallels these findings in that we found high grade evidence that subcutaneous immunotherapy improves allergic rhinitis/rhinoconjunctivitis symptom scores. Furthermore, we found high grade evidence that subcutaneous immunotherapy improves other relevant allergic rhinitis/rhinoconjunctivitis outcomes, including combined nasal, ocular, and bronchial symptoms, combined asthma plus rhinitis/rhinoconjunctivitis medication use, and disease-specific quality of life.

In a recently updated systematic review of 88 asthma trials by Abramson et al., the investigators concluded that there was a significant reduction in asthma symptoms and asthma medications, as well as improvement in allergen specific bronchial hyper-reactivity following subcutaneous immunotherapy.[28] There was also a modest reduction in nonspecific bronchial hyperreactivity, but no consistent effect on lung function.[28] Not surprisingly, the investigators also observed significant heterogeneity between studies. [28] Our review was more restrictive in that we only included studies in which the diagnosis of asthma was confirmed using objective measures such as significant response to bronchodilator, positive bronchial provocation testing, or other previously established guidelines for the diagnosing asthma. We found 35 subcutaneous immunotherapy studies that met these criteria. We found similar results in that we found high grade evidence to support that subcutaneous immunotherapy improves asthma symptoms and asthma medication use. We also found consistent improvement in specific bronchial reactivity to allergens following subcutaneous immunotherapy.

Subcutaneous immunotherapy has served as routine treatment in children with allergic rhinitis with or without asthma. Prior systematic reviews evaluating the efficacy of subcutaneous immunotherapy have included pediatric studies, although few have exclusively focused on children. The Cochrane review by Calderon et al. reported significant reduction in seasonal allergic rhinitis symptoms and medication use with subcutaneous immunotherapy, but noted that among their 51 included studies, none were conducted exclusively in children.[187] A systematic

review, by Roder et al., reviewed immunotherapy for allergic rhinoconjunctivitis in children and adolescents and identified six subcutaneous immunotherapy studies in children which showed conflicting results for clinical efficacy.[188] The recent meta-analysis by Abramson, et al, reported improvement in asthma symptoms, medication use, and improved bronchial hyper-reactivity and included multiple studies exclusively evaluating subcutaneous immunotherapy in children, although separate results for this subpopulation were not reported.[28]

Sublingual Immunotherapy

The first large systematic review of sublingual immunotherapy was reported in 2003 [189] and was updated in 2011.[190] The recent update reported significant reductions in symptoms and medication use with sublingual immunotherapy, which is in agreement with our findings. Radulovic et al. noted the same issues with heterogeneity in scoring systems, safety data reporting, and dosing that we described. Their review also found no serious systemic reactions.

There have been other systematic reviews that focus on the efficacy of sublingual immunotherapy on a particular clinical outcome. A recent systematic review examined the efficacy of sublingual immunotherapy for treating allergic conjunctivitis.[187] The authors concluded that sublingual immunotherapy was effective in reducing ocular symptoms of allergy. We found moderate strength grade evidence to support the use of sublingual immunotherapy in allergic conjunctivitis. Another review published in 2008 focused on the effect of sublingual immunotherapy in reducing symptoms of asthma.[191] These authors concluded sublingual immunotherapy is beneficial for asthma treatment, but found the magnitude of effect was not large. Our findings are consistent, as we also concluded that sublingual immunotherapy is efficacious in treating asthma symptom. We found high grade evidence to support that sublingual immunotherapy improves asthma symptoms.

Other systematic reviews of sublingual immunotherapy have focused on a particular allergen. In 2009, Compalati performed a meta-analysis of the efficacy of dust mite sublingual immunotherapy,[80] and concluded that symptoms were significantly reduced with use. Our systematic review found similar results, with 11 of 14 dust mite studies demonstrating statistically significant improvement in clinical outcomes. Grass allergen sublingual immunotherapy was the focus of a systematic review by Di Bona in 2010.[192] These authors found grass allergen sublingual immunotherapy significantly reduced symptoms with a clinically modest benefit. Our review included 14 grass pollen/grass mix studies, with nine of 14 studies finding improvement in clinical outcomes.

Sublingual immunotherapy has been considered to be a favorable alternative to subcutaneous immunotherapy, especially for children, based on convenience and ease of administration without multiple injections.[193] Calderon et al. pooled nine studies that included participants aged four to 17 years and showed significant reduction in allergic conjunctivitis symptoms in children treated with sublingual immunotherapy.[187] Our study included 3 pediatric studies and concluded that there is low-strength evidence to support that sublingual immunotherapy reduces conjunctivitis symptoms.

Wilson et al. did a subgroup analysis with a small number of pediatric studies using sublingual immunotherapy for allergic rhinitis and did not find a significant treatment effect for symptoms of allergic rhinitis or medication use.[189] In contrast, our systematic review included 12 pediatric studies evaluating rhinitis/ rhinoconjunctivitis symptoms and we found high strength evidence that sublingual immunotherapy reduces rhinitis/ rhinoconjunctivitis symptoms in children.

Sopo et al. evaluated the clinical efficacy of sublingual immunotherapy in children with respiratory allergies and systematically reviewed 8 studies.[194] No significant clinical results were found using sublingual immunotherapy in children with respiratory allergies due to seasonal allergens or rhinoconjunctivitis due to house dust mites, although low to moderate clinical effects were found with the use of sublingual immunotherapy in children with mild to moderate persistent asthma due to house dust mites. In our study, high strength of evidence was found that sublingual immunotherapy reduces asthma symptoms and asthma combined with rhinitis/rhinoconjunctivitis symptoms in children and adolescents based upon 11 studies with 808 subjects.

Penagos et al. performed a meta-analysis of nine studies on the efficacy of sublingual immunotherapy in pediatric patients with allergic asthma and found significant reduction in asthma symptoms and medication use [195] Our study similarly found high strength of evidence for sublingual immunotherapy in children for reducing asthma symptoms, and moderate evidence for reduction of medication use. Olaguibel et al. also performed a meta-analysis with 7 studies on the efficacy of sublingual immunotherapy on asthma, rhinitis, and conjunctivitis symptoms in children with allergic rhinitis or asthma. They found statistically significant reductions in asthma and medication scores, but not for rhinitis or conjunctivitis symptoms, although decreasing trends were observed for all symptoms.[196] Our study demonstrated moderate strength evidence in improving combination symptoms scores. They too found sublingual immunotherapy to be safe without any reports of severe or systemic reactions, with oral and gastrointestinal complaints as the most common side effects.

Future Research Needs

Additional RCTs are needed to examine the efficacy, effectiveness, and safety of SIT. These should be done with attention to the design elements that reduce bias, such as clear concealment of allocation and masking of the intervention throughout the study, to allow for more definitive conclusions. Future studies will benefit from standardized methods to report symptoms and symptom scoring, adverse events, and dosing quantity, frequency, and formulation. Published guidelines for allergen immunotherapy clinical trials recommend that the combined symptom-medication score be used as the primary outcome measure[197]; future studies should be encouraged to comply with these guidelines.[198-200]

There is a specific need for studies investigating the efficacy and safety of multiple allergen regimens, as these are commonly used in the United States. There is increasing discussion in the scientific community on the clinical use and efficacy of single allergen versus multiple allergen therapy, and there are an insufficient number of studies which compare these head-to-head. Future studies are needed to directly compare the effectiveness of single allergen versus multiple allergen regimens for desensitization. On the other hand, studies restricting immunotherapy to a single allergen will allow for a greater understanding of a dose effect, dosing strategy effect, and effect of treatment duration on relevant clinical outcomes.

Studies including asthmatic subjects should clearly describe how subjects were diagnosed with asthma. Restricting asthma severity in studies to mild, moderate, or severe asthma would be helpful in assessing whether there is a subgroup of patients with asthma that may benefit from immunotherapy. Adequately powered trials with appropriate subgroups of patients and utilizing correct methodology are needed to address the efficacy and safety of allergen immunotherapy in specific subpopulations (such as pregnant women, monosensitized vs. polysensitized patients, severe asthmatics, urban vs. rural patients).

There is a need to document with future research that immunotherapy has a disease-modifying activity. Especially in the pediatric population, there is a need to determine if immunotherapy can prevent or modify the atopic march in children at high risk for allergic rhinitis and asthma. Additional considerations for pediatric studies include identifying the optimal age for initiation of immunotherapy and evaluating the differential effects of immunotherapy based on the developmental stage of children and adolescents.

Although our studies and others have found sublingual immunotherapy effective for improving symptoms of allergic rhinoconjunctivitis and asthma, there are several unanswered questions. The target maintenance dose, dosing strategies, and the necessary duration of treatment for sublingual immunotherapy with various allergens have not yet been fully determined.

Finally, there is a need for studies that directly compare sublingual to subcutaneous immunotherapy to strengthen this evidence base in children and adults. Future studies comparing subcutaneous to sublingual immunotherapy should use doses previously shown to be effective in earlier, high quality studies, and direct statistical comparisons between the outcomes of the two groups would be useful in regard to ensuring a fair comparison of the two therapies.

Conclusion

In summary, we found sufficient evidence to support the effectiveness and safety of subcutaneous and sublingual immunotherapy for treatment of allergic rhinitis and asthma, particularly using single allergen immunotherapy regimens in adults and children. Strengthening the evidence for the effectiveness and safety of multiple allergen regimens should be high priority for future studies. There are far fewer pediatric studies than adult studies; hence the evidence is less strong for the pediatric population. Additional pediatric studies may strengthen the evidence the effectiveness and safety of allergen immunotherapy in the pediatric population. When comparing subcutaneous to sublingual immunotherapy, the existing evidence is insufficient and inconclusive. Additional trials are needed to establish the efficacy and safety of these two interventions compared directly, in the usual care settings, given the expectation of differences in adherence.

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Appendix A. Search Strategy

PubMed (6498)

(allergen-specific immunotherapy[tiab] OR allergen immunotherapy[tiab] OR immunotherapy[tiab] OR immunotherapy[mesh] OR immunotherap*[tiab]) AND ((rhinitis[mh] OR rhinitis[tiab] OR hay fever[mh] OR hay fever[tiab] OR rhinoconjunctivitis[tiab] OR conjunctivitis[mh] OR "allergic conjunctivitis"[tiab] OR pollinosis[mh] OR pollinosis[tiab] OR pollenosis[tiab] OR asthma[mh] OR asthma[tiab]) NOT ("occupational diseases"[mh] OR "trachoma"[mh])) NOT (animals[mh] NOT humans[mh])

1	allergen-specific immunotherapy[tiab] OR allergen immunotherapy[tiab] OR immunotherapy[tiab] OR immunotherapy[mesh] OR immunotherap*[tiab]
2	rhinitis[mh] OR rhinitis[tiab] OR hay fever[mh] OR hay fever[tiab] OR rhinoconjunctivitis[tiab] OR conjunctivitis[mh] OR "allergic conjunctivitis"[tiab] OR pollinosis[mh] OR pollinosis[tiab] OR pollenosis[tiab] OR asthma[mh] OR asthma [tiab]
3	"occupational diseases"[mh] OR "trachoma"[mh]
4	2 NOT 3
5	(animals[mh] NOT humans[mh])
6	1 AND 4
7	6 NOT 5

EMBASE (9327)

('immunotherapy'/exp OR desensiti*ation) AND ('rhinitis'/exp OR 'allergic rhinitis'/exp OR 'hay'/exp AND 'fever'/exp OR 'rhinoconjunctivitis'/exp OR 'conjunctivitis'/exp OR 'allergic conjunctivitis'/exp OR ‘asthma'/exp) AND [humans]/lim AND [embase]/lim

1	'immunotherapy'/exp OR desensiti*ation
2	'rhinitis'/exp OR 'allergic rhinitis'/exp OR 'hay'/exp AND 'fever'/exp OR 'rhinoconjunctivitis'/exp OR 'conjunctivitis'/exp OR 'allergic conjunctivitis'/exp OR ‘asthma'/exp
3	[humans]/lim
4	embase]/lim
5	3 AND 4
6	1 AND 2 AND 5

COCHRANE (840)

Immunotherapy AND (rhinitis OR allergic rhinitis OR rhinoconjunctivitis OR conjunctivitis OR allergic conjunctivitis OR asthma)

LILACS (99)

Immunotherapy AND (rhinitis OR allergic rhinitis OR rhinoconjunctivitis OR conjunctivitis OR allergic conjunctivitis OR asthma

Appendix B. Screening and Data Abstraction Forms

Abstract Review Form

KEY QUESTIONS

- KQ1: What is the evidence for efficacy and effectiveness of allergen-specific immunotherapy (SIT) in the treatment of allergic rhinoconjunctivitis and/or asthma?
- KQ2: What is the evidence for safety of allergen-specific immunotherapy in patients with allergic rhinoconjunctivitis and /or asthma?
- KQ3: Is the safety and effectiveness of allergen-specific immunotherapy different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma? (children, adults, elderly, patients with severe asthma, monosensitized patients, pregnant women, minorities ,inner-city, rural)

OUTCOMES

- Cost, Laboratory measures, compliance-adherence.

	Include article for review (check box if *yes*)
☐	Yes, applies to at least one of the key questions without an exclusion
	Note for *included* article if:
☐	Non-English language
☐	Is a letter to the editor or editorial with new data
☐	Is an abstract published later than July 1, 2009
☐	Case series or case report that addresses harms
	Exclude article because… (may check one or more, but always check #4 if applicable)
☐	1. Does not apply to any of the key questions
☐	2. No subjects with allergic rhinoconjunctivitis and/or asthma
☐	3. No SIT
☐	4. Therapy NOT AVAILABLE in the U.S (please skip to question 4 and check box)
☐	5. No comparison group and no report of harms
☐	6. Number of subjects in study is 6 or fewer on active treatment
☐	7. Study evaluates outcomes in animals only (no humans evaluated)
☐	8. No original dataPajno

9. Other reason for exclusion (specify)
Note for Exclusion criteria number 4 “Therapy not available to the practicing physician in the U.S”
Not FDA approved or not available in the U.S. as an “off-label product
Currently in clinical trials or under development
Old technology/Abandoned
Status unknown
Get article
Unclear or no abstract
Meta-analysis or Systematic Review or just useful reference
I do not read this language
Comment

Article Review Form

KEY QUESTIONS

- KQ1: What is the evidence for efficacy and effectiveness of allergen-specific immunotherapy (SIT) in the treatment of allergic rhinoconjunctivitis and/or asthma?
- KQ2: What is the evidence for safety of allergen-specific immunotherapy in patients with allergic rhinoconjunctivitis and /or asthma?
- KQ3: Is the safety and effectiveness of allergen-specific immunotherapy different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma? (children, adults, elderly, patients with severe asthma, monosensitized patients, pregnant women, minorities ,inner-city, rural)

1.	**Exclude article because -**	
☐	It does not meet ALL the inclusion criteria below	
☐	Does not apply to any of the key questions	
☐	No SIT	
☐	Therapy NOT AVAILABLE in the U.S	
☐	Number of subjects in study is 6 or fewer on active treatment (Unless it reports harms)	
☐	Study evaluates outcomes in animals only or in vitro	
☐	No original data	
☐	Other reason for exclusion (specify):	
☐	Exclude but Keep for harms analysis	
2.	**Include article if -** **(Included articles must have all four criteria checked)**	
☐	a. Includes patients with allergic rhinoconjunctivitis and/or allergic asthma as confirmed by skin tests or RAST AND asthma is confirmed by pulmonary lung function (FEV; metacholine challenge). AND	
☐	b. Includes a relevant comparison group.	
☐	c. Has dose AND units specified	
☐	d. Reports meaningful outcomes (see below for outcomes)	
3.	**Study Design**	
☐	RCT	
☐	Observational	
☐	Non-randomized controlled trial	

Clear Response	
4.	**Check if:**
☐	Study addresses Severe HARMS (Anaphylaxis, Hospitalization, Death)
Clear Response	
5.	**Non-English article**
☐	specify if possible
Clear Response	
6.	**Comments:**

	Relevant Outcomes
	Symptom scores (Rhinitis, conjunctivitis, or asthma)
	Medication scores
	Provocational tests results (Nasal, conjunctival, bronchial challenge)
	Quality of life (QOL)
	Long -term effects of SIT with continued treatment (maintenance control)
	Disease modification (Effect of SIT post- discontinuation)
	Effect of SIT on preventing new sequelae (rhinitis progression to sinusitis, otitis or asthma);
	Effect of SIT on development of new allergen sensitivities;
7.	Safety (Serious Harms)

Study Design Triage Form

Please indicate the article's study design and comparators

Included study design

☐ Randomized controlled trial
Clear Response

☐ Trials where investigators did not assign treatment randomly
☐ Trials where clinicians did not assign treatment randomly
☐ Cohorts with treatments assigned
☐ Before/after studies
☐ Observational studies and case series
☐ Non-randomized controlled trial
☐ Allocation based on patient preference
Clear Response

☐ SCIT Vs. Other Treatments
☐ SLIT Vs. Other Treatments
☐ SCIT Vs. SLIT
☐ SIT (route not specified) Vs. Other Treatment

Inclusion and Exclusion Criteria Form

Invert exclusion criteria (other than age) to reflect the article's inclusion criteria (i.e. if the study excluded polysensitized individuals, click "monosensitized individuals only" as an inclusion criteria)

INCLUSION CRITERIA

Please check all that apply

- ☐ Age (specify) _____
- ☐ No previous immunotherapy
- ☐ Positive specific IgE test
- ☐ Positive skin test
- ☐ Monosensitized individuals only
- ☐ Polysensitized individuals only
- ☐ Minimum duration of disease _____

EXCLUSION CRITERIA

- ☐ Age (specify) _____
- ☐ Pregnancy _____

COMMENTS

Study Characteristics Form

Study Characteristics

What is being compared?

- ○ SCIT Vs. Other Treatments
- ○ SLIT Vs. Other Treatments
- ○ SCIT Vs. SLIT

Clear Response

Author, year

Country (check all that apply)

- ☐ United States of America
- ☐ Denmark
- ☐ Finland
- ☐ France
- ☐ Germany
- ☐ Italy
- ☐ Spain
- ☐ Turkey
- ☐ United Kingdom
- ☐ Multiple European countries
- ☐ Other

What was the diagnosis of study participants? (Check all that apply)

- ☐ Asthma
- ☐ Rhinoconjunctivitis
- ☐ Allergic rhinitis
- ☐ Conjunctivitis

Other

Did the article study a single allergen or multiple allergens?

Single allergen only
Multiple allergens
Clear Response

What was the funding source?

Government
Non-profit
Industry
Other
Not stated

Was the study one part of a bigger trial?

Yes (If possible specify which)	
No	
Unspecified	
Clear Response	

COMMENTS

Intervention Characteristics Form

Answer the following for the ENTIRE study
To be included, studies must report either:

Intended duration of **treatment**

Intended duration of **follow-up**

How many patients were **randomized**?

Answer the following for each group included in the study.
Include only information directly reported in the study (do NOT calculate values)

What was the intervention studied? (Arm 1)	**What was the comparator? (Arm 2)**	**What was the comparator? (If applicable, Arm3)**
Check box if intervention allows conventional therapy and/or rescue medication ☐ Allows conventional therapy ☐ Allows ONLY rescue medication *Check box if intervention is an alum-precipitated extract* ☐ alum-precipitated extract How many patients were enrolled in the intervention group? (Denominator) Specify the n for each diagnosis in this arm *If severity of asthma is specified, please describe it in the "COMMENTS" box below* ☐ Asthma ☐ Rhinoconjunctivitis ☐ Allergic rhinitis ☐ Conjunctivitis	*Check box if comparator allows conventional therapy and/or rescue medication* ☐ Allows conventional therapy ☐ Allows ONLY rescue medication *Check box if comparator is an alum-precipitated extract* ☐ alum-precipitated extract How many patients were enrolled in the comparison group? (Denominator) Specify the n for each diagnosis in this arm *If severity of asthma is specified, please describe it in the "COMMENTS" box below* ☐ Asthma ☐ Rhinoconjunctivitis ☐ Allergic rhinitis	*Check box if comparator allows conventional therapy and/or rescue medication* ☐ Allows conventional therapy ☐ Allows ONLY rescue medication *Check box if comparator is an alum-precipitated extract* ☐ alum-precipitated extract How many patients were enrolled in the comparison group? (Denominator) Specify the n for each diagnosis in this arm *If severity of asthma is specified, please describe it in the "COMMENTS" box below* ☐ Asthma ☐ Rhinoconjunctivitis ☐ Allergic rhinitis

Combined asthma and rhinitis

Not specified

Other

Targeted maintenance dose

Actual maintenance dose

Targeted cumulative dose

Actual cumulative dose

Dosing interval for maintenance dose

Daily

Weekly

Biweekly

Monthly

Cluster

Rush

Other

Dose units

If dose is reported as drops, select "other" and write in the number and concentration of drops

µg of major protein (if applicable)

Conjunctivitis

Combined asthma and rhinitis

Not specified

Other

Targeted maintenance dose

Actual maintenance dose

Targeted cumulative dose

Actual cumulative dose

Dosing interval for maintenance dose

Daily

Weekly

Biweekly

Monthly

Cluster

Rush

Other

Dose units

If dose is reported as drops, select "other" and write in the number and concentration of drops

µg of major protein (if applicable)

Conjunctivitis

Combined asthma and rhinitis

Not specified

Other

Targeted maintenance dose

Actual maintenance dose

Targeted cumulative dose

Actual cumulative dose

Dosing interval for maintenance dose

Daily

Weekly

Biweekly

Monthly

Cluster

Rush

Other

Dose units

If dose is reported as drops, select "other" and write in the number and concentration of drops

µg of major protein (if applicable)

COMMENTS

Patient Characteristics From

Please fill the entire study column ONLY when the information is not separated by arm

Arm 1: ***Either SCIT or SLIT, not placebo***	**Arm 2:**	**Arm 3:**	**Entire study:**
Age as mean	Age as mean	Age as mean	Age as mean
☐ Mean	☐ Mean	☐ Mean	☐ Mean
☐ Standard deviation	☐ Standard deviation	☐ Standard deviation	☐ Standard deviation
Age as median	Age as median	Age as median	Age as median
☐ Median	☐ Median	☐ Median	☐ Median
☐ Range	☐ Range	☐ Range	☐ Range
Other age measure	Other age measure	Other age measure	Other age measure
Sex	Sex	Sex	Sex
☐ % Male	☐ % Male	☐ % Male	☐ % Male
☐ % Female	☐ % Female	☐ % Female	☐ % Female
☐ n Male	☐ n Male	☐ n Male	☐ n Male
☐ n Female	☐ n Female	☐ n Female	☐ n Female
Race	Race	Race	Race
☐ % Caucasian/white	☐ % Caucasian/white	☐ % Caucasian/white	☐ % Caucasian/white
☐ % African American/black	☐ % African American/black	☐ % African American/black	☐ % African American/black
☐ % Hispanic/Latino	☐ % Hispanic/Latino	☐ % Hispanic/Latino	☐ % Hispanic/Latino
☐ % Asian	☐ % Asian	☐ % Asian	☐ % Asian
☐ % Other	☐ % Other	☐ % Other	☐ % Other

☐ n Caucasian/white	☐ n Caucasian/white	☐ n Caucasian/white	☐ n Caucasian/white
☐ n African American/black	☐ n African American/black	☐ n African American/black	☐ n African American/black
☐ n Hispanic/Latino	☐ n Hispanic/Latino	☐ n Hispanic/Latino	☐ n Hispanic/Latino
☐ n Asian	☐ n Asian	☐ n Asian	☐ n Asian
☐ n Other	☐ n Other	☐ n Other	☐ n Other
Does this group contain any subpopulations of interest? (check all that apply)	Does this group contain any subpopulations of interest? (check all that apply)	Does this group contain any subpopulations of interest? (check all that apply)	Does this group contain any subpopulations of interest? (check all that apply)
☐ Children	☐ Children	☐ Children	☐ Children
☐ Elderly	☐ Elderly	☐ Elderly	☐ Elderly
☐ Inner-city residents	☐ Inner-city residents	☐ Inner-city residents	☐ Inner-city residents
☐ Minorities	☐ Minorities	☐ Minorities	☐ Minorities
☐ Monosensitized individuals	☐ Monosensitized individuals	☐ Monosensitized individuals	☐ Monosensitized individuals
☐ Patients with severe asthma	☐ Patients with severe asthma	☐ Patients with severe asthma	☐ Patients with severe asthma
☐ Polysensitized individuals	☐ Polysensitized individuals	☐ Polysensitized individuals	☐ Polysensitized individuals
☐ Pregnant women	☐ Pregnant women	☐ Pregnant women	☐ Pregnant women
☐ Rural residents	☐ Rural residents	☐ Rural residents	☐ Rural residents
Mean number of years affected with disease	Mean number of years affected with disease	Mean number of years affected with disease	Mean number of years affected with disease
Mean baseline Ig E (units)	Mean baseline Ig E (units)	Mean baseline Ig E (units)	Mean baseline Ig E (units)
Mean duration follow-up:	Mean duration follow-up:	Mean duration follow-up:	Mean duration follow-up:
Dropouts (n)	Dropouts (n)	Dropouts (n)	Dropouts (n)

COMMENTS

Multiple Allergen Form

Please fill one row for EACH allergen being studied

What was the allergen being studied?	Dose	Dose units
☐ Trees ☐ Grass ☐ Weeds ☐ Molds ☐ Animals ☐ Cockroaches ☐ Dust mites		
What was the allergen being studied?	Dose	Dose units
☐ Trees ☐ Grass ☐ Weeds ☐ Molds ☐ Animals ☐ Cockroaches ☐ Dust mites		

COMMENTS

Primary Outcomes Form

Please enter the final timepoint where outcomes were measured

Was interval data reported?

- No
- Yes (specify timepoint[s])

- ***Please report statistics recorded at last follow-up NOT at baseline visit***
- ***Report scores using the following guide: Max= Most symptomatic, Min= Least symptomatic***
- ***Note that "% Improv" refers to the percent improvement of score***
- ***Record standard deviations of mean scores (SD) in the box immediately following the score***

Were rhinitis symptom scores reported?

- Not reported
- Reported

Clear Response

Rhinitis symptom scores

Scale	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**
Description of scale	Value pre	Value pre	Value pre	Value pre
Minimum value	SD	SD	SD	SD
Maximum value	Value post	Value post	Value post	Value post
	SD	SD	SD	SD
	% Improv	% Improv	% Improv	% Improv
	SD	SD	SD	SD

Statistics

Comparator A	Comparator B	P-value	Standard deviation	Standard error	Confidence interval

Comparator A	Comparator B	P-value	Standard deviation	Standard error	Confidence interval

Comparator A	Comparator B	P-value	Standard deviation	Standard error	Confidence interval

Comparator A	Comparator B	P-value	Standard deviation	Standard error	Confidence interval

Were conjunctivitis symptom scores reported?

- Not reported
- Reported

Were combination rhinitis and conjunctivitis symptom scores reported?

- Not reported
- Reported

Clear Response

Were asthma symptom scores reported?

- Not reported
- Reported

Were combination rhinitis and asthma symptom scores reported?

- Not reported
- Reported

Clear Response

Were medication scores reported?

Not reported

Reported

Were combined symptom and medication scores reported?

Not reported

Reported

Clear Response

Were nasal provocation challenge scores reported?

Not reported

Reported

Were ocular provocation challenge scores reported?

Not reported

Reported

Were allergen bronchial provocation challenge scores reported?

Not reported

Reported

Clear Response

Were chemical bronchial provocation challenge scores reported?

Not reported

Reported

Were other symptom and/or medication scores reported?

Not reported

Reported

Clear Response

Were other symptom and/or medication scores reported or were other challenges reported?

Not reported

Reported

SECONDARY OUTCOMES

Secondary outcomes of interest by category:

- **Long term outcomes**: Quality of life, aderence, convenience, maintenance control, disease modification, prevention of sinusitis, prevention of otitis, prevention of asthma, development of new allergen sensitivities
- **Biomarkers:** IgE, IgG, IgG-4, IL-10, IL-12, serum antibody levels CD4 and CD25, TGF-b, other laboratory measures
- **Cost:** Healthcare utilization, missed days of school, missed days or work

Were any secondary outcomes reported? *(If no secondary outcomes were reported proceed to the next form)*

Not reported

Reported

Not reported

Reported

Arm 1	**Arm 2**	**Arm 3**	**Arm 4**
Quality of life Reported Not reported Clear Response	Quality of life Reported Not reported Clear Response	Quality of life Reported Not reported Clear Response	Quality of life Reported Not reported Clear Response
Adherence Reported Not reported Clear Response	Adherence Reported Not reported Clear Response	Adherence Reported Not reported Clear Response	Adherence Reported Not reported Clear Response
Convenience	Convenience	Convenience	Convenience

Reported Not reported Clear Response	Reported Not reported Clear Response	Reported Not reported Clear Response	Reported Not reported Clear Response
Maintenance control Reported Not reported Clear Response	Maintenance control Reported Not reported Clear Response	Maintenance control Reported Not reported Clear Response	Maintenance control Reported Not reported Clear Response
Disease modification Reported Not reported Clear Response	Disease modification Reported Not reported Clear Response	Disease modification Reported Not reported Clear Response	Disease modification Reported Not reported Clear Response
Prevention of sinusitis Reported Not reported Clear Response	Prevention of sinusitis Reported Not reported Clear Response	Prevention of sinusitis Reported Not reported Clear Response	Prevention of sinusitis Reported Not reported Clear Response
Prevention of otitis Reported Not reported Clear Response	Prevention of otitis Reported Not reported Clear Response	Prevention of otitis Reported Not reported Clear Response	Prevention of otitis Reported Not reported Clear Response
Prevention of asthma Reported Not reported Clear Response	Prevention of asthma Reported Not reported Clear Response	Prevention of asthma Reported Not reported Clear Response	Prevention of asthma Reported Not reported Clear Response
Development of new allergen sensitivities Reported Not reported Clear Response	Development of new allergen sensitivities Reported Not reported Clear Response	Development of new allergen sensitivities Reported Not reported Clear Response	Development of new allergen sensitivities Reported Not reported Clear Response

Were any biomarkers reported?

Not reported

Reported

Arm 1	Arm 2	Arm 3	Arm 4
IgE Reported Not reported Clear Response	IgE Reported Not reported Clear Response	IgE Reported Not reported Clear Response	IgE Reported Not reported Clear Response
IgG Reported Not reported Clear Response	IgG Reported Not reported Clear Response	IgG Reported Not reported Clear Response	IgG Reported Not reported Clear Response
IgG-4 Reported Not reported Clear Response	IgG-4 Reported Not reported Clear Response	IgG-4 Reported Not reported Clear Response	IgG-4 Reported Not reported Clear Response
IL-10 Reported Not reported Clear Response	IL-10 Reported Not reported Clear Response	IL-10 Reported Not reported Clear Response	IL-10 Reported Not reported Clear Response
IL-12 Reported Not reported Clear Response	IL-12 Reported Not reported Clear Response	IL-12 Reported Not reported Clear Response	IL-12 Reported Not reported Clear Response
Serum antibody levels CD4 Reported Not reported Clear Response	Serum antibody levels CD4 Reported Not reported Clear Response	Serum antibody levels CD4 Reported Not reported Clear Response	Serum antibody levels CD4 Reported Not reported Clear Response
Serum antibody levels CD25 Reported	Serum antibody levels CD25 Reported	Serum antibody levels CD25 Reported	Serum antibody levels CD25 Reported

Not reported Clear Response	Not reported Clear Response	Not reported Clear Response	Not reported Clear Response
T helpers levels Reported Not reported Clear Response	T helpers levels Reported Not reported Clear Response	T helpers levels Reported Not reported Clear Response	T helpers levels Reported Not reported Clear Response
TGF-b Reported Not reported Clear Response	TGF-b Reported Not reported Clear Response	TGF-b Reported Not reported Clear Response	TGF-b Reported Not reported Clear Response
Other laboratory measures Reported Not reported Clear Response	Other laboratory measures Reported Not reported Clear Response	Other laboratory measures Reported Not reported Clear Response	Other laboratory measures Reported Not reported Clear Response

Were any costs reported?

Not reported

Reported

Arm 1	Arm 2	Arm 3	Arm 4
Healthcare utilization Reported Not reported Clear Response	Healthcare utilization Reported Not reported Clear Response	Healthcare utilization Reported Not reported Clear Response	Healthcare utilization Reported Not reported Clear Response
Missed days of school Reported Not reported Clear Response	Missed days of school Reported Not reported Clear Response	Missed days of school Reported Not reported Clear Response	Missed days of school Reported Not reported Clear Response
Missed days of work Reported Not reported	Missed days of work Reported Not reported	Missed days of work Reported Not reported	Missed days of work Reported Not reported

Clear Response	Clear Response	Clear Response	Clear Response

COMMENTS

Safety Form

Were harms reported?
If harms were reported, please fill ONE FORM for EACH ARM of the study that reports harms

Not reported

Reported

Which arm of the study corresponds to THIS form?
Please specify the denominator for each arm (people, events or treatments)

If denominator is in events please fill the appropriate boxes and note it below

Denominator is events

Were specific local reactions for SLIT reported?

Not reported

Reported

Clear Response

Reaction: *Report n or % for that reaction in text box*	Reported as	Severity
Reaction: *Report n or % for that reaction in text box*	Reported as	Severity
Reaction: *Report n or % for that reaction in text box*	Reported as	Severity
Reaction: *Report n or % for that reaction in text box*	Reported as	Severity
Reaction: *Report n or % for that reaction in text box*	Reported as	Severity

Please DO NOT report anaphylaxis systems as local or systemic reactions. Note them ONLY in the anaphylaxis section

Unspecified reaction

- n
- %

Local reaction (mouth, throat or skin; irritation, swelling, pain)

- n with unspecified local reaction
- n with mild reaction OR not requiring treatment
- n with moderate reaction with or without treatment
- n with severe reaction requiring treatment
- % with unspecified local reaction
- % with mild reaction OR not requiring treatment
- % with moderate reaction with or without treatment
- % with severe reaction requiring treatment

Systemic reaction

- n with unspecified systemic reaction
- % with unspecified systemic reaction

Gastrointestinal: Nausea/pain/diarrhea

- n with mild reaction OR not requiring treatment
- n with moderate reaction with or without treatment
- n with severe reaction requiring treatment
- n with unspecified severity of reaction
- % with mild reaction OR not requiring treatment
- % with moderate reaction with or without treatment

% with severe reaction requiring treatment

% with unspecified severity of reaction

Respiratory: Rhinitis/asthma

n with mild reaction OR not requiring treatment

n with moderate reaction with or without treatment

n with severe reaction requiring treatment

n with unspecified severity of reaction

% with mild reaction OR not requiring treatment

% with moderate reaction with or without treatment

% with severe reaction requiring treatment

% with unspecified severity of reaction

Cutaneous: Rash/urticaria/angioedema

n with mild reaction OR not requiring treatment

n with moderate reaction with or without treatment

n with severe reaction requiring treatment

n with unspecified severity of reaction

% with mild reaction OR not requiring treatment

% with moderate reaction with or without treatment

% with severe reaction requiring treatment

% with unspecified severity of reaction

Cardiac: Arrhythmia/rapid pulse

n with mild reaction OR not requiring treatment

n with moderate reaction with or without treatment

n with severe reaction requiring treatment

☐ n with unspecified severity of reaction

☐ % with mild reaction OR not requiring treatment

☐ % with moderate reaction with or without treatment

☐ % with severe reaction requiring treatment

☐ % with unspecified severity of reaction

N with **anaphylaxis** as defined by:
Check all that apply

The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and respiratory compromise

☐ The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and symptoms of end-organ dysfunction

☐ The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and reduced blood pressure

☐ Involvement of the skin/mucosal tissue and respiratory compromise occurring rapidly after exposure to a likely allergen for that patient

☐ Involvement of the skin/mucosal tissue and reduced blood pressure or associated symptoms occurring rapidly after exposure to a likely allergen for that patient

☐ Involvement of the skin/mucosal tissue and persistent gastrointestinal symptoms occurring rapidly after exposure to a likely allergen for that patient

☐ Reduced blood pressure after exposure to a known allergen

☐ Unspecified anaphylaxis

Death

☐ n

☐ %

COMMENTS

Quality Form for Trials

Defined as studies where the treatment was assigned by the investigator

1. Were patients **randomly allocated** to groups?

- ☐ Yes--low risk of bias
- ☐ No--high risk of bias OR unclear/unspecified

2. Was the **allocation process concealed** from the investigators and participants?

- ☐ Yes--low risk of bias
- ☐ No--high risk of bias OR unclear/unspecified OR impossible

3. Was **knowledge of the interventions concealed** from the participants, investigators, and outcome assessors (all of them) **throughout the study**?

- ☐ Yes--low risk of bias
- ☐ No--high risk of bias OR unclear/unspecified

4. Did the investigators **adequately** address **incomplete outcome data**?
***Yes if**: Low risk of bias because no missing data, missingness balanced across groups, no pattern to missingness, or proper imputation of missing data*
***No if**: High risk of bias because badly imbalanced missingness across treatment groups or unclear or incorrect handling of missing data*

- ☐ Yes--low risk of bias
- ☐ No--high risk of bias OR unclear/unspecified

5. Was the study free of other issues that put it at risk of biased outcomes?
***Yes if**: Low risk of bias*
***No if**: High risk of bias because of extreme imbalance in groups at baseline, or inequality in treatments besides study intervention, or inequality in methods of outcome assessment between groups*

- ☐ Yes--low risk of bias
- ☐ No--high risk of bias OR unclear/unspecified

6. Did the sponsoring company have a role in the design, conduct or reporting of the study?
***Yes if**: Potential risk of bias, OR if the sponsoring company's role was unspecified*
***No if**: low risk of bias, OR not sponsored by a company with financial interests*

- ☐ Yes--high risk of bias OR unclear/unspecified
- ☐ No--low risk of bias

Include data for submission?

- ☐ Yes
- ☐ No, exclude article

SECOND REVIEWER INITIALS

Completed Abstraction Form

Did you fill out a quality form independent of the first reviewer?

Yes

No

Check box to indicate that the second review of this refID is complete

Second review complete

Second review incomplete

COMMENTS

Appendix C. Population, Intervention, Comparators, Outcomes and Dosage Specification

1. POPULATION

Patients with allergic rhinoconjunctivitis and/or allergic asthma due to airborne allergies.
Includes:

- Children (no age group distinction)
- Adults (no gender distinction)
- Elderly
- Pregnant women
- Minorities (we will include all the races and ethnicities found in the literature)
- Inner-city and rural residents
- Patients with severe asthma
- Monosensitized individuals

Allergic rhinoconjunctivitis must be confirmed by skin tests or RAST (radioallergosorbent test)
Asthma must be confirmed by pulmonary lung function (FEV; metacholine challenge). Asthma diagnosis needs to be objective; response to bronchodilator needs to be assessed.

2. INTERVENTION AND COMPARATORS

Table of comparators and definitions

Comparator	SCIT	SLIT
SCIT	YES*	YES
SLIT	YES	YES*
Non-SIT	YES	YES
SLIT-Tablet	NO	NO
Other	NO	NO

Treatments (**) to be included in the review;

SCIT**:
U.S. FDA-approved aqueous extracts for subcutaneous injection (SCIT)
SLIT**: Aqueous sublingual extracts - available in U.S. as off-label products from U.S. manufacturers, and the comparable aqueous extracts from European manufacturers (off-label in U.S.; approved in EU)
Non-SIT**: Placebo; pharmacotherapy; usual care; environmental control; homeopathy

Treatments to be excluded (§§) from the review:

SLIT-Tablet[§§]: sublingual dissolvable tablet products [not available in U.S.; approved in Europe (eg: Grassax; Oralair)]
Modified Allergens[§§]: tyrosine-absorbed extracts; allergoids; polymerized allergens [not available in U.S.; approved in Europe]
Adjuvants[§§]: CpG-oligonucleotides; MPL; alum-precipitated extracts; pyridine-extracted alum extracts [not available in U.S. except in clinical trials; some approved in Europe]
Peptides[§§]: treatment with specific allergen epitope sequences [not available in U.S. or Europe except in cx trials]
Recombinant Allergens[§§]: alteration of the allergen molecule by substitution of an amino acid [not available in U.S. or Europe except in clinical trials]
Combination Products[§§]: European products in which several of the above are coupled (ex: Timothy Quattro: aqueous Timothy grass extract prepared as an allergoid modification + Tyrosine absorption + incorporation of an MPL adjuvant onto the molecule)
Other[§§]: lymphatic injection of allergen; local nasal IT; bronchial inhaled IT; epicutaneous IT; etc [not available in U.S. or Europe except in clinical trials]

3. SPECIFIC OUTCOMES FOR RHINOCONJUNCTIVITIS OR ASTHMA STUDIES

A) Rhinitis /Rhinoconjunctivitis Studies:
Primary Outcomes:
a) Symptom diary score (Nasal Symptom Score, Ocular Symptom Scores, Combined Symptom Score)
b) Medication score (Rhinitis-Rhinoconjunctivitis medication use)
c) Combined symptom-medication scores

Additional Secondary Endpoints:
a) Individual symptoms (sneezing/nasal congestion/rhinorrhea/itchy nose/ocular symptoms/etc)
b) QOL
c) symptom-free days
d) Days with no use of rescue medicine (e.g.: antihistamine; decongestant)
e) Visual analog score
f) Asthma symptoms (asthma may develop in a patient for the first time during the study)
g) Adverse events
h) Safety blood indices

B) Asthma Studies:

Primary Outcomes:
a) Symptom diary score (Total Asthma Symptom Score)
b) Asthma medication score

c) Combined asthma symptom-medication scores
d) QOL

Secondary Endpoints:
a) Pulmonary function tests (FEV1/FVC/ratio)
b) PEFR (peak expiratory flow readings; done at home)
c) Challenge function tests
d) Adherence
e) Convenience and compliance
f) Long term outcomes
g) Adverse events

4. ALLERGEN UNITAGE SPECIFICATIONS, CHARACTERIZATION, AND STANDARDIZATION

UNITAGE SPECIFICATIONS

BIOEQUIVALENT ALLERGY UNITS/ML (BAU/ML)- biological potency unit assigned to standardized grass pollen and cat allergenic extracts, following in-vitro comparison of the test extract to a FDA CBER reference standard. The FDA CBER reference standard is assigned a specific BAU unitage based on quantitative skin testing.
ALLERGY UNITS/ML (AU/ML) - biological potency unit assigned to standardized mite and short ragweed pollen allergenic extracts, following in-vitro comparison of the test extract to a FDA CBER reference standard. The FDA CBER reference mite standard is assigned a specific AU unitage based on quantitative skin testing. For the short ragweed pollen allergen extract FDA CBER reference mite standard is assigned a specific AU unitage based on specific ragweed allergen content.
MAJOR PROTEIN UNITS (µg Ag/ML) – micrograms of the major protein moiety(s) of the specific allergen (e.g. ragweed, Amb a 1; cat, Fel d 1)
PROTEIN NITROGEN UNIT (PNU) - potency unit based on the micro-Kjeldahl measurement of protein nitrogen in an acid precipitated extract. Compared with other protein determination methods, 1 mg of protein nitrogen typically equals 100,000 PNU.
WEIGHT TO VOLUME (W/V) - potency unit expressed as a ratio of the weight of allergen source material extracted to the volume of diluting fluid, and adjusted based on subsequent dilutions.
HISTAMINE EQUIVALENT PRICK (HEP) – histamine equivalent prick unitage for standardization of an allergen.
BIOLOGIC UNITS/ML (BU/ML) – biological unitage assigned to define allergen potency.
STANDARDISED QUALITY-UNIT (SQ-U) - biological potency unit assigned to certain allergen extracts by a manufacturer.
OTHER – we will include other allergen characterization unitage were noted in a paper.

CHARACTERIZATION AND STANDARDIZATION

Many (some) of the allergens currently commercially available for use have been characterized by manufacturers or researchers based on major (and minor) proteins, but many others (most trees, molds, and pollens) have not. The FDA has characterized and standardized certain of the

allergens that are currently commercially available (see below). The FDA feels that "biological" potency is a more robust and accurate methodology for assaying allergens as opposed to major protein, alone (ie: various other proteins in an allergen's make-up may be important and would be overlooked by only assaying and defining a product based on 1 or 2 proteins). Hence, the FDA and the WHO are not in agreement on standardization, and the U.S. and European manufacturers "march to a different drum" (often their own internal standardization methods (SQ units/IR units/etc)].

FDA STANDARDIZED ALLERGENS:

a) Ragweed: FDA actually standardized this allergen based on Amb a 1 content prior to the development of BAU/AU (and because 95% of RW's allergenicity is recognized as being due to Amb a 1, they never felt the need to rename it based on BAU) [a RW extract containing 350 +/- 20% µg Amb a 1 would be considered = to a 100,000 AU product];

Background Information: "FDA would like to add the following unit of measure to UCUM: Amb a 1 Units/ML – an arbitrary unit for the measurement of Amb a 1, a 38 kD glycoprotein that is the major allergen in short ragweed pollen allergen extracts. The amount of Amb a 1 units are determined by an in-vitro comparison of a test short ragweed extract to a FDA CBER Amb a 1 reference standard.

Antigen E and Amb a 1 are synonymous. Antigen E is the old term that was in the regulations for allergenics back in the 80s. The more up-to-date scientific name is Amb a 1. [However, you will still have manufacturers using the old term of Antigen E since that is in their license].

In the old regulations (which have since been removed), the Radial Immuno Diffusion (RID) method for determining Antigen E potency was specified. The number of units/ml is simply that which is obtained by comparison of a test sample (lot for release) against the US reference standard that has a labeled content of Antigen E (also a US reference preparation of anti-antigen E serum is used in the test). The requirement is for the assayed value of the US reference for antigen E to be within +/- 25% of the labeled value.

The general working theory is that a Unit/mL of Antigen E(Amb a 1) is equivalent to a microgram of AntigenE(Amb a 1)/mL but we are still looking for solid references discussing this fact - this was not an FDA mandated unit expression due to the incorporation of the old methods specified under the regulation into the firm's BLAs under 52 FR 37605. FDA has not since initiated the legal process required under the 680s for a unit change (see below discussion on BAU/mL). The benefit of a unit change for allergenics always has to be balanced against the risk to patients on incorrect dosing that may occur despite all best education efforts when such a change is made".

1. Amb a 1 is the up-to-date term for the short ragweed pollen allergen that was originally described as Antigen E. They are synonyms. Although Antigen E is no longer used in the scientific literature, its meaning is unambiguous. The manufacturers are still licensed to use Antigen E as the designation.
2. Amb a 1 U = AgE U
3. The relationship between AgE U and BAU (350 AgE U/mL = 100,000 BAU/mL) was based on studies done decades ago, reportedly on 15 study subjects. CBER considered mandating a conversion to BAU/mL in the labeling of short ragweed pollen products, based on AgE content, but this was never implemented.
4. CBER provides two US standard reagents to manufacturers for their determination of Amb a 1 content, a reference standard and a reference serum. The assay used is a radial immunodiffusion assay (RID).

5. Solid references discussing the relationship between Antigen E U/mL/Amb a 1 U/mL and micrograms of Antigen E U/mL/Amb a 1/mL are being researched]".

b) Grasses: Bermuda grass (10,000 BAU/ml) and eight related Northern Pasture grasses [Timothy, Kentucky bluegrass, perennial rye grass, orchard grass, meadow fescue, red top, and sweet vernal] (expressed as 100,000 BAU/ml); these were initially standardized by quantitative skin testing in highly allergic subjects, and subsequently standardized to the standard extract by in vitro methods];
c) House Dust Mites (Dermatophagoides pteronyssinus and farina): expressed as either 10,000 or 5,000 BAU/mL [initially standardized by quantitative skin testing in highly allergic subjects (identified by hx), and subsequently standardized to the standard extract by in vitro methods];
d) Cat hair or pelt: The potency of Standardized Cat Hair Extract is based on the amount of Fel d 1 allergen in the extract. Extract containing 5-9.9 units per mL is assigned a potency of 5,000 Bioequivalent Allergy Units (BAU/mL). Extract containing 10-19.9 Fel d1 units is assigned a potency of 10,000 BAU/mL. [BAU/mL values are based on quantitative skin testing].

Background Information: "The primary allergen of Standardized Cat Hair Extract is Fel d1. Standardized Cat Pelt Extract contains Fel d1, as well as non-Fel d1 allergens. The latter are believed to be components of cat serum, such as albumin. Pelt extracts have a higher protein content than hair extracts, and the isoelectric focusing (IEF) pattern of the pelt extract reveals protein bands that are not present in cat hair extracts. The IEF pattern of cat hair extracts shows primarily Fel d1 allergen without serum components. The importance of Fel d1 as a means of standardizing the potency of cat extract is based on the following observations:
The intensity of skin reactions to cat extract correlates with the Fel d1 content of the extract in most cat sensitive patients1; the absorption of cat extract with monospecific antisera to Fel d1 causes a reduction in the allergenic activity of cat extract1; the precipitin arc of Fel d1 in cat extract binds most of the IgE antibody in sera obtained from cat-allergic individuals"].

WHO standardized extracts also include dog (based on Can 1), alternaria (based on Alt 1), and various grasses (based on Phl p 5; Lol p 1; etc), birch (based on Bet v 5).

Appendix D. Evidence Tables for Subcutaneous Immunotherapy

TABLE D1. - STUDY CHARACTERISTICS SCIT

a) Table D1a. Study characteristics- SCIT- Asthma

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Creticos 1996[1] USA	Asthma	Seasonal	Single	Weeds: Short ragweed	No previous immunotherapy Positive skin test Monosensitized individuals only	Government Other
Hill 1982[2] Australia	Asthma	Seasonal	Single	Grass: rye	Age: Children Positive skin test Minimum duration of disease: 3 years	Non-profit Industry
Altintas 1999[3] Turkey	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive skin test	Not stated
Bousquet 1985[4] France	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Positive skin test	Unclear
Bousquet 1988[5] France	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Positive skin test	Not stated
Garcia-Ortega 1993 [6] Spain	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: 13 – 45 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 1 year Excluded Pregnancy	Not stated
Pifferi 2002[7] Italy	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Monosensitized individuals only	Not stated
Van Bever 1991[8] Belgium	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Positive specific IgE test Positive skin test	Not stated
Van Bever 1990[9] Belgium	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Positive specific IgE test Positive skin test	Not stated
Wang 2006[10] China	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: 6-45 years Positive specific IgE test Positive skin test	Industry
Schubert 2009[11] Germany	Asthma	Perennial	Single	Dust mites: Unspecified dust mites	Positive specific IgE test Positive skin test	Not stated

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Kohno 1998[12] Japan	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Positive specific IgE test Positive skin test	Non-profit
Maestrelli 2004[13] Italy	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: 8-43 years Positive specific IgE test Positive skin test Minimum duration of disease: 1 year	Government Industry
Olsen 1997[14] Denmark	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: >18 years Positive specific IgE test Positive skin test Excluded Pregnancy	Not stated
Ohman 1984[15] USA	Asthma	Perennial	Single	Animals: Cats	No previous immunotherapy Positive skin test	Government Non-profit
Van Metre1988[16] USA	Asthma	Perennial	Single	Animals: Cats	Positive specific IgE test Positive skin test	Government Other
Valovirta 1986[17] Valovirta 1984[18] Denmark- Finland	Asthma	Perennial	Single	Animals: Dogs	Age: 5-18 years No previous immunotherapy Positive specific IgE test Positive skin test	Government Non-profit
Malling 1986 Denmark-Sweden[19]	Asthma	Seasonal	Single	Mold: Cladosporium	No previous immunotherapy Positive skin test Excluded Pregnancy	Government Industry
Adkinson 1997[20] Limb 2006[21] USA	Asthma	Seasonal and Perennial	Multiple	Dust mites : Dermatophagoides pteronyssinus and farinae Trees : white oak Weeds: Short ragweed and English plantain Grass: Grass mix and Bermuda grass Molds: Alternaria, aspergillus cladosporium	Age: 5-12 years Positive specific IgE test Positive skin test Minimum duration of disease:1 year	Government Industry

b) Table D1b. Study characteristics- SCIT- Rhinitis

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Polosa 2004[22] Polosa 2003[23] Italy	Rhinitis	Seasonal	Single	Weeds: Parietaria	Positive skin test Monosensitized individuals only	Industry
Van Metre1980[24] USA	Rhinitis	Seasonal	Single	Weeds: Ragweed	Positive specific IgE test Positive skin test	Government Non-profit

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Van Metre1982 [25] USA	Rhinitis	Seasonal	Single	Weeds: Ragweed	Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Government Non-profit
Franklin 1967[26] USA	Rhinitis	Seasonal	Multiple	Multiple allergens including ragweed	Positive skin test	Government
Ariano 1997[27] France-Italy	Rhinitis	Seasonal	Multiple	Trees: Tree mix (Cypress-Cedar)	Positive skin test	Not stated
Durham 1999[28] England and Canada	Rhinitis	Seasonal	Single	Grass: Timothy grass	Positive skin test	Government Industry
Reid 1986[29] USA	Rhinitis	Seasonal	Multiple	Grass: Grass mix	Age: Older > 18 years old Positive skin test No previous immunotherapy	Not stated
Junqueira de Queiros 2008[30] Brasil	Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive skin test Excluded Pregnancy	Government Non-profit
McHugh 1990[31] Ewan 1988 [32] UK	Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive skin test	Government Non-Profit
Nanda 2004[33] USA	Rhinitis	Perennial	Single	Cat	Age: Older > 18 years old Positive skin test No previous immunotherapy Excluded pregnancy	Government

c) Table D1c. Study characteristics- SCIT- Rhinoconjunctivitis

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Crimi 2004[34] Italy	Rhinoconjunctivitis	Seasonal	Single	Weeds: Parietaria	Positive skin test	Industry
Bernstein 1976[35] USA	Rhinoconjunctivitis	Seasonal	Single	Weeds: Ragweed	Positive skin test	Industry Not stated
Frew 2006[36] UK	Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy grass	Age: 18 – 60 years No previous immunotherapy Positive specific IgE test Positive skin test	Industry

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Varney 1991[37] Durham 2010[38] Durham 1996[39] UK	Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Shamji 2012[40] UK	Rhinoconjunctivitis	Seasonal	Single	Grass: Unspecified grass	Age: 18-60 years No previous immunotherapy Positive skin test	Industry
James 2011[41] UK	Rhinoconjunctivitis	Seasonal	Multiple	Grass: grass mix	Positive skin test	Government
Walker 2001[42] UK	Rhinoconjunctivitis	Seasonal	Multiple	Grass: grass mix	No previous immunotherapy Monosensitized individuals only Positive skin test	Industry
Frostad 1983[43] Norway	Rhinoconjunctivitis	Seasonal	Multiple	Grass mIx: Timothy grass, Cocksfoot Meadow fescue And ryegrass	Age: adults No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Not stated
Klimek 1999[44] Germany	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix Trees: trees mix	Age: 15-50 years No previous immunotherapy Positive skin test	Government Industry
Leynadier 2000[45] France	Rhinoconjunctivitis	Seasonal	Multiple	Grass mix: Orchard Meadow Perennial ryegrass sweet vernal grass and Timothy	Age 18-44 years No previous immunotherapy Positive specific IgE test Positive skin test	Industry
The PAT study Möller 2002[46] Niggeman2006[47] Jacobsen 2007[48] Multiple European countries	Rhinoconjunctivitis	Seasonal	Multiple	Trees: Birch Grass: Timothy grass	Age: Children No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Olsen 1995[49] Denmark	Rhinoconjunctivitis	Seasonal	Multiple	Weeds: Mugwort Trees: Birch Grass: Timothy	Age >18 years No previous immunotherapy Positive skin test Minimum duration of disease: 2 years Excluded Pregnancy	Not stated
Zenner 1996[50] Germany	Rhinoconjunctivitis	Seasonal	Multiple	Grass mix: Rye- Secale cereal and Grass mix	Age: 16-53 years Positive skin test	Industry

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Dreborg 2011[51] UK	Rhinoconjunctivitis	Perennial	Multiple	Grass: Timothy Dust mite	Age: 17-55 years No previous immunotherapy Positive skin test Excluded Pregnancy	Industry

d) Table D1d. Study characteristics- SCIT- Asthma and rhinitis

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Ariano 2006[52] Italy	Asthma and Rhinitis	Seasonal	Single	Weeds: Parietaria judaica	Age: 18-50 years No previous immunotherapy Minimum duration of disease: 2 years	Not stated
Ferrer 2005[53] Spain	Asthma and Rhinitis	Seasonal	Single	Weeds: Parietaria judaica	Age: 15 – 55 years Positive specific IgE test Positive skin test Monosensitized individuals only	Industry
Naclerio 1997[54] Iliopoulos 1991[55] USA	Asthma and Rhinitis	Seasonal	Single	Weeds: Ragweed	Positive skin test	Government
Arvidsson 2004[56] Arvidsson 2002[57] Sweden	Asthma and Rhinitis	Seasonal	Single	Trees: White birch	No previous immunotherapy Positive specific IgE test Positive skin test	Industry
Munoz Lejarazu, 1993[58] Spain	Asthma and Rhinitis	Seasonal	Single	Grass: Timothy grass	No previous immunotherapy Positive skin test Positive specific IgE test Monosensitized individuals only	Government
Nouri-Aria 2003[59] Walker 2001[42] UK	Asthma and Rhinitis	Seasonal	Single	Grass: Timothy grass	No previous immunotherapy Positive skin test	Government Non-profit
Muro 1999[60] Spain	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: 5-50 years No previous immunotherapy Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Industry
Tabar 2005[61] Spain	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Positive specific IgE test Positive skin test	Industry Government
Newton 1978[62] UK	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides farinae	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Prieto 2010[63] Spain	Asthma and Rhinitis	Seasonal	Single	Mold: Alternaria	Positive skin test	Industry

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Horst 1989[64] France	Asthma and Rhinitis	Seasonal	Single	Mold: Alternaria	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Not stated
Tabar 2007[65] Spain	Asthma and Rhinitis	Seasonal	Single	Mold: Alternaria	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Government Industry
Akmanlar 2000[66] Turkey	Asthma and Rhinitis	Perennial	Multiple	Dust mites:Dermatophagoides pteronyssinus and farinae	Age: children No previous immunotherapy Positive skin test Monosensitized individuals only	Not stated
Pichler 1996[67] Switzerland and Denmark	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Positive specific IgE test Positive skin test	Industry
Varney 2003[68] UK	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Petersen 1988[69] Denmark	Asthma and Rhinitis	Perennial	Multiple	Trees: White birch and Tree mix	Positive skin test pregnant women were excluded	Industry
Hedlin 1999[70] Denmark-Sweden	Asthma and Rhinitis	Perennial	Multiple	Animals: Cats Dust mites: Dermatophagoides pteronyssinus Weeds	Age: Children Positive skin test Minimum duration of disease: 2 years	Non-profit Industry
Cantani 1997[71] Italy	Asthma and Rhinitis	Seasonal and Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus Grass: Perennial ryegrass Weeds: Parietaria	No previous immunotherapy Positive skin test	Not stated

e) Table D1e. Study characteristics- SCIT- Asthma and Rhinoconjunctivitis

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Mirone 2004[72] Italy	Asthma and Rhinoconjunctivitis	Seasonal	Single	Weeds: Short ragweed	No previous immunotherapy Positive skin test Positive specific IgE test Monosensitized individuals only	Industry

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76] Denmark	Asthma and Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy grass	Monosensitized individuals only	Government Industry
Pence 1975[77] USA	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Mountain cedar	No previous immunotherapy Positive skin test	Non-profit
Rak 2001[78] Rak 2005[79] Denmark- Sweden	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Birch	Positive specific IgE test Positive skin test	Government Industry
Dreborg 1986[80] Multiple European countries	Asthma and Rhinoconjunctivitis	Seasonal	Single	Mold: Cladosporium	No previous immunotherapy Positive specific IgE test Positive skin test	Industry
Kuna 2011[81] Poland	Asthma and Rhinoconjunctivitis	Seasonal	Single	Mold: Alternaria	Age: Children 5-18 years Positive skin test Positive specific IgE test Duration of disease: 2 years	Not stated
Weyer 1981[82] France	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Positive skin test	Industry Non-profit
Bousquet 1991[83] Bousquet 1991[84] France-Germany	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Orchard grass Trees: London plane and Olive Weeds: Parietaria	No previous immunotherapy Positive specific IgE test Positive skin test	INSERM Grant
Chakraborty 2006[85] India	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Trees: date sugar palm/wild date palm	No previous immunotherapy Positive skin test	Government Non-profit
Dolz 1996[86] Spain	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Timothy Orchard ryegrass	Age: 15-35 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Industry
Alvarez-Cuesta 1994[87] Spain	Asthma and Rhinoconjunctivitis	Perennial	Single	Animals: cat	Age: 14-55 years Positive specific IgE test Positive skin test Minimum duration of disease: 1 year	Not stated
Varney 1997[88] UK	Asthma and Rhinoconjunctivitis	Perennial	Single	Animals: Cats	No previous immunotherapy Positive skin test	Not stated
Tabar 2010[89] Spain	Asthma and Rhinoconjunctivitis	Perennial	Single	Dust mite	Age: 5-45 years Positive skin test Positive specific IgE test	Government

TABLE D2.- PATIENT CHARACTERISTICS SCIT

a) Table D2a. Patient characteristics- SCIT- Asthma

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Creticos. 1996[1]	90	SCIT Placebo	36 +/- 10 35 +/- 10	51/49 50/50	37/8 53/16	At least 1
Hill 1982[2]	20	SCIT Placebo	Range 9-14 Range 9-14	Entire study 65/35	11/NR 9/NR	3 3
Altintas 1999[3]	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
Bousquet 1985[4]	30	SCIT (Rush) Placebo extract (rush)	29 +/- 5(Range 18-41) 27 +/- 6(Range 19-42)	65/35 70/30	20/0 10/0	6.3 9.1
Bousquet 1988[5]	215	SCIT (Rush) Control (No SIT)	24 +/- 13(Range 3-72) 24 +/- 11(Range 3-72)	Entire study 68.0/32.0	171/NR 44/NR	12 9.8
Garcia-Ortega 1993[6]	36	SCIT Control (conventional therapy)	Range 13-45 Range 13-45	Entire study N 16/20	18/NR 18/NR	NR
Pifferi 2002[7]	29	SCIT no treatment	11 +/- 3 10 +/- 2	Entire Study 55/45	15/0 14/4	NR
Van Bever 1991[8]	18	SCIT Placebo	9 (Range 7-11) 12 (Range 8-22)	NR	9/0 9/0	NR
Van Bever 1990[9]	19	SCIT Placebo (after 1 year of SCIT)	12.2 (Range 8- 16) 12 (Range 9-14)	NR	9/NR 10/NR	NR
Wang 2006[10]	132	SCIT Placebo	Range 6-45	56/44 61/39	64/2 65/1	7.1 +/- 0.81 7.3 +/- 0.79
Schubert 2009[11]	34	SCIT Cluster SCIT Classic	10 8.5	NR NR	20/2 14/2	NR
Kohno 1998[12]	16	SCIT Placebo	25.8 26.3	75/25 66/34	8/0 6/2	NR

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Maestrelli 2004[13]	95*	SCIT Placebo	20 +/- 8 23 +/- 10	61/39 71/29	41/8 31/15	1
Olsen 1997[14]	31	SCIT Placebo	32 (Range 18-56) 40.7 (Range 22-64)	NR	NR	NR
Ohman 1984[15]	17	SCIT Placebo	26 (Range 22-31) 30 (Range 24-48)	NR NR	9/0 8/0	NR
Van Metre 1988[16]	22	SCIT Placebo	Range 21-52 Range 21-52	N 5/6 N 5/6	11/1 11/0	NR
Valovirta 1986[17] Valovirta 1984[18]	27	SCIT Placebo	11 (Range 5-18) 10.5 (Range 5-16)	60/40 58/42	15/0 12/0	NR
Malling 1986[19]	23	SCIT Placebo	25 (Range 17-43) 31 (Range 16-54)	64/36 82/19	11/1 11/0	16 24
Adkinson 1997[20] Limb 2006[21]	121	SCIT Placebo	9 +/- 2 9 +/- 2	80/20 76/24	61/8 60/3	greater than 1 greater than 1

b) Table D2b. Patient characteristics- SCIT-Rhinitis

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Polosa 2004[22] Polosa 2003 [23]	30	SCIT Placebo	32 (Range 21-54) 34 (Range 20-53)	67/33 33/67	15/0 15/0	7.8 8.2
Van Metre 1980[24]	39*	SCIT Placebo	Range 18-50 Range 18-50	80/20 71/29	15/0 14/0	NR
Van Metre 1981[25]	44	SCIT-Weekly Placebo- weekly SCIT- clustered Placebo-clustered	Range18-50 Range18-50 Range18-50 Range18-50	N 11/4 N 4/1 N 13/5 N 2/4	15/0 5/0 18/0 6/0	NR

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Franklin 1967[26]	25	SCIT high dose SCIT low dose	NR	NR	12/NR 13/NR	NR
Ariano 1997[27]	20	SCIT Placebo	27-42 years	50/50 All study	10/ 10/	2-6 years
Durham 1999[28]	32	SCIT discontinued SCIT no treatment	Median 38 (Range 32-48) Median 42 (Range 32-48) Median 33 (Range 32-48)	69/31 50/50 66/34	16/2 16/3 15/	NR
Reid 1986[29]	23 5 dropouts entire study	SCIT Control	26 (Range 20-39) 29 (Range 22-36)	44/66 66/44	9/0 9/0	NR
Junqueira de Queiros 2008[30]	50*	SCIT Placebo	22 +/- 14 21 +/- 13	66/34 34/66	25/10 25/10	NR
McHugh 1990[31] Ewan 1988[32]	80	SCIT- purified SCIT- crude Placebo	Range 17-52 Range 17-52 Range 17-52	NR	30/3 20/2 30/2	NR
Nanda 2004[33]	28	SCIT high dose SCIT medium dose SCIT low dose Placebo	Older than 18	NR	7/1 7/0 7/0 7/1	NR

c) Table D2c. Patient characteristics- SCIT-Rhinoconjunctivitis

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Crimi 2004[34]	30	SCIT Placebo	32 (Range 21-54) 34 (Range 20-53)	67/33 33/67	15/1 15/0	7.8 8.2
Bernstein 1976[35]	148	SCIT Placebo	Entire study 30.0	Entire study 53/57	68/NR 60/NR	At least 3 At least 3

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Frew 2006[36]	410	SCIT 100,000 SQ-U SCIT 10,000 SQ-U Placebo	38 +/- 9 (Range 18-60) 37 +/- 9 (Range 20-58) 38 +/- 9 (Range 19-59)	54/46 57/43 61/39	203/34 104/17 103/12	20.6 20.2 19.9
Varney 1991[37] Durham 2010[38] Durham 1996[39]	40	SCIT Placebo	38(Range 32-48) 42(Range 33-50)	69/31 50/50	21/2 19/3	NR
James 2011[41]	13	SCIT 4 years SCIT 2 years + Placebo 2 years	33 (Range 32-36) 35 (Range 30-37)	57/43 66/34	7/0 6/0	NR
Walker 2001[42]	44	SCIT Placebo	32 (Range 22-64) 32 (Range 23-59)	45/55 59/41	22/2 22/5	NR
Shamji 2012[40]	221	SCIT 100.000 SCIT 10.000 Placebo	38 +/- 9(Range 18-60) 37 +/- 9(Range 20-58) 38 +/- 9(Range 19-59)	54/46 56/44 60/40	112/NR 54/NR 55/NR	20 (eye-nose) 16 (lung)
Frostad 1983[43]	60	SCIT purified Timothy SCIT crude Timothy SCIT grass mix Control	Median age 25	NR	24/4 17/3 19/3 30/NR	NR
Klimek 1999[44]	48	SCIT Pharmacotherapy	30 (Range 21-49) 31 (Range 15-50)	63/37 66/34	24/0 24/0	Median: 13 Median: 12
Leynadier 2000[45]	29	SCIT Placebo	29 (Range 18-44) 31 (Range 20-42)	47/53 54/46	16/1 13/1	8 11
The PAT study Möller 2002[46] Niggeman2006[47] Jacobsen2007[48]	205	SCIT Placebo	Entire study 16 (Range 11-20)	Entire study 66/34	103/NR 102/NR	NR
Olsen 1995[49]	25*	SCIT-Artemisia SCIT- Betula /Phleum extract	Range 18-45	Entire study 40.0/60.0	9/3 11/2	NR
Zenner 1996[50]	86	SCIT Placebo	28 (Range 18-53) 29 (Range 16-49)	N 30/15 N 29/12	45/1 41/0	13 12
Dreborg 2011[51]	20	SCIT Timothy SCIT dust mite	29 (Range 17-55)	55/45	9/2 11/4	NR

d) Table D2d. Patient characteristics- SCIT-Asthma and rhinitis

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Ariano 2006[52]	30	SCIT Pharmacotherapy	35 +/- 10 32 +/- 11	55/45 60/40	20/NR 10/NR	2 2
Ferrer 2005[53]	57	SCIT Placebo	36 +/- 11 33 +/- 10	39/61 52/48	28/6 29/9	NR
Naclerio 1997[54] Iliopoulos 1991[55]	20	SCIT Placebo	NR NR	NR NR	10/0 10/0	1 1
Arvidsson 2004[56] Arvidsson 2002[57]	49*	SCIT placebo	33 (Range 21-45) 31 (Range 19-45)	38/62 44/56	22/1 22/1	NR
Munoz Lejarazu, 1993[58]	60	SCIT-Perennial SCIT-Seasonal	19 +/- 10 18 +/- 9	62/38 56/44	26/5 28/6	4.7 +/- 3.1 4.9 +/- 3.4
Nouri-Aria 2003[59] Walker 2001[42]	44	SCIT Placebo	32 (Range 22-64) 32 (Range 23-59)	45/55 59/41	22/2 22/5	NR
Muro 1999[60]	63	SCIT Cluster SCIT Conventional Control	16 SE: 1 16 SE: 2 19 SE: 2	70/30 73/27 80/20	29/2 19/1 15/2	NR
Tabar 2005[61]	239	Cluster Conventional	19 +/- 10 18 +/- 9	63/37 60/40	120/23 119/20	4 4
Newton 1978 [62]	16	SCIT Placebo	29 (Range 20-38) 30 (Range 18-44)	43/57 57/43	7/1 7/1	16 7.7
Prieto 2010[63]	40	SCIT Placebo	25 (Range 22-29) 22 (Range 18-26)	43/57 72/28	21/5 18/0	NR
Horst 1989[64]	24	SCIT Placebo	12 +/- 5 (Range 7-23) 13 +/- 15 (Range 5-56)	75/25 74/26	13/0 11/2	NR
Tabar 2007[65]	28	SCIT Placebo	13 SE 4 15 SE 6	86/14 93/7	14/1 14/4	NR
Akmanlar 2000[66]	18	SCIT Rush SCIT Conventional	7 +/- 2.6 9 +/- 4	NR NR	9/0 9/0	NR
Pichler 1996[67]	30 3 dropouts whole study	SCIT Placebo	29 (Range 20-46) 32 (Range 20-42)	63/37 72/28	16/NR 14/NR	Rhinitis: 5.6; Asthma:3.9 Rhinitis: 6.4;

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
						Asthma:5.1
Varney 2003[68]	36	SCIT Placebo	33 (Range 19-48) 37(Range 23-55)	N 6/9 N 7/6	15/4 13/4	NR
Petersen 1988[69]	54	SCIT SCIT	30 (Range 15-72) 32 (Range 15-56)	48/52 41/59	27/4 27/5	8.3 6.8
Hedlin 1999[70]	32 3 dropouts whole study	SCIT SCIT and Placebo	11.7 (Range 7-16) 12 (Range 10-16)	53/57 43/57	15/NR 14/NR	NR
Cantani 1997[71]	300	SCIT Pharmacotherapy	Entire study 4 (Range 3.-7)	Entire study 58/42	151/NR 149/NR	NR

e) Table D2e. Patient characteristics- SCIT-Asthma and Rhinoconjunctivitis

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Mirone 2004[72]	32	SCIT Placebo	37 (Range 27-54) 36 (Range 23-60)	44/56 69/31	16/3 16/4	NR
Osterballe1982[73] Osterballe1981[74] Osterballe1980[75] Osterballe1982[76]	40	SCIT- partially purified extract SCIT- Ag 19 25	24 (Range 15-43) 24 (Range 15-38)	70/30 60/40	20/0 20/1	7.5 10
Pence 1975[77]	40	SCIT Placebo	37 44	41/59 40/60	17/3 15/5	NR
Rak 2001[78] Rak 2005[79]	41	SCIT Nasal steroid	30 (Range 18-41) 29 (Range 21-42)	43/57 65/35	21/0 20/0	NR
Dreborg 1986[80]	30	SCIT Placebo	11 (Range 5-17) 11 (Range 5-17)	NR	16/NR 14/NR	NR

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Kuna 2011[81]	50	SCIT Placebo	12 +/-4 11 +/-4	50/50 50/50	30/NR 20/NR	2 years
Weyer 1981[82]	33	SCIT Placebo	26 (Range 9-42) 26 (Range 15-46)	N 7/10 N 9/7	17/NR 16/NR	5 6
Bousquet 1991[83] Bousquet 1991[84]	70 4 dropouts in the entire study	SCIT grass Placebo grass SCIT multiple Placebo multiple	21 +/- 10 (Range14-44) 22 +/- 12 (Range 14-44) 24 +/- 8 (Range 14-44) 26 +/- 13 (Range 14-44)	44/46	16/NR 17/NR 16/NR 17/NR	9.6 10 8.5 9.2
Chakraborty 2006[85]	35	SCIT Placebo	32 33	NR	18/0 17/0	NR
Dolz 1996[86]	28	SCIT Placebo	18.3 21.5	NR	18/NR 10/NR	4.7 years 4.8 years
Alvarez-Cuesta 1994[87]	28	SCIT Placebo	23 (Range 15-65) 29 (Range 15-65)	21/79 22/78	14/0 14/0	NR
Varney 1997[88]	28	SCIT Placebo	34 (Median) Range 22-46 32 (Median) Range 19-50	N 3/10 N 7/8	13/NR 15/NR	NR
Tabar 2010[89]	142	SCIT 5 years SCIT 3 years Control	18 12.5 19	30/70 55/45 52/48	70/21 72/8 27	NR

TABLE D3. INTERVENTION CHARACTERISTICS –SCIT

a) Table D3a. Patient characteristics- SCIT-**Asthma**

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Creticos 1996[1]	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
Hill 1982[2]	SCIT Rye grass Rush Placebo	conventional therapy	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
Altintas 1999[3]	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 ≡ 1/1000w/v)	NR	Every 4 weeks	NR	2 years
Bousquet 1985[4]	SCIT Rush Placebo	NR	3000 BU(=to 0.1 ml of 1/100 w/v)	NR	Weekly	NR	7 weeks (not clearly stated)
Bousquet 1988[5]	SCIT Dust mite No treatment	conventional therapy	3000 BU	NR	Weekly for 6 weeks; then every 2 weeks for 1 year	NR	1 year
Garcia-Ortega 1993[6]	SCIT Dust mite Cluster Pharmacotherapy	conventional therapy	100000 SQ	2000000 SQ	Every 15 days		7 months
Pifferi 2002[7]	SCIT Dust mite HDM No treatment	conventional therapy	800 U	24758.33 U (mean)	4 -6 weeks	NR	3 years
Van Bever 1991[8]	SCIT Dust mite Cluster Placebo	conventional therapy	1000 BU	16497 BU	Every 4 weeks	NR	1 year

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Van Bever 1990[9]	SCIT Dust mite Cluster SCIT HDM Placebo	conventional therapy	1000 BU	16497 - 28497 (Year1: 16,497 Year 2: 12000) Year1: 16,497 Year 2:placebo	Every 4 weeks	NR	2 year
Wang 2006[10]	SCIT dust mite alum-precipitated Placebo	ONLY rescue medication	100000 SQ-U	NR	6 weeks	9.8 µg Der p1	1 year
Schubert 2009[11]	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
Kohno 1998[12]	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
Maestrelli 2004[13]	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
Olsen 1997[14]	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
Ohman 1984[15]	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

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Van Metre 1988[16]	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
Valovirta 1986[17] Valovirta 1984[18]	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
Malling 1986[19]	SCIT Cladosporidium Placebo	conventional therapy	18,000 BU mean "maintenance" dose 46,000 BU mean "top" dose 100000 BU target "top" dose; (only 1 patient)	444,000 BU	Every 4 weeks	NR	5-7 months
Adkinson 1997[20] Limb 2006[21]	SCIT Multiple allergen Placebo	conventional therapy and rescue therapy	0.7 mL of concentrate	NR	Biweekly for 24 months, every 3 weeks after 24 months	4.3 µg Der p1- 5 µg Der f1- 26 µg Amb a1 38 µg group 1 (Grass mix – timothy orchard - ryegrass) 6 µg Alt a1 Not reported for Bermuda grass English plantain white oak Cladosporium Aspergillus fumigatus	27 months

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

b) Table D2b. Patient characteristics- SCIT- **Rhinitis**

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Polosa 2004[22] Polosa 2003[23]	SCIT Parietaria alum-precipitated Placebo	ONLY rescue medication	80000 SQ U (equivalent to 8000 BU)		Every 4 weeks	4.8 µg Par j 1	3 years
Van Metre 1980[24]	SCIT Ragweed Placebo	conventional therapy		84.9 µg AgE range: 18.1 - 351.2 µg AgE	Weekly	84.9 µg AgE (median cumulative)	7 months
Van Metre 1981[25]	SCIT-Ragweed-weekly Placebo-weekly SCIT- Ragweed cluster Placebo-clustered	conventional therapy	9.4 µg AgE (median) 18.7 µg AgE (target) 4.7 µg AgE (median) 18.7 µg AgE (target)	70 µg AgE 17.5 µg AgE	Every 1 to 3 weeks Every 3 weeks	9.4 µg AgE 4.7 µg AgE	7 months
Franklin 1967[26]	SCIT high dose SCIT low dose	conventional therapy	0.3-0.5ml of 1:50 conc 0.3-0.4 ml of 1:1000 conc	NR	6 injections 3months prior to ragweed season	NR	>6 months
Ariano 1997[27]	SCIT tree Placebo	conventional therapy	21090 PNU Cryp J I – Cryp J II	151090 year1 321090 year2 491090 year3	Every 3 weeks	NR	3 years
Durham 1999[28]	3 years SCIT Timothy followed by maintenance alum-precipitated 3 years SCIT Timothy followed by placebo	ONLY rescue medication	100000 SQ units (=10,000 BU)	NR	Every 4 weeks	20 µg Phl p 5	3 years
Reid 1986[29]	SCIT grass mix SCIT non grass	ONLY rescue medication	9.3 µg RGGI	NR	Twice a week	9.3 µg RGGI (Ryegrass Antigen group 1)	7 months

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Junqueira de Queiros 2008[30]	SCIT Dust mite Placebo	conventional therapy	3.4 µg of Der p 1	NR	Every 4 weeks	3.4 µg Der p 1	1 year
McHugh 1990[31] Ewan 1988[32]	SCIT Dust mite purified- alum-precipitated SCIT Dust mite crude- alum-precipitated	conventional therapy	100000 BU 10000 PNU	NR	Weekly	100000 BU=260000 IU D Pter Non immunologically characterized	1 year
Nanda 2004[33]	SCIT cat high dose SCIT cat medium dose SCIT cat low dose Placebo	Conventional medication	15 µg Fel d1 3 µg Fel d1 0.6 µg Fel d1	NR	Weekly for 4 weeks then q2weeks for 2w then monthly	15 µg Fel d1 3 µg Fel d1 0.6 µg Fel d1	1 year

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

c) Table D3c. Patient characteristics- SCIT-**Rhinoconjunctivitis**

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Crimi 2004[34]	SCIT Parietaria alum-precipitated Placebo	ONLY rescue medication	80000 SQU = 800 BU	NR	Every 4 weeks	4.8 µg of Par J 1	3 years
Bernstein 1976[35]	SCIT Ragweed alum-precipitated Placebo	conventional therapy	6000 PNU (target)	7287 to 23945 PNU (actual)	Weekly		pre-seasonal and during season

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Frew 2006[36]	SCIT Timothy 100,000 SQU alum-precipitated SCIT Timothy 10,000 SQU alum-precipitated Placebo	conventional therapy	100000 SQ-U 10000 SQ-U	NR	every 6 (+/- 2) weeks	20 µg of Phl p 5 2 µg of Phl p 5	winter and spring of 2002; and June 1 to Aug 13 2002
Varney 1991[37] Durham 2010[38] Durham 1996[39]	SCIT Timothy aluminum-Alutard Placebo	conventional therapy	30000 BU/ml	BU/ml	Monthly	30000 BU = 100000 SQ phleum pratense	7 months
James 2011[41]	SCIT 4 years SCIT 2y + Placebo 2 y	NR	100,000 SQ units	NR	Monthly	20 µg Phl p5	4 years
Walker 2001[42]	SCIT Placebo	NR	100,000 SQ units			20 µg Phl p5 (P pratense)	3 years
Shamji 2012[40]	SCIT 100.000 SCIT 10.000 Placebo	NR	100000 SQ-U 10000 SQ-U	NR	Every 6 +/- 2 weeks	20 µg Phl p5 (100000 SQ-U) 2 µg Phl p5 (10000 SQ-U)	8 months
Frostad 1983[43]	SCIT Timothy purified SCIT Timothy crude SCIT grass mix	ONLY rescue medication		103000 BU 276000 BU 238000 BU			3 years

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Klimek 1999[44]	SCIT Grass-rye alum-precipitated Pharmacotherapy	conventional therapy	No maintenance; total of 7 injections in weekly intervals before the grass pollen season (units in SE; 1000 SE = approximately 1.5 µg grass major allergen)	2042 SE (equivalent to 3.1 µg grass group 5 major allergen		3.1 µg grass group 5 major allergen	7 weeks
Leynadier 2000[45]	SCIT Orchard meadow rye vernal timothy Placebo	conventional therapy	30 IR	220.4 IR (mean)	every 2 weeks preseasonal; once monthly during pollen season (with 50% dose reduction)	2.1 µg Phl p 5 (maintenance) 15.4 µg Phl p5 (mean cumulative dose)	1 year
The PAT study Möller 2002[46] Niggeman 2006[47] Jacobsen 2007[48]	SCIT Grass and Birch alum-precipitated Placebo	conventional therapy	100,000 SQ U/ml(Alutard SQ)	not specified	every 6 +/- 2 weeks interval	20 µg Phl p 5 (grass) and 12 µg Bet v 1 (Birch)	3 years
Olsen 1995[49]	SCIT-Artemisia alum-precipitated SCIT- Betula /Phleum extract alum-precipitated	NR	Up to 100000 SQU/mL (or highest tolerated dose)	NR	every 6 +/- 2 weeks interval		2 years
Zenner 1996[50]	SCIT Grass mix alum-precipitated Placebo	conventional therapy	No maintenance; total of 7 injections at weekly intervals before the expected beginning of the grass pollen season	2043 SE		3.1 µg of grass group 5 major allergen	7 weeks
Dreborg 2011[51]	SCIT Timothy SCIT dust mite	conventional therapy					

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

d) Table D3d. Patient characteristics- SCIT-**Asthma and rhinitis**

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Ariano 2006[52]	SCIT Parietaria Pharmacotherapy	NR	4 IR (only during pollen season) to 8 IR	NR	Every 4 weeks		3 years
Ferrer 2005[53]	SCIT Parietaria alum-precipitated Placebo	ONLY rescue medication	20 BU	NR	Every 4 weeks	1.2 µg of Par j 1	20 months
Naclerio 1997[54] Iliopoulos 1991[55]	SCIT Ragweed Placebo after SCIT	NR	5000 AU	NR	every 2 weeks	12 µg of Amb a 1	SCIT arm: 4years Placebo arm: 3 years SCIT + 1 year placebo.
Arvidsson 2004[56] Arvidsson 2002[57]	SCIT White birch Cluster alum-precipitated Placebo	NR	100000 SQ-U	NR	every 6 weeks		2 years
Munoz Lejarazu 1993[58]	SCIT- Timothy Perennial SCIT- Timothy Seasonal	NR	20 BU	613 BU (perennial) 393 BU (seasonal)	Every 4 weeks	NR	3 years
Nouri-Aria 2003[59] Walker 2001[42]	SCIT Timothy alum-precipitated Placebo	ONLY rescue medication	100,000 SQ U(=10,000 BU)	NR	Every 4 weeks	20 µg Phl p 5	2 years
Muro 1999[60]	SCIT Dust mite Cluster SCIT Dust mite Conventional Control	conventional therapy	8 BU	NR	Every 4 weeks	3.2 µg Der p 1	18 months after reaching maintenance

Tabar 2005[61]	SCIT Dust mite Cluster alum-precipitated SCIT Dust mite Conventional alum-precipitated	conventional therapy	8 BU(reached at week 8) 8 BU(reached at week 12)	At 18 weeks 41.3 BU At 18 weeks 38.65 BU	Every 4 weeks	3.2 µg Der p 1 and 1.6 µg Der p 2 (maintenance) 3.2 µg Der p 1 and 1.6 µg Der p 2	1 year
Newton 1978[62]	SCIT Dust mite alum-precipitated Placebo	NR	0.7 ml at 4000 PNU/ml	57 640 PNU	Every 3 weeks		15 months
Prieto 2010[63]	SCIT Alternaria alum-precipitated Placebo	conventional therapy	0.8 ml		Every 4 weeks	0.2 µg /ml Alt a 1	1 year
Horst 1989[64]	SCIT Japanese Cedar Rush Placebo	conventional therapy	2000 BU	NR	Weekly for 6 weeks then every 2 weeks for 1 year		1 year
Tabar 2007[65]	SCIT Alternaria Placebo	ONLY rescue medication	1670 UBE (reached after 14 weeks)	NR	Every 4 weeks	0.167 mg of lyophilized extract Alt a 1 =0.1 µg (maintenance)	15 months
Akmanlar 2000[66]	SCIT Dust mite Rush SCIT Dust mite Conventional	conventional therapy	100000 SQ-U 50000- 100000 SQ-U	NR	Biweekly Every 4 weeks		3 years
Pichler 1996[67]	SCIT Dust mite Cluster HDM alum-precipitated Placebo	conventional therapy		100000 SQ-U	Every 8 weeks		12 months
Varney 2003[68]	SCIT Dust mite alum-precipitated Placebo	ONLY rescue medication	100000 SQ-U (10000 BU)	NR	Monthly	7 µg/mL of Der p1	12 months after reaching maintenance

Petersen. 1988[69]	SCIT-Birch + Pollen mix alum-precipitated SCIT-Birch alone alum-precipitated	ONLY rescue medication	10,000 SQ units for 1st year; then 100,000 SQ units after the 1st year 100,000 SQ units	1392000 SQU 1408000 SQU	Every 4 to 6 weeks	144 g Bet v 1 324 g Bet v 1	3 years
Hedlin 1999[70]	SCIT-perennial (cat or dust mite) alum-precipitated SCIT-seasonal (birch or timothy) + Placebo	conventional therapy	100,000 SQU 100,000 SQU	NR	Every 6 weeks	15.0 µg Fel d 1; 7.0 µg Der p 1 (maintenance) 20 µg Phl p 5; 23 µg Bet v 1 (maintenance)	3 years
Cantani 1997[71]	SCIT Dust mite Parietaria ryegrass alum-precipitated Pharmacotherapy	conventional therapy	500 BU per month	26000 BU	Every 4 weeks		3 years

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

e) Table D3e. Patient characteristics- SCIT-**Asthma and Rhinoconjunctivitis**

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Mirone 2004[72]	SCIT Ragweed alum-precipitated Placebo	ONLY rescue medication		11140 PNU		31.2 µg of antigen E (for year 2)	preseasonal for 2 years (January to August)
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76]	SCIT Timothy partially purified alum-precipitated SCIT Ag 19 25 alum-precipitated	ONLY rescue medication	10000 BU	NR	Every 4 weeks		3 years

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Pence 1975[77]	SCIT Mountain cedar Placebo	ONLY rescue medication	0.3 cc of a 1:50 w/v concentration.	Mean = 58 mg (range = 1 mg -157 mg of extracted pollen	Weekly	6 mg of extracted pollen per dose (maintenance)	10 months
Rak 2001[78] Rak 2005[79]	SCIT Birch alum-precipitated Nasal Corticosteroids	ONLY rescue medication	100000 SQ U (budesonide) 200 µg: one puff	120-150 µg of allergen protein		allergen protein: 23 µg maintenance 120-150 µg cumulative	3 years
Dreborg 1986[80]	SCIT Cladosporium Placebo	conventional therapy	100000 BU (reached after 18 weeks	NR	Every 4 weeks		10 months
Kuna 2011[81]	SCIT Placebo	ONLY rescue therapy	1.0 ml (5000 TU/ml) or the highest tolerated dose	24.6 ml =123,000 TU (range, 109,000-158,000 TU).	Every 4 to 6 weeks	8 µg/mL Alt a 1	3 years
Weyer 1981[82]	SCIT Grass mix alum-precipitated Placebo	ONLY rescue medication		19.3 ± 3.4 µg protein (four grass pollen extract)		19.3 ± 3.4 µg protein (cumulative)	6 months
Bousquet 1991[83] Bousquet 1991[84]	SCIT grass pollen Placebo	NR	2000 BU	15897 BU (mean for grass group) 16371 BU (mean for multiple pollen group	2000 BU weekly for five weeks; then 1000 BU every 2 weeks for 6 months		Preseason and during season (approximately 7 to 8 months)
Chakraborty 2006[85]	SCIT Date trees Placebo	NR	0.5 to 1.0 µg of Fr IIa	NR	Biweekly	0.5 to 1.0 µg of Fr IIa	2 years

Study	ARMS	Conventional/Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Dolz 1996[86]	SCIT Timothy-Orchard-Ryegrass Rush Aluminum-Alutard Placebo	conventional therapy	100000 USQ/ml	NR	Every 4 weeks	100000 USQ/ml PDL (Phleum-Dactilis-Lolium)	3 years
Alvarez-Cuesta 1994[87]	SCIT Cat Placebo	conventional therapy	40 BU	NR	Every 4 weeks	13.2 µg Fel d l antigen	1 year
Varney 1997[88]	SCIT Cat alum-precipitated Placebo	ONLY rescue medication	100000 SQ U	NR	Every 4 weeks	15 µg Fel d 1 (maintenance)	treatment not specified
Tabar 2010[89]	SCIT 5 years SCIT 3 years Control		0.8 mL = 3.6 µg Der p 1	NR	Monthly	3.6 µg Der p 1	5 years

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

TABLE D4.- QUALITY ASSESSMENT -SCIT

a) Table D4a. Quality assessment- SCIT-Asthma

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Creticos 1996[1]	Low risk	Low risk	High risk	High risk	High risk	No	Medium risk
Hill 1982[2]	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
Altintas 1999[3]	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
Bousquet 1985[4]	Low risk	Low risk	High risk	High risk	High risk	Yes or unclear	High risk
Bousquet 1988[5]	Low risk	High risk	High risk	High risk	Low risk	No	Medium risk

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Garcia-Ortega 1993[6]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Pifferi 2002[7]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
Van Bever 1991[8]	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
Van Bever 1990[9]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Wang 2006 [10]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Schubert 2009[11]	Low risk	High risk	High risk	High risk	High risk	No	High risk
Kohno 1998 [12]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
Maestrelli 2004 [13]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Olsen 1997 [14]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
Ohman 1984 [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Van Metre 1988 [16]	Low risk	High risk	Low risk	High risk	High risk	No	Medium risk
Valovirta 1986[17] Valovirta 1984[18]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Malling 1986 [19]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Adkinson 1997[20] Limb 2006[21]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias;
Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

b) Table D4b. Quality assessment - SCIT-**Rhinitis**

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Polosa 2004 [22] Polosa 2003 [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Van Metre 1980[24]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Van Metre 1981[25]	Low risk	High risk	High risk	High risk	High risk	No	High risk
Franklin 1967 [26]	Low risk	High risk	High risk	High risk	High risk	No	High risk
Ariano 1997 [27]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Durham 1999 [28]	Low risk	Low risk	High risk	High risk	High risk	Yes or unclear	High risk
Reid 1986 [29]	Low risk	High risk	Low risk	High risk	Low risk	No	Medium risk
Junqueira de Queiros 2008[30]	Low risk	Low risk	Low risk	High risk	Low risk	No	Medium risk
McHugh1990[31] Ewan 1988[32]	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
Nanda 2004 [33]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias;
Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

c) Table D4c. Quality assessment - SCIT-Rhinoconjunctivitis

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Crimi 2004 [34]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
Bernstein 1976 [35]	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
Frew 2006 [36]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Varney 1991[37] Durham 2010 [38] Durham1996[39]	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
James 2011 [41]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Walker 2001 [42]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Shamji 2012[40]	Low risk	Low risk	Low risk	High risk	High risk	Yes or unclear	Medium risk
Frostad 1983 [43]	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Klimek 1999 [44]	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Leynadier 2000 [45]	Low risk	Low risk	High risk	High risk	Low risk	No	Medium risk
The PAT study Möller 2002[46] Niggeman 2006[47] Jacobsen, 2007[48]	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Olsen 1995[49]	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
Zenner 1996 [50]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Dreborg 2011 [51]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias;
Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

d) Table D4d. Quality assessment - SCIT-Asthma and rhinitis

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Ariano 2006 [52]	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
Ferrer 2005 [53]	Low risk	Low risk	High risk	Low risk	High risk	Yes or unclear	Medium risk
Naclerio 1997[54] Iliopoulos 1991[55]	Low risk	Low risk	Low risk	Low risk	High risk	No	Low risk
Arvidsson 2004[56] Arvidsson 2002[57]	Low risk	Low risk	High risk	Low risk	High risk	Yes or unclear	Medium risk
Munoz Lejarazu 1993[58]	Low risk	High risk	High risk	High risk	Low risk	No	Medium risk
Nouri-Aria 2003[59] Walker 2001[42]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Muro 1999[60]	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Tabar 2005[61]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Newton 1978[62]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Prieto 2010 [63]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Horst 1989 [64]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
Tabar 2007 [65]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
Akmanlar 2000 [66]	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
Pichler 1996[67]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Varney 2003[68]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Petersen 1988[69]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Hedlin 1999[70]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Cantani 1997[71]	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias;
Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

e) Table D4e. Quality assessment - SCIT-Asthma and Rhinoconjunctivitis

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Mirone 2004[72]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Pence 1975[77]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Rak 2001[78] Rak 2005[79]	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Dreborg 1986[80]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
Kuna 2011[81]	Low risk	Low risk	Low risk	Low risk	High risk	Yes or unclear	Medium risk
Weyer 1981[82]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Bousquet 1991[83] Bousquet 1991[84]	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Chakraborty 2006[85]	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
Dolz 1996[86]	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
Alvarez-Cuesta 1994[87]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Varney 1997[88]	Low risk	Low risk	Low risk	High risk	High risk	No	Medium risk
Tabar 2010[89]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Medium risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias;
Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

TABLE D5 - ASTHMA SYMPTOM SCORES -SCIT

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Wang 2006[10]	Dust mite	SCIT Placebo	1 year	Total daily asthma symptom score		0.998 +/- 0.148 1.133 +/- 0.155	0.178 +/- 0.032 0.397 +/- 0.085	SCIT vs Placebo pre p=0.543 SCIT vs Placebo post p=0.019
Maestrelli 2004[13]	Dust mite	SCIT Placebo	3 years	Median monthly asthma symptom scores (4-point scale)	0-3	5 (Year 1) (baseline score NR) 14 (Year 1) (baseline score NR)	0.3 5	SCIT pre vs post p NS Placebo pre vs post p NS SCIT vs Placebo p NS
Pichler 1996[67]	Dust mites	SCIT Placebo	12 months	asthma symptom scores		5.5 13	3.5 7	SCIT pre vs post p=0.014 Placebo pre vs post p=0.85 SCIT vs Placebo post p=0.09
Kohno 1998[12]	Dust mite	SCIT - Rush Bronchodilators	6 months	Sum of asthma symptom scores	4 symptom domains with various scales (largest scale was 0-12)	16.63 ± 2.24 11.33 ± 1.82	1.00 ± 0.42 10.17 ± 2.14	SCIT pre vs post p < 0.03 Bronchodilators pre vs post p NS
Olsen 1997[14]	Dust mite	SCIT Placebo	1 year	Mean asthma symptom score per week	NR	22 25	9.5 22	SCIT pre vs post p<0.001 Placebo pre vs post p NS

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Pifferi 2002[7]	Dust mite	SCIT Pharmacotherapy	3 years	Numbers of asthma exacerbations per year		8 8.5	1 4.5	SCIT vs Pharm p < 0.01
Bousquet 1988[5] (Reported data for patients allergic to Dpt only)	Dust mite	SCIT – Rush Control – No SIT	12 months	Severity of asthma (as measured by symptoms)	0-4	3.2 +/- 0.3 3.0 +/- 0.4	1.1 +/- 0.9 3.2 +/- 0.3	SCIT pre vs post p <0.0001 Control pre vs post p NS SCIT vs Control p <0.0001
Tabar 2005[61]	Dust mite	SCIT Cluster SCIT Conventional	1 year	Asthma symptom score		2.1 1.8	0.6 0.7	Cluster pre vs post p <0.001 Conventional pre vs post p <0.001
Tabar 2010[89]	Dust mite	SCIT 3 years SCIT 5 years	5 years	Global asthma score	0-5		80.9% reduction 79.9% reduction	3 vs 5 years, p=0.330
Nouri-Aria 2003[59] Walker 2001[42]	Timothy grass	SCIT Placebo	2 years	Median chest symptom scores during grass pollen season	Scale of 0-3; totaled daily	268 63	26 90% improvement 56 11% improvement	SCIT vs Placebo p < 0.05
Creticos 1996[1]	Short ragweed	SCIT Placebo	Year 2	7 point scale	0-6	4.6 4.3	2.9 3.5	SCIT vs Placebo p=0.3
Hill 1982[2]	Rye grass	SCIT Placebo	Year 1 (preseasonal IT >4 months)	Median asthma symptom score	Calculated score from 3 domains	3 (before season) 4 (before season)	7 (during season) 5 (during season)	SCIT pre vs post p <0.05 Placebo pre vs post p NS
Hill 1982[2]	Rye grass	SCIT Placebo	Year 2 (No IT given)	Median asthma symptom score	Calculated score from 3 domains	3 (before season) 2 (before season)	3 (during season) 5 (during season)	SCIT pre vs post p NS Placebo pre vs post p significant, value not reported (No report of statistical comparison between year 1 and year 2)

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Dreborg 1986[80]	Cladosporium	SCIT – Cluster Placebo	6 months (during 2 weeks of highest spore counts)	Bronchial symptoms	0-3	210 240	170 260	SCIT vs Placebo p NS
Malling 1986[19]	Cladosporium	SCIT Placebo	5 to 7 months	Symptom score (includes symptoms plus peak flow)	Comparison of number of subjects who were improved, unchanged or deteriorated	NR NR	NR NR	SCIT vs Placebo p = 0.07
Kuna 2011[81]	Alternaria	SCIT Placebo	3 years	Mean asthma symptom scores (Visual analog scale)	0-400	88.6 85.5	22.4 42	SCIT vs Placebo p = 0.0005
Ohman 1984[15]	Cats	SCIT Placebo	17 weeks	Time to first increase in symptoms on exposure to cats		NR NR	NR NR	SCIT pre vs post p <0.05 Placebo pre vs post p NS SCIT vs Placebo p <0.05 (comparison of change scores from baseline)
Adkinson 1997[20] Limb 2006[21]	Multiple	SCIT Placebo	last follow up (≥18 months)	Symptom score		0.34 0.37	-0.08 (change from baseline) -0.16 (change from baseline)	SCIT pre vs post p= 0.02 Placebo pre vs post p= 0.003 SCIT vs Placebo p = 0.5 (Mean difference pre = 0.003; post = -0.08)
Cantani 1997[71]	Dust mites ryegrass and parietaria	SCIT pharmacotherapy	Year 3	Mean percentage of NIGHTS with asthma		NR NR	40 66	SCIT vs Pharm p<0.0005
Cantani 1997[71]	Dust mites ryegrass and parietaria	SCIT control	Year 3	Mean percentage of DAYS with asthma		NR NR	32 56	SCIT vs Control p=0.0001

TABLE D6-COMBINED ASTHMA AND RHINOCONJUNCTIVITIS SYMPTOM SCORES - SCIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Horst 1989[64]	Alternaria	SCIT Placebo	1 year	Combined total symptoms and Medication score		NR NR	0.64 +/- 0.83 2.65 +/- 1.89	SCIT vs Placebo p <0.005 (favors SCIT)
Ariano 2006[52]	Parietaria	SCIT Pharmacotherapy	6 years	Ordinal scale (0, 1, 2, and 4)	0-4	13.45 +/- 2.42 12.90 +/- 2.02	2.55 +/- 1.32 10.7 +/- 1.57	SCIT vs Pharmacotherapy pre = NS SCIT vs Pharmacotherapy post p< 0.001
Nouri-Aria 2003[59] Nouri-Aria 2003[42]	Timothy	SCIT Placebo	2 years	Median total symptom score (chest, nose, eye, mouth, and throat)	Each symptom: 0-3; totaled daily	2576 1962	1277 50% improvement 1386 29% improvement	SCIT vs Placebo p = 0.01
Arvidsson 2004[56] Arvidsson 2002[57]	White birch	SCIT-cluster Placebo	2 years	Median daily symptom score per patient (combined for bronchial, nasal, and eye)	Each of 4 domains on scale of 0-3	NR NR	2.6 range: 0-6.5 4.3 range 2.4-9.1	SCIT vs Placebo p =0.005 (favors SCIT)
Varney 1997[88]	Cat	SCIT Placebo	3 months	Cat visit Combined symptom score (chest, nose, eyes, throat)	Each symptom domain on scale of 0-3	61.6 (SE 9.1) 64.7 (SE 13.6)	17.1 (SE 7.6) 62.1 (SE 10.0)	SCIT pre vs post p<0.001 Placebo pre vs post p NS

TABLE D7- ASTHMA MEDICATION SCORES – SCIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Wang 2006[10]	Dust mite	SCIT Placebo	Year 1	Daily medication score	Assigned score of 1 to each dose of rescue medication	0.407 +/- 0.082 0.259 +/- 0.045	0.184 +/- 0.04 0.292 +/- 0.10	SCIT vs Placebo pre p= 0.115 SCIT vs Placebo post p=0.308

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Pifferi 2002[7]	Dust mite	SCIT Pharmacotherapy	3 years	Days of therapy/year (Salbutamol)		40 50	7 40	SCIT vs Pharmacotherapy p <0.01
Pifferi 2002[7]	Dust mite	SCIT Pharmacotherapy	3 years	Days of therapy/year (systemic steroids)		22 25	1 12	SCIT vs Pharmacotherapy p <0.01
Maestrelli 2004[13]	Dust mite	SCIT Placebo	3 years	Proportion of subjects who did not use bronchodilators		22.1% 26.4%	28.5% 25.3%	SCIT pre vs post p < 0.01 (difference = +6.4%) Placebo pre post p NS (difference = -1.1)
Pichler 1996[67]	Dust mites	SCIT Placebo	18 months	number of patients taking steroids		6 4	4 2	NR
Pichler 1996[67]	Dust mites	SCIT Placebo	18 months	number of patients taking beta-2 agonists		11 9	8 6	NR
Olsen 1997[14]	Dust mite	SCIT Placebo	1 year	Asthma rescue medication consumption (inhaled beta-2 agonists)	Mean number of puffs per week	27 52	14 46% decrease 46	SCIT pre post p<0.05 Placebo pre vs post p NS
Olsen 1997[14]	Dust mite	SCIT Placebo	1 year	Inhaled steroid consumption	Mean number mg per week	4.7 1.4	2.9 38% decrease 2.6	SCIT pre post p<0.05 Placebo pre post p NS
Bousquet 1988[5]	Dust mite	SCIT – Rush Control – No SIT	12 months	Medication scores	0-5	5.5 +/- 2.5 5.1 +/- 2.3	1.3 +/- 1.5 5.3 +/- 1.9	SCIT pre vs post p <0.0001 Placebo pre vs post p NS SCIT vs Placebo (post) p <0.0001
Malling 1986[19]	Cladosporium	SCIT Placebo	5 to 7 months	Medication score	Comparison of number of subjects who were improved unchanged or deteriorated	NR	NR	SCIT vs Placebo p =0.1

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Hill 1982[2]	Rye grass	SCIT Placebo	Year 1 (preseasonal IT x >4 months)	Median asthma drug score		4 (before season) 1 (before season)	5 (during season) 2 (during season)	SCIT pre vs post p <0.05 Placebo pre vs post p NS
Hill 1982[2]	Rye grass	SCIT Placebo	Year 2 (No IT given)	Median asthma drug score		4 (before season) 1 (before season)	4 (during season) 2 during season)	SCIT pre vs post p NS Placebo pre vs post p NS
Creticos 1996[1]	Short ragweed	SCIT Placebo	Year 2	Medication score		33 +/- 7 28 +/- 4	29 +/- 8 33 +/- 8	SCIT vs Placebo p=0.7
Rak 2001[78] Rak 2005[79]	Birch	SCIT Nasal steroid	6 weeks	Asthma medication usage		NR	NR	No significant differences were found between the groups with respect to medication for asthma
Adkinson 1997[20] Limb 2006[21]	Multiple allergen	SCIT Placebo	27 months	10 point ordinal scale medication score	0-10	4.9 5.0	-1.4 -1.2 (change from baseline)	SCIT pre vs post p <0.001 Placebo pre vs post p <0.001 SCIT vs Placebo p =0.37 (Mean difference pre = 0.11; post = 0.22)
Cantani 1997[71]	Dust mite-Parietaria-ryegrass	SCIT Placebo	3 year	Mean drug usage for asthma attacks		NR	52 180	SCIT vs Placebo p= 0.0003

TABLE D8. ASTHMA STUDIES REPORTING ASTHMA AND RHINOCONJUNCTIVITIS MEDICATION SCORES - SCIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Nouri-Aria 2003[59] Walker 2001 [42]	Timothy	SCIT Placebo	2 years	Median total medication score (chest, nose, eye)	Daily scores were totaled	1815 2124	357 80% improvement 1851 18% improvement	SCIT vs Placebo p =0.007
Ariano 2006[52]	Parietaria	SCIT Pharmacotherapy	6 years	Combined drug consumption scores	Assigned score of 1 or 2 depending on amount of drug used	8.10 +/- 1.12 8.40 +/- 1.35	2.15 +/- 0.99 7.70 +/- 1.16	SCIT vs pharmacotherapy pre, p = NS SCIT vs pharmacotherapy post, p<0.001
Arvidsson 2004[56] Arvidsson 2002[57]	Birch	SCIT – cluster Placebo	2 years	Highest mean daily medication score (combined for bronchial, nasal, and eye)	Scores assigned to various rescue medications	NR NR	8 15.5	SCIT vs Placebo p =0.004
Dreborg 1986[80]	Cladosporium	SCIT Placebo	6 months (during 2 weeks with highest spore count)	Total daily medication score	Sum of doses per day	1370 1170	1180 1630	SCIT vs Placebo p<0.01
Kuna 2011[81]	Alternaria	SIT Placebo	Baseline-3yr	Mean daily medication score		13.8 11.2	2.3 21.4	SCIT pre vs Post p<0.001 Placebo pre vs Post p=0.001 SCIT vs Placebo p=0.001

TABLE D9- ASTHMA STUDIES REPORTING COMBINED SYMPTOM AND MEDICATION SCORES-SCIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Garcia-Ortega 1993[6]	Dust mite	SCIT cluster Conventional Pharmacotherapy	7 months	Clinical score (sum of symptom and medication scores)	Symptom: 1-5 Medication: 1-5	38±21 31±28	10 ± 14 27 ± 31	SCIT vs pharmacotherapy p NS
Akmanlar 2000[66]	Dust mites	SCIT rush SCIT conventional	3 years	Combined total symptoms and Medication score	Symptom 0-3 Medication 0-7	NR NR	NR NR	SCIT rush pre vs post p = 0.0003 SCIT conventional pre vs post p = 0.0003 SCIT vs placebo p NS
Altintas 1999[3]	Dust mite	SCIT-Adsorbed aluminum SCIT-Adsorbed calcium SCIT-aqueous Placebo	2 years	Combined asthma symptom medication score (SMS)	Symptom 0-3 Medication 0-7	6.2 5.1 4.6 4.0	0.7 2.4 1.4 3.2	SMS was significantly reduced after IT period (p <0.05); most significant improvement occurred in Arm 1 and least improvement in Arm 4 (placebo) with no significant difference among the IT group.
Malling 1986[19]	Cladosporium	SCIT Placebo	5 to 7 months	Combined total symptom and Medication score	Comparison of number of subjects who were improved unchanged, or deteriorated	NR	NR	SCIT vs placebo, p =0.03 (favors SCIT)
Horst 1989[64]	Alternaria	SCIT – Rush Placebo	1 year	Combined total symptoms and Medication score asthma and rhino-conjunctivitis	Asthma: 0-3 for symptoms; 1-3 for medications Rhinoconjunctivitis: 0-1 for symptoms; 1-3 for medications	NR NR	0.84 +/- 0.93 3.55 +/- 2.00	SCIT vs placebo, p <0.005
Kuna 2011[81]	Alternaria	SIT Placebo	3 years	Combined symptom medication score		75 75	30 62	SCIT vs Placebo p<0.001 (65% reduction when compared to placebo)
Horst 1989[64]	Alternaria	SCIT Placebo	1 year	Global symptom and medication score			0.84 +/- 0.93 3.55 +/- 2.00	SCIT vs placebo p <0.005

Alvarez-Cuesta 1994[87]	Cat	SCIT Placebo	1 year	Combined symptom and medication score (asthma and rhino-conjunctivitis)	NR	NR NR	0.14% 1.42%	SCIT vs placebo p<0.001 (favors SCIT)
Alvarez-Cuesta 1994[87]	Cat	SCIT Placebo	1 year	Patient self evaluation	Improvement in symptoms during direct contact with cats	NR NR	81.3% 20.7%	SCIT vs placebo p < 0.001 (favors SCIT)
Reid 1986[29]	Multiple (including grass)	SCIT grass SCIT non grass	7 months	Total asthma symptom-medication scores		NR NR	47 178	Grass vs non grass p<0.05

TABLE D10- ASTHMA PFT RESULTS -SCIT

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Wang 2006[10]	Dust mite	SCIT Placebo	1 year	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
Wang 2006[10]	Dust mite	SCIT Placebo	1 year	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
Wang 2006[10]	Dust mite	SCIT Placebo	1 year	FEV1 (% predicted)	87.96 +/-1.43 87.97 +/-1.74	NR NR	SCIT pre vs post p NS Placebo pre vs post p NS
Wang 2006[10]	Dust mite	SCIT Placebo	1 year	FVC (% predicted)	94.15 +/-1.39 95.17 +/-1.71	NR NR	SCIT pre vs post p NS Placebo pre vs post p NS
Maestrelli 2004[13]	Dust mite	SCIT Placebo	3 years	Morning PEF scores (% predicted)	95 97	104 101	SCIT pre vs post p<0.05

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Newton 1978[62]	Dust mites	SCIT Placebo	15 months	Mean morning peak flow	245 288	232 257	SCIT vs Placebo p= NS
Tabar 2005[61]	Dust mite	SCIT Cluster SCIT conventional	1 year	PEF variability (%)	6.8 6.8	4.6 6.3	Cluster pre vs post p <0.001 Conventional pre vs post p = 0.02
Kohno 1998[12]	Dust mite	SCIT - Rush Bronchodilators	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 < .03 B2 pre vs post p NS
Bousquet 1988[5]	Dust mite	SCIT – Rush Control – No SIT	12 months	FEV1 (% predicted values)	82.3 +/- 23.2 85.6 +/- 26.1	98.6 +/- 16.3 83.4 +/- 18.9	SCIT pre vs post p <0.0001 B2 pre vs post p NS SCIT vs B2 (post) p<0.0001
Ohman 1984[15]	Cats	SCIT Placebo	17 weeks	Percentage drop peak flow after exposure to cats	9 3	1 4	SCIT pre vs post p NS Placebo pre vs post p NS SCIT vs Placebo p NS
Varney 1997[88]	Cats	SCIT Placebo	3 months	Mean Fall in peak flow induced by cat exposure (L/min)	85± 15 (SE) 118 ±23(SE)	29 ± 6 (SE) 78 ± 20(SE)	SCIT pre vs post p=0.004 Placebo pre vs post p= 0.002
Adkinson 1997[20] Limb 2006[21]	Multiple	SCIT Placebo	last follow up (18 months or more)	PEFR	81.9 84.8	2.5 (change from baseline) -1.4 (change from baseline)	SCIT vs Placebo p = 0.05 (mean difference pre = 2.9; post = -3.8)
Rak 2001[78] Rak 2005[79]	Birch	SCIT Nasal steroid	6 weeks	Peak expiratory flow% predicted	NR	104 97	No differences were found between the two groups
Arvidsson 2004[56] Arvidsson 2002[57]	White birch	SCIT Placebo	2 years	Peak flow	NR NR	NR NR	SCIT vs Placebo p NS
Creticos 1996[1]	Short ragweed	SCIT Placebo	Year 2	Mean daily PEFR during peak season	454 444	480 461	SCIT vs Placebo p=0.03
Dreborg 1986[80]	Cladosporium	SCIT Placebo	6 months	Mean PEF	290 310	280 340	SCIT vs Placebo p NS

TABLE D11- BRONCHIAL CHALLENGES SCORES - SCIT

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Newton 1978[62]	Dust mites	SCIT Placebo	15 months	Mean dose of allergen in PNU to achieve 25% fall in PEF	234 298	408 215	SCIT vs Placebo p<0.005 (ED50)
Kohno 1998[12]	Dust mite	SCIT Bronchodilators	6 months	Airway responsiveness to histamine provocative concentration causing a 20% decrease in FEV1 (PC20 in mug/mL)	397.1±206.9 241.3±61.1	1391.3±283.3 252.3±45.0	SCIT pre vs post, p<0.03 Bronchodilators pre vs post, p=NS
Akmanlar 2000[66]	Dust mites	SCIT-Rush SCIT-conventional	3 years	Allergen bronchial provocation test	20470 20470	NR NR	Rush vs Conventional, p=0.41 Rush pre vs post p<0.1 Conventional pre vs post p<0.01 0.4 improved in both arms
Altintas 1999[3]	Dust mite	SCIT-Adsorbed aluminum SCIT-Adsorbed calcium SCIT-aqueous Placebo	2 years	Allergen bronchial provocation test	7244 4786 2137 4786	31622 39810 31153 7100	No significant difference among treatment groups, p>0.05 All SCIT vs Placebo, p<0.05
Garcia-Ortega 1993[6]	Dust mite	SCIT-Cluster Conventional treatment	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
Bousquet 1985[4]	Dust mite	SCIT Placebo	7 weeks	Allergen bronchial provocation challenge (PD20 FEV1)	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 p<0.01
Van Bever 1990[9]	Dust mite	SCIT Placebo	2 years	Allergen bronchial provocation, PD 20 BU)	5.03±1.60 6.06±0.46	5.20±1.59 5.72±0.87	SCIT, pre vs post, p=0.922 Placebo, pre vs post, p=0.287
Olsen 1997[14]	Dust mite	SCIT Placebo	1 year	Bronchial sensitivity to Dpt (mean PC20 in SQ-U/ml allergen challenge	25000 11000	37000 14000	SCIT, pre vs post, p=0.022 Placebo pre vs post, p=0.60 SCIT vs Placebo pre, p=0.20 SCIT vs Placebo post, p=0.037
Olsen 1997[14]	Dust mite	SCIT Placebo		Bronchial sensitivity to Dfa (mean PC20 in SQ-U/ml)	31000 29000	46000 20000	Arm1, pre vs post, p=0.039 Placebo pre vs post, p=0.75 SCIT vs Placebo pre, p=0.92 SCIT vs Placebo post, p=0.041 (favors SCIT)

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Kohno 1998[12]	Dust mite	SCIT Bronchodilators	6 months	Airway responsiveness to allergen (threshold concentration of dust mite extract causing a 20% decrease in FEV1 in wt/vol)	1:303.7±123. 1:230.0±154.5	1:65.0±13.2 1:291.7±158.9	SCIT pre vs post, p<0.03 Bronchodilators pre vs post, p=NS
Van Bever 1991[8]	Dust mite	SCIT Placebo	1 year	Median PD 20 house dust mite (BU)	238 303	477 385	SCIT pre vs post, p=0.04 Placebo, pre vs post, p=0.11 SCIT vs Placebo p = 0.8
Van Bever 1991[8]	Dust mite	SCIT Placebo	1 year	Median PD 20 Histamine (mg/mL)	0.37 0.13	0.40 0.25	Arm1, pre vs post, p=0.89 Placebo, pre vs post, p=0.67 SCIT vs Placebo, p=0.25
Wang 2006[10]	Dust mite	SCIT Placebo	1 year	PC20 Histamine	1.367 ± 0.172 1.489 ± 0.21	3.58 ± 0.393 3.42 ± 0.385	SCIT vs Placebo, pre p=0.65 SCIT vs Placebo,post p=0.77 SCIT pre vs post p<0.001
Maestrelli 2004[13]	Dust mite	SCIT Placebo	3 years	PD20 FEV1 (µg methacholine)	158 95	183 (95% CI: 104-322) 175 (95% CI: 101-305)	SCIT pre vs post = NS Placebo pre vs post = NS
Pichler 1996[67]	Dust mites	SCIT Placebo	12 months	Methacholine provocation test	46 NR	130 97.5	SCIT pre vs post p<0.005 Placebo pre vs post p=NS SCIT vs Placebo p=NS
Garcia-Ortega 1993[6]	Dust mite	SCIT-Cluster Conventional treatment	7 months	Methacholine bronchial provocation (inhalatory units; IU)	18±26 19±27		SCIT vs Conventional p=NS
Pifferi 2002[7]	Dust mite	SCIT Pharmacotherapy	3 years	Methacholine PD20 FEV1 (ug)	93.5 ± 56.3 374.3 ± 505.5	997.7±974.0 (70% improvement) 388.5±516.4 (20% improvement)	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
Ohman 1984[15]	Cats	SCIT Placebo	17 weeks	Allergen bronchial provocation, PD20 FEV1 (in BU)	4.27 8.8	20.7 12.3	SCIT pre vs post p <0.05 SCIT vs Placebo, p NS
Alvarez-Cuesta 1994[87]	Cats	SCIT Placebo	1 year	Allergen bronchial provocation test		3.42 times improvement 1.08 times improvement	SCIT, pre vs post, p<0.05 Placebo, pre vs post,p=NS SCIT vs Placebo, p<0.05

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Van Metre 1988 [16]	Cats	SCIT Placebo	1 year	Cat extract PD 20 (Comparison of the median ratios values of the measurements at 1 year baseline values)		2.8 0.80	SCIT vs Placebo, p<0.01
Ohman 1984[15]	Cats	SCIT Placebo	17 weeks	PD FEV1 in BU (Methacholine)	3.0 1.7	4.7 3.8	SCIT pre vs post, p NS Arm 2 vs Arm 2, p NS
Adkinson 1997[20] Limb 2006[21]	Cats	SCIT Placebo	last follow up	Bronchial provocation to methacholine (methacholine sensitivity in mg/mL)	0.23 0.32	0.41 0.39 (change from baseline)	SCIT pre vs post p= 0.008 Placebo pre vs post p=0.003 SCIT vs Placebo, p > 0.99
Alvarez-Cuesta 1994[87]	Cats	SCIT Placebo	1 year	Chemical bronchial provocation test	0.56 0.81	0.57 0.58	SCIT, pre vs post, p=NS Placebo, pre vs post,p=NS
Valovirta 1986[17] Valovirta 1984[18]	Dogs	SCIT Placebo	1 year	Bronchial provocation test to dog dander extract		40 17	Arm1, pre vs post, p<0.1 SCIT vs Placebo, p=NS
Horst 1989[64]	Alternaria	SCIT Placebo	6 months	Airway responsiveness to allergen (threshold concentration of dust mite extract causing a 20% decrease in FEV1 in wt/vol)	1:303.7±123.7 1:230.0±154.5	1:65.0±13.2 1:291.7±158.9	SCIT, pre vs post, p<0.03 Placebo, pre vs post, p=NS
Horst 1989[64]	Alternaria	SCIT Placebo	6 months	Airway responsiveness to histamine provocative concentration causing a 20% decrease in FEV1 (PC20 in mug/mL)	397.1±206.9 241.3±61.1	1391.3±283.3 252.3±45.0	SCIT, pre vs post, p<0.03 Placebo, pre vs post, p=NS
Prieto 2010[63]	Alternaria	SCIT Placebo	1 year	AMP (adenosine 5'monophosphate) Bronchial responsiveness index (%/log mg/dl)	3.6 3.7	4.1 4.8	SCIT vs Placebo, p=0.50; mean difference 0.7 (-1.3 to 2.6)
Prieto 2010[63]	Alternaria	SCIT Placebo	1 year	Methacholine Bronchial responsiveness index (%/log mg/dl)	7.2 7.1	7.4 6.6	SCIT vs Placebo, p=0.61; mean difference -0.7 (-3.2 to 1.9)

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Dreborg 1986[80]	Cladosporium	SCIT Placebo	10 week period during peak season	Bronchial provocation test	NR NR	NR NR	SCIT vs Placebo p<0.05 SCIT pre vs post, p<0.01 (higher bronchial tolerance in SCIT group than in placebo after treatment)
Arvidsson 2004[56] Arvidsson 2002[57]	White birch	SCIT Placebo	2 years	Allergen Bronchial provocation test PD20	120 600	800 450	SCIT pre vs post p< 0.001 Placebo pre vs post p=NS SCIT vs Placebo, p < 0.0.01
Arvidsson 2004[56] Arvidsson 2002[57]	White birch	SCIT Placebo	2 years	Methacholine provococation test	0.62 0.50	0.9 2.3	Comparison between pre and post (before final allergen challenge) not reported
Rak 2001[78] Rak 2005[79]	Birch	SCIT Nasal corticosteroids	6 weeks (end of pollen season)	Methacholine challenge (rhinitis patients only)			SCIT pre vs post, p<0.01 Placebo, pre vs post, p=0.02 SCIT vs Placebo, p=NS Methacholine sensitivity increased significantly (p = 0.0007) only in rhinitis, from PC20 >16 mg/mL before the season to a median of 3.0 mg/mL (range, 1.075-16) during the season.
Rak 2001[78] Rak 2005[79]	Birch	SCIT Nasal corticosteroids	6 weeks (end of pollen season)	Methacholine challenge (asthma patients only)			Arm1, pre vs post, p=NS Placebo pre vs post, p=0.01 SCIT vs Placebo, p=0.08 Methacholine sensitivity did not increase in asthmatics.
Creticos 1996[1]	Short ragweed	SCIT Placebo	2 Year	Amount of allergen causing 20% drop in FEV1	-1.4 -1.5	-0.273 ± 0.045 -0.662 ±0.135	SCIT vs Placebo, p=0.03
Hedlin 1999[70]	Cat, dust mite, Birch, Timothy	SCIT– pollen + cat/dust mite SCIT- pollen + Placebo	3 years	Bronchial allergen challenge;median PC-20 allergen (SQU/mL)	1900 1400	100000 5600 (SQU/ml)	SCIT, pre vs post, p<0.001 Placebo, pre vs post, p<0.01 SCIT vs Placebo p=0.001

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Hedlin 1999[70]	Cat, dust mite, Birch, Timothy	SCIT– pollen + cat/dust mite SCIT- pollen + Placebo	3 years	Bronchial histamine challenge ; median PC-20 histamine (mg/mL)	0.18 0.28	1.68 0.54 (mg/ml)	SCIT pre vs post, p=0.002 Placebo, pre vs post, p<0.05 SCIT vs Placebo p=NS

TABLE D12- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES (ONLY NASAL AND OCULAR SYMPTOMS) -SCIT

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Creticos 1996[1]	Short ragweed	SCIT Placebo	Year 2	6 point scale Total nasal symptom score	0-5	4.1 +/- 0.3 4.5 +/- 0.3	3.1 +/- 0.4 3.8 +/- 0.5	SCIT vs Placebo p=0.04
Durham 1999[28]	Timothy grass	SCIT Placebo	3 years (pollen season)	Score for nasal symptoms	0-21		679 422	SCIT vs Placebo p = 0.98 CI -462 to 462
Nouri-Aria 2003[59] Walker 2001 [42]	Timothy grass	SCIT Placebo	2 years	Total nasal symptom score		1.9 2.3	2.0 3.3	SCIT vs Placebo p = 0.01 CI 0.25 to 1.75
Nouri-Aria 2003[59] Walker 2001 [42]	Timothy grass	SCIT Placebo	2 years	Combined nasal and ocular symptom score		2576 1962	1277 (49%improvement) 1386 (15% improvement)	SCIT vs Placebo p=0.01 CI (241.5 1928.6)
Crimi 2004[34]	Parietaria	SCIT Placebo	1 month (august-september 1972)	Nasal and ocular symptom score	0-3	1.097	1.378	SCIT vs Placebo p<0.05
Bernstein 1976[35]	Short ragweed	SCIT Placebo	3 years	Nasal and ocular symptom score	0-400	140 133	145 (16% improvement) 310 (-121% improvement)	SCIT vs Placebo p=0.001

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Frew 2006[36]	Timothy grass	SCIT100,000 SQU SCIT 10,000 SQU Placebo	end of season	4 point scale nasal symptom score	0-4		1.88 2.19 2.75	SCIT100,000 vs 10,000 p= 0.16 CI -1.05 to -0.07 SCIT100,000 vs Placebo p< 0.0001 CI -1.28 to -0.44 SCIT 10,000 vs Placebo p= 0.025 CI -1.05 to -0.07
Frostad 1983[43]	Timothy and grass mix	SCIT pure SCIT crude SCIT grass mix Control	3 years	Nasal and ocular symptom score	0-5		0.5 1.8 3.1 NR	Timothy pure Vs control p< 0.001 Timothy crude Vs control p= 0.02 Timothy pure Vs grass p= 0.001 Other comparisons NS
Junqueira de Queiros 2008[30]	Dust mite	SCIT Placebo	1 year	Rhinitis symptom score		22 22	7 7	SCIT pre vs post p<0.05 Placebo pre vs post p<0.05 SCIT vs Placebo p NS
McHugh 1990[31] Ewan 1988[32]	Dust mite	SCIT purified-pharmalgen SCIT crude-allpyral Placebo	3 months	Unspecified nasal symptom scores		48.1 +/- 3.8 53.8 +/- 5.6 43.8 +/- 3.9	36.2 +/- 4.7 33.9 +/- 5.9 42.3 +/- 4.8	purified-pharmalgen vs Placebo p NS crude-allpyral vs Placebo p NS
Klimek 1999[44]	Grass mix-Trees mix	SCIT Pharmacotherapy	44 weeks	median nasal symptoms score			106.5 264	SCIT vs Pharmacotherapy p= 0.02
Leynadier 2000[45]	Grass mix	SCIT Placebo	1 year	Unspecified nasal symptom scores			33.5 38.6	SCIT vs Placebo p NS
Ohman 1984[15]	Cat	SCIT Placebo	17 weeks	Time to increase in nasal symptoms on exposure				SCIT pre vs post p NS Placebo pre vs post p NS SCIT 1 vs placebo p NS
Polosa 2004[22] Polosa 2003 [23]	Parietaria	SCIT Placebo	3 years	Unspecified nasal symptom scores	0-3	140 133	145 16% improvement 310 210% improvement	SCIT vs Placebo p =0.001
PAT study Möller 2002[46] Niggeman 2006[47] Jacobsen, 2007[48]	SCIT Grass and Birch	SCIT Placebo	5 years	VAS Nose symptom score		0 0	-21.5 -7.4	SCIT vs Placebo p <0.01

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Olsen 1995[49]	Mugwort Birch Timothy	SCIT- Artemisia SCIT- Betula /Phleum extract	2 years	Nasal and ocular symptom score		20	21	SCIT pre vs post p NS
Varney 1991[37] Durham 2010[38] Durham 1996[39]	Timothy	SCIT Placebo	7 months	Total nasal symptom score			49 143	SCIT vs Placebo p=0.002 CI 38 to 111
Zenner. 1996[50]	Grass mix	SCIT Placebo	10 weeks	Unspecified nasal symptom scores			44.5 63.3	SCIT vs Placebo p =0.014
Tabar 2007[65]	Alternaria	SCIT Placebo	12 months after maintenance dose began	Unspecified nasal symptom scores	0-3	0. 67 +/- 0.48 0.65 +/- 0.52	0.79 +/- 0.54 0.39 +/- 0.29	SCIT vs Placebo p= 0.002
Kuna 2011[81]	Alternaria	SCIT Placebo	3 years	Mean rhinitis symptom scores (Visual analog scale)	0-500	311.1 331.0	78.7 145.0	SCIT vs Placebo p = 0.028
Pichler, 1996[67]	Dust mites	SCIT Placebo	12 months	Subjective rhinitis score		22 39.5	8 26	SCIT pre vs post p=0.0064 Placebo pre vs post p=0.57 SCIT vs Placebo p= 0.0393
Varney, 2003[68]	Dust mites	SCIT Placebo	12 months	Total nasal score		135 +/- 18 153 +/- 27	40 +/- 12 111 +/- 18	SCIT pre vs post p=0.013 Placebo pre vs post p NS SCIT vs Placebo p= 0.04
Mirone 2004[72]	Short ragweed	SCIT Placebo	1 year	Rhinitis symptoms score		7.5 5.8	4.5 9.3	SCIT pre vs post p NS Placebo pre vs post p NS
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76]	Timothy	SCIT partially purified SCIT Ag 19 25	3 year	Rhinitis symptoms score		0 0	52 20	NR

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Rak 2001[78] Rak 2005[79]	Birch	SCIT Nasal steroid		symptom score for rhinoconjunctivitis		13.4±6.5 8.3±4.9	21.6±3.6 11.4±2	SCIT vs Placebo 0.04
Bousquet 1991[83] Bousquet 1991[84]	Orchard Olive Parietaria	SCIT Grass placebo	End of season	symptom score for rhinitis and rhinoconjunctivitis			4.9 9.8	SCIT vs Placebo p< 0.03
Dolz 1996[86]	Timothy-Orchard-Ryegrass	SCIT Placebo	3 year	Unspecified nasal symptom scores		0 0	0 35	SCIT pre vs post <0.0001
Ariano 1997[27]	Cypress-Cedar	SCIT Placebo	3 year	Unspecified symptoms scores	0-8	3.5 3.6	1.6 4.0	NR
Franklin 1967[26]	Multiple allergens including ragweed	SCIT high dose SCIT low dose	6 months	Mean symptom scores -Baseline and peak season scores		0.29 +/-0.45 0.27+/-0.51	1.37+/-0.98 2.03+/-0.92	High vs Low p<0.05

TABLE D13- OCULAR SYMPTOM SCORES-SCIT

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Durham 1999[28]	Timothy grass	SCIT Placebo after IT	3 years	Ocular symptom scores	0-21		82 98	SCIT vs Placebo p=0.55 CI -164 to 308
Nouri-Aria 2003[59] Walker 2001 [42]	Timothy grass	SCIT Placebo	2 years	Ocular symptom scores	0-3	1.5 0.8	1.4 1.8	SCIT vs Placebo p=0.008 CI (0.25,2.3)
Frew 2006[36]	Timothy grass	SCIT 100,000 SQU SCIT 10,000 SQU Placebo	End of season	4 point eye scale; nature of scale not described			0.87 0.96 1.37	SCIT high Vs Placebo p<0.001 CI (-0.72,-0.28) SCIT low Vs Placebo p=0.0019 CI (-0.67 -0.15) SCIT 100,000 Vs SCIT 10,000 p=0.43 CI (-0.31 to 0.13)

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Varney 1991[37] Durham 2010[38] Durham 1996[39]	Timothy	SCIT Placebo	7 months	Ocular symptom scores			37 87	SCIT pre vs post p=0.02 CI 10 to 82
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76]	Timothy grass	SCIT- partially purified extract SCIT- Ag 19 25	3 years	conjunctivitis symptom score		0 20	0 0	
Klimek 1999[44]	Grass mix	SCIT Pharmacotherapy		Conjunctival symptoms			21 40	SCIT vs Placebo p=0.099
Dolz 1996[86]	Mix grass	SCIT Placebo		Ocular symptom scores			0 34	SCIT pre vs post p<0.001
Tabar 2007[65]	Alternaria	SCIT Placebo	12 months after maintenance dose began	median score of the weekly average of the active group from 1/08/89 to 30/11/89	0-3	0.33±0.34 0.13±0.27	0.33±0.47 0.11±0.18	
Kuna 2011[81]	Alternaria	SCIT Placebo	3 years	Mean conjunctivitis symptom scores (Visual analog scale)	0-100	71 88	6 49	SCIT vs Placebo p = 0.001
Dreborg 1986[80]	Cladosporium	SCIT Placebo	10 weeks	None	0-3			SCIT vs Placebo p>0.05
Ferrer 2005[53]	Parietaria judaica	SCIT Placebo	20 months	Ocular symptom scores	0-3	0.52±0.42 0.63±0.60	0.39±0.45 0.69±0.66	SCIT pre vs post p=0.0413 Placebo pre and post p NS SCIT vs Placebo 0.0480
Ohman 1984[15]	Cats	SCIT Placebo	17 weeks	Time to first increase in ocular symptoms on exposure to cats				SCIT pre vs post p<0.05 SCIT vs Placebo NS

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Zenner. 1996[50]	Rye- Secale cereal and Grass mix	SCIT Placebo	10 weeks	Ocular symptom scores			26.6 mean 28.3 mean	SCIT vs Placebo 0.256
Leynadier 2000[45]	Orchard Meadow ryegrass sweet vernal and Timothy	SCIT Placebo	1 year	Unspecified ocular scale			16 17.3	SCIT vs Placebo p NS
PAT study Möller 2002[46] Niggeman 2006[47] Jacobsen, 2007[48]	Birch and Timothy grass	SCIT Placebo	5 year	VAS- Ocular symptoms	0-100mm		-29.4 mm Change from baseline -11.8 mm Change from baseline	SCIT vs Placebo p<0.01

TABLE D14- RHINITIS AND ASTHMA SYMPTOM SCORES (INCLUDING NASAL, OCULAR AND LUNG SYMPTOMS)-SCIT

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Weyer 1981[82]	Grass mix	SCIT Placebo	8 months	Total symptom scores	0-100		16 +/- 10 24 +/- 18	SCIT vs Placebo p≤ 0.09
Walker 2001[42]	Grass Mix	SCIT Placebo	2 years	Combined Symptoms (lung,nasal,eye)		2576 1962	1277 1386	SCIT vs Placebo p=0.01
Frew 2006[36]	Timothy	SCIT 100,000 SQU SCIT 10,000 SQU Placebo	End of pollen season	total nose eye and lung symptom score	0-12		3.13 3.44 4.39	High vs Low p =0. 34 CI -0.95 to 0.33 Low vs Placebo p =0.13 CI -1.69 to -0.20 High vs Placebo p =0.001 CI -1.89 to -0.62

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Munoz Lejarazu, 1993[58]	Timothy	SCIT-Perennial SCIT-Seasonal	3 years	Combined Symptom Score			53.4+/-49 46.1+/-47.55	
Tabar 2007[65]	Alternaria	SCIT Placebo	12 months after maintenance dose began	average of the lung ocular and nasal scores	0-3	0.5 +/- 0.39 0.43+/-0.35	0.55 +/- 0.49 0.41 +/- 0.4	Significant improvement in both groups at 6 months (p<0.005) but not at 12 months
Varney 2003[68]	Dust mites	SCIT Placebo	12 months	total symptom score	1-3/7	171 +/- 23 195 +/- 42	72 +/- 26 132 +/- 48	SCIT pre vs post p = 0.002 Placebo pre vs post p NS SCIT vs Placebo p NS
Pence 1975[77]	Mountain cedar	SCIT Placebo	Peak of pollen season	Combined total symptoms score			5.46 8.83	SCIT vs Placebo p <0.01
Dreborg 2011[51]	Dust Mite Timothy	SCIT Timothy SCIT dust mite	3 years	Combined Symptom Score				Timothy pre vs post p=0.041 Dust mite pre vs post p=0.018 Timothy vs Dust mite NS

TABLE D15- RHINITIS MEDICATION SCORES-SCIT

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Varney 1991[37] Durham 2010[38] Durham 1996[39]	Timothy	SCIT Placebo	7 months	Nasal drug score intake			78 232	SCIT vs Placebo p=0.001 CI 178 to 574
Durham 1999[28]	Timothy grass	SCIT Placebo	3 years (pollen season)	Rescue medication score			672 357	SCIT pre vs post p = 0.88
McHugh1990[31] Ewan 1988[32]	Dust mite	SCIT purified-pharmalgen SCIT crude-allpyral	3 months	Medication score for rhinitis		1.42 +/- 0.42 0.94 +/- 0.29	0.19 +/- 0.12 1.02 +/- 0.57	SCIT Pure pre vs post p< 0.05 Pure vs Crude p< 0.05
Klimek 1999[44]	Grass mix-Trees mix	SCIT Pharmacotherapy	44 weeks	topical antihistamine doses			71 546	SCIT vs Pharm p= 0.02

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Leynadier 2000[45]	Grass mix	SCIT Placebo	1 year	Medication score		11.1 5.0	40.8 -1.2	SCIT vs Placebo p=0.005
Polosa 2004[22] Polosa 2003 [23]	Parietaria	SCIT Placebo	3 years	Unspecified medication score		12 18	0 75	SCIT vs Placebo p =0.002
Bernstein 1976[35]	Ragweed	SCIT Placebo	1 month	days where drugs were required	0-1		0.41 0.58	SCIT vs Placebo p =0.01
Frostad 1983[43]	Timothy	SCIT purified SCIT crude SCIT grass mix	3 years	Percent of patients using antihistamines			14 48 56	Pure vs Crude p =0.02 Pure s Mix p =0.01
Olsen 1995[49]	Timothy-Birch-Mugwort	SCIT Placebo	2 years	medication score		50	0	SCIT pre vs post p =0.067
Ferrer 2005[53]	Parietaria	SCIT Placebo	20 months	nasal medication scores	1-3	0.48+/-0.41 0.67+/-0.74	0.32+/-0.4 0.62+/-0.84	SCIT pre vs post p= 0.007 Placebo pre vs post NS SCIT vs Placebo p =NS
Ariano 1997[27]	Cypress-Cedar	SCIT Placebo	3 year	Medication scores	0-15	5.0 43.6	2.8 5.2	NR
Franklin 1967[26]	Multiple allergens including ragweed	SCIT high dose SCIT low dose	6 months	Mean medication scores -Baseline and peak season scores		0.19 +/-0.66 0.53+/-0.97	1.66+/-1.04 1.98+/-1.14	High vs Low p NS

TABLE D16- RHINITIS STUDIES REPORTING RHINITIS AND ASTHMA MEDICATION SCORES - SCIT

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Varney 1991[37] Durham 2010[38] Durham 1996[39]	Timothy	SCIT Placebo	7 months	total drug score intake			129 627	SCIT vs Placebo p=0.002 CI 178 to 574
Frew 2006[36]	Timothy grass	SCIT100,000 SQU SCIT 10,000 SQU Placebo	end of season	assigned scores to medications according to dose used	0-4		2.85 3.55 4.21	High vas Low p= 0.79 SCIT high vs Placebo p= 0.0007 SCIT low vs Placebo p= 0.16

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Polosa 2004[22] Polosa 2003[23]	Parietaria	SCIT Placebo	3 years	Unspecified medication score		12 18	0 75	SCIT vs Placebo p =0.002
Crimi 2004[34]	Parietaria	SCIT Placebo	3 years	sum of scores		12 18	5 59% improvement 78 -263% improvement	SCIT vs Placebo p =0.001
Ferrer 2005[53]	Parietaria	SCIT Placebo	20 months	total bronchial nasal and ocular medication scores	1-3	1.00 +/- 1.48 0.73 +/- 0.84	0.35 +/- 0.47 0.92 +/- 1.73	SCIT pre vs post p= 0.033 Placebo pre vs post p NS SCIT vs Placebo p =0.039
Varney 2003[68]	Dust mites	SCIT Placebo	12 months	Total Medication score		74 +/- 31 65 +/- 26	59 +/- 15 66+/- 35	SCIT vs Placebo p NS
Mirone 2004[72]	Short ragweed	SCIT Placebo	1 year	Rescue medication score		3 1.9	0.6 2.8	SCIT pre vs post p=0.006 Placebo pre vs post p NS
Weyer 1981[82]	Grass mix	SCIT Placebo	8 months	Unspecified medication score			3 +/- 5 11 +/- 13	SCIT vs Placebo p≤ 0.007
Dolz 1996[86]	Timothy-Orchard-Ryegrass	SCIT Placebo	3 year	Medication score			20 65	SCIT pre vs post <0.01
Tabar 2007[65]	Alternaria	SCIT Placebo	12 months after maintenance dose began	Medication score	0-3	0.37 +/- 0.57 1.77 +/- 2.43	0.51 +/- 1.19 0.21 +/- 0.36	SCIT vs Placebo p= 0.002
Walker 2001[42]	Grass Mix	SCIT Placebo	2 years	Combined medications (lung,nasal,eye)		1815 2124	357 1851	SCIT vs Placebo p=0.007
Munoz Lejarazu1993[58]	Timothy Grass	SCIT-Perennial SCIT-Seasonal	3 years	Combined Medication Score			15.7+/-25.30 8.7+/-11.61	NR

TABLE D17- RHINITIS COMBINED SYMPTOMS AND MEDICATION SCORES-SCIT

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Van Metre 1980[24]	Ragweed	SCIT Placebo	End of pollen season	Total symptom and medication scores	0-1		0.41 0.58	SCIT vs Placebo p =0.01
Van Metre 1981[25]	Ragweed	SCIT-Weekly Placebo-weekly SCIT- clustered Placebo-clustered	End of pollen season	Total symptom and medication scores		2.2 1.2 2.2	3.0 5.8 1.8	Weekly vs Cluster p <0.01 Weekly vs Placebo p NS Cluster vs Placebo p <0.01
Tabar 2005[61]	dust mite	SCIT-cluster SCIT-conventional Placebo	1 year	total bronchial nasal and ocular medication scores	0-8	6 6.2	2.6 2.7 2.65 +/- 1.89	Cluster pre vs post p<0.001 SCIT Conventional pre vs post p <0.001
Tabar 2007[65]	Alternaria	SCIT Placebo	12 months after maintenance dose began	Unspecified symptom and Medication score	0-3	0.44 +/- 0.42 1.07 +/- 1.23	0.53 +/- 0.54 0.23 +/- 0.23	No significant changes in the percentage of symptom-free and medication-free days in either goup
Kuna 2011[81]	Alternaria	SCIT Placebo	3rd year-peak season Baseline – peak season	Sum of symptom and medication scores recorded daily during allergy season (July, August, and September)	3 yr: Baseline: 75	At baseline SLIT: 75 plac: 75	At 3rd year: SLIT: 28 plac: 62	SCIT vs Placebo Baseline: p=0.73 year 3 p<0.0001 AUC year 1 10.8%, AUC year 2 38.7%, AUC year 3 63.5%
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76]	Timothy	SCIT partially purified SCIT Ag 19 25	3 years	Combined total symptoms and Medication score		113 197	1 130	partially purified vs Ag 19 25 p significant
Weyer 1981[82]	Grass mix	SCIT Placebo	8 months	Total symptom and medication scores	NR	8+/-6 12+/-10	10+/- 7 18 +/- 15	SCIT vs Placebo p≤ 0.03
Chakraborty 2006[85]	Date trees	SCIT Placebo	2 years	Combined symptom and medication score	0-3		57% improvement	SCIT pre vs post p <0.001 Placebo pre vs post p NS
James 2011 [41]	Grass	SCIT+2 yrs SCIT SCIT+Placebo	4 years	Combined rhinitis-medication score				SCIT+2 yrs SCIT Pre-Post p=0.03 SCIT+Placebo Pre-post p=0.03

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Shamji 2012[40]	Grass	SCIT 100.000 SCIT 10.000 Placebo	8 months	Combined symptom (nasal/eye)-medication score			5.84+/-0.57 7.05+/-0.76 8.63+/-0.77	SCIT high vs Placebo p=0.001
Petersen 1988[69]	Birch Pollen	SCIT-Birch + Pollen mix alum-precipitated SCIT-Birch alone alum-precipitated	3 Years	Combined Symptom Medication Score				No difference between groups
Reid 1986[29]	Multiple (including grass)	SCIT grass SCIT non grass	7 months	Total rhinitis symptom-medication scores		NR NR	281 489	Grass vs non grass p=0.11
Franklin 1967[26]	Multiple allergens including ragweed	SCIT high dose SCIT low dose	6 months	Total rhinitis symptom-medication scores		0.38 +/-0.69 0.73+/-0.97	2.08+/-0.91 2.31+/-0.91	NS

TABLE D18.- RHINITIS QOL - SCIT

Study	ARMS	QOL
Frew 2006[36]	SCIT 100,000 SQU SCIT 10,000 SQU Placebo	RQLQ- 183* significant RQLQ-88 RQLQ-92
Ferrer 2005[53]	SCIT Placebo	Reported Not significant Difference
Tabar 2007[65]	conventional SCIT Placebo	QOL improved but not statistically significant. When different domains of the questionnaire were analyzed separately a significant improvement in symptoms was observed in the asthmatic active group ($p<0.05$) Among patients with rhinitis a significant improvement in emotional status was found in the placebo group
Cantani 1997[71]	SCIT Control (drug-treated)	Reported Not significant Difference
Walker 2001[42]	SCIT Placebo	Overall increase in QOL p=0.02
Petersen 1988[69]	SCIT SCIT	Reported subjective assessments- Improved but no statistical data

Study	ARMS	QOL
Kuna 2011[81]	SCIT Control	3 years : Improvement in RQLQ p<0.05
Tabar 2010[89]	SCIT 3 years SCIT 5 years	QOL (RQLQ and AQLQ) Both groups demonstrated significant and clinically relevant changes in RQLQ and AQLQ.

RLQL: AQLQ

TABLE D19 -NASAL AND OCULAR CHALLENGES SCORES - SCIT

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Pichler 1996[67]	Dust mites	SCIT Placebo	12 months	Conjunctival provocation test	100000 100000	100000 100000	SCIT pre vs post p=0.469 Placebo pre vs post p=0.4062 SCIT vs Placebo p=0.0196
Muro 1999[60]	Dust mites	SCIT-Cluster SCIT- Conventional	18 months after maintenance	Conjunctival provocation test	7.4 (BU/ml) 14.6		Cluster pre vs post, p<0.01 Converntional, pre vs post p<0.01 Cluster vs conventional p<0.05
Arvidsson 2004[56] Arvidsson 2002[57]	White birch	SCIT Placebo	2 years	Conjunctival provocation test	NR NR	NR NR	SCIT vs Placebo p= NS
Dreborg 2011 [51]	Dust Mite Timothy	SCIT Timothy SCIT dust mite	3 years	Conjunctival Provocation Challenge	6166 724	100000 26915	Timothy: 16 fold increase p<0.05 Dust Mite: 32 fold increase, p<0.05
Dreborg 1986[80]	Cladosporium	SCIT Placebo	10 week period during peak season	Conjunctival provocation tets	NR NR	NR NR	SCIT vs Placebo p>0.05 SCIT pre vs post, p=0.01
Alvarez-Cuesta 1994[87]	Cats	SCIT Placebo	1 year	Conjunctival provocation test		78% had improved conjunctival sensitivity 21%	There was a significant difference in the threshold dose that caused pruritis, p<0.001
Varney 1997[88]	Cat	SCIT Placebo	3 months	Conjunctival provocation threshold	4025 2109	NR NR	SCIT vs Placebo p<0.001
Valovirta1986[17] Valovirta1984[18]	Dog	SCIT Placebo	1 year	Conjunctival provocation test			SCIT vs Placebo p<0.001

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Olsen 1997[14]	Mugworth, Birch, Timothy grass	SCIT- Artemesia SCIT- Betula	2 years	Conjunctival provocation test with Artemesia	3.6 3.6	4.5 3.5	Artemisia, pre vs post, p<0.01 Betula, pre vs post, p<0.05
Olsen 1997[14]	Mugworth, Birch, Timothy grass	SCIT- Artemesia SCIT- Betula	2 years	Conjunctival provocation test with Betula	3.8 3.8	3.3 5.2	Artemisia, pre vs post, p<0.01
The PAT study Möller 2002[46] Niggeman2006[47] Jacobsen2007[48]	Timothy grass, Birch	SCIT Placebo	5 years	Ocular provocation test			SCIT vs Placebo p<0.001
Bousquet 1991[83] Bousquet 1991[84]	Grass and tree pollen	SCIT-grass Placebo-grass SCIT-multiple pollen Placebo-multiple pollen	End of season	Nasal provocation (Mean number of pollen grains needed to cause reaction)		69175±70655 1544±558 28687±51437 3086±7510	Grass vs Placebo, p<0.01 Multiple vs Placebo, p=NS Single vs Multiple, p=NS
Leynadier 2000 [45]	Grass mix	SCIT Placebo	1 year	Nasal provocation test (Amount of allergen needed in IR)	21.4 31	63.4 37.7	SCIT, pre vs post, p<0.05 SCIT vs Placebo p>0.05
Kuna 2011[81]	Alternaria	SCIT Control		Nasal challenge	207 199	67 185	SCIT pre v. post p p<0.05 Placebo, pre vs post, p=0.07 SCIT vs Placebo p=0.04
Horst 1989[64]	Alternaria	SCIT Placebo	1 year	Nasal challenge	2.8±0.6 2.8±1.0	1.6±1.2 2.5±1.1	SCIT, pre vs post, p<0.001 Placebo, pre vs post, p=NS SCIT vs Placebo p<0.05
Ariano 1997[27]	Cypress-Cedar	SCIT Placebo	3 year	Nasal challenge	83.17 84.64	88.34 85.16	NR
McHugh 1990[31] Ewan 1988[32]	Dust mite	SCITpurified SCITcrude Placebo	1 year	Nasal provocation challenge	48.1±3.8 53.8±5.6 43.8±3.9	36.2±4.7 33.9±5.9 42.3±4.8	SCIT pure pre vs post, p<0.05 SCIT crude pre vs post, p<0.05 SCIT pure vs placebo, p<0.05
Naclerio 1997[54] Iliopoulos 1991[55]	Rag weed	SCIT Placebo	1 year	Nasal provocation challenge			SCIT pre vs post, no significant changes

TABLE D20.- ASTHMA OTHER OUTCOMES -SCIT

Study	ARMS	QOL	Adherence
Kuna 2011[81]	SCIT Placebo	QOL SIT was associated with significant improvement in QOL with regard to asthma (p<0.05) and rhinoconjunctivitis (p<0.05)	
Tabar 2010[89]	SCIT 3 years SCIT 5 years	QOL (RQLQ and AQLQ) Both groups demonstrated significant and clinically relevant changes in RQLQ and AQLQ.	At T3, patients who had withdrawn from SIT and those who had an irregular compliance were excluded." This introduces selection bias. 80.9% reduction in SCIT 3 year group at year 3 was maintained at year 5.

Outcomes not reported Adherence Convenience Maintenance control Prevention of Sinusitis Prevention of Otitis and Disease modification and Development of new sensitivities

TABLE D21.- RHINITIS SECONDARY OUTCOMES - SCIT

Study	ARMS	Prevention of asthma
Polosa 2004[22] Polosa 2003 [23]	SCIT Placebo	2 developed asthma 7 developed asthma (p=0.056)
The PAT study Möller 2002[46] Niggeman 2006[47] Jacobsen 2007[48]	SCIT Placebo	No significant increase in the number of patients reporting symptoms of asthma. OR 2.68 (1.3-5.7 p<0.05) in favor of hypothesis that SIT can prevent development of asthma 39% reported asthma symptoms (p<0.01)
Tabar 2010[89]	SCIT 3 years SCIT 5 years	At T3, patients who had withdrawn from SIT and those who had an irregular compliance were excluded." This introduces selection bias. 80.9% reduction in SCIT 3 year group at year 3 was maintained at year 5.

Outcomes not reported: Adherence, Convenience, Maintenance control, Prevention of Sinusitis, Prevention of Otitis, and Disease modification and Development of new sensitivities

TABLE D22. SAFETY – SCIT

SCIT LOCAL REACTIONS- Reported as patients

Study	Allergen	Number of patients in arm	Number of events and Description	% of patients	Severity
Akmanlar 2000[66]	Dust mites: Der P and F Rush vs Cluster Cluster	18	3 patients Local swelling > 3 cm: required adjust dosing	17%	Moderate
Altintas 1999[3]	Dust mites: Dermatophagoides pteronyssinus	34	2 patients Local swelling > 3 cm: required adjust dosing	5%	Unspecified
Newton 1978[62]	Dust mites: Dermatophagoides farina Placebo	7 7	1 patient/2 local reactions 1 patient recurrent local pruritus at site of injection	14% 14%	Unspecified

Study	Allergen	Number of patients in arm	Number of events and Description	% of patients	Severity
Tabar 2010[89] Tabar 2010[90]	Dust mite SCIT 5 years-SCIT 3 years	142 total	9 local reactions (1 patient presented nodes)	6%	unspecified
Tabar 2007[65]	Alternaria	14	2 patients/2 reactions: skin itching	14%	Unspecified
Kuna 2011[81]	Alternaria	30	4 patients /11 reactions (987 injections): Local edema	13%	Mild
Malling 1986[19]	Cladosporium	11	6 patients had delayed local reactions (swelling at the injection site >8cm)	58%	Unspecified
Dreborg 1986[80]	Cladosporium	16	4 patients had local reactions: defined as reaction > 10 cm diameter	25%	Mild
Dolz 1996[86]	Grass mix: Timothy grass Orchard grass, ryegrass	18	4 patients had local reactions	22%	Moderate
Leynadier 2000[45]	Grass mix: Orchard grass meadow fescue perennial ryegrass sweet vernal grass timothy grass	16	6 patients: Swelling and erythema > 5 cm at the injection site	37%	Mild
Van Metre 1980[24]	Ragweed	15	4 patients/ 5 Local reactions (>5 cm)	27%	Mild
Bernstein 1976[35]	Short ragweed	68	24 patients had unspecified local reactions	35%	Unspecified
Ohman 1984[15]	Cats	9	2 patients/3 reactions: Large local reaction required modifications of the immunotherapy schedule	22%	severe
Alvarez-Cuesta 1994[87]	Cats	28	7 patients had local reactions	25%	Unspecified
Chakraborty 2006[85]	Trees: date sugar palm/wild date palm	18 patients (2095 injections)	1 patient had local inflammation 4 patients had local urticaria	5%	Unspecified

SCIT LOCAL REACTIONS- Reported as events

Study	Allergen	Number of patients in arm	Number of events and Description	% of injections	Events per Patient	Severity
McHugh 1986[31] Ewan 1987 [32]	Dermatophagoides pteronyssinus (purified)	30 (205 injections)	13 moderate indurations (2.5-5 cm) 7 reactions presented as flares	6% 3%	0.43	Moderate Mild
	Placebo	30 (244 injections)	4 presented flares	2%	0.13	Mild

Study	Allergen	Number of patients in arm	Number of events and Description	% of injections	Events per Patient	Severity
Schubert 2009[11]	Dust mites (cluster schedule)	20 (341 injections)	185 local events: Redness: 97 (28%), Swelling <5cm: 57 (16%), Swelling > 5cm: 22 (6%), painful swelling >3h: 8 (2%)	54%	9.25	Mild
	Dust mites (classic schedule)	10 (151 injections)	80 local events: Redness: 40 (26%), Swelling <5cm: 20 (13%), Swelling > 5cm: 17 (11%), painful swelling >3h: 3 (2%)	53%	8	Mild
Varney 1991[37] Durham [38]	Timothy grass	21 (523 injections)	22 local reactions > 8X8 cm	4%	1	Mild
Van Metre 1988[16]	Cats	11 (339 injections)	26 local reactions: Induration > 5 cm (7.7 reactions/ 100 injections)	7.7%	26	Unspecified
Varney 1997[88]	Cats	13 (168 injections)	6 large local reactions (168 injections)	3%	0.46	Unspecified
	Placebo	15 (178 injections)	6 large local reactions (178 injections)	3%	0.4	Unspecified
Klimek 1999[44]	Grass mix	24 (175 injections)	Induration > 5 cm after 16 of the 175 total injections (Number of patients presenting reactions not specified)	9%	0.66	Unspecified
Zenner 1996[50]	Grass mix and Secale cereal	45 (309 injections)	30 of 309 injections	9.7%	0.66	Unspecified
	Placebo	41 (284 injections)	6 of 284injections Local reactions defined as (>5 cm) at the injection site (swelling – erythema)	2.1%	0.14	Unspecified
Van Metre 1981[25]	Ragweed (weekly)	15 (405 injections)	33 local reactions >5 cm	8%	2.2	Unspecified
	Ragweed (clustered)	18 (298 injections)	15 local reactions >5 cm	5%	0.83	Unspecified
Studies where harms where reported as reactions but total number of injections was not reported						
Prieto 2010[63]	Alternaria	21	17 local reactions: pruritus, pain and swelling at injection site: treated with antihistamines	NA	0.81	Moderate
	Placebo	18	16 local reactions: pruritus, pain and swelling at injection site: treated with antihistamines		0.88	Moderate
Valovirta 1986[17]	Dogs	15	309 local reactions: 227<1cm, 71 1-3cm, 11>3cm	NA	20	Mild
	Placebo	12	251 local reactions: 163<1cm, 82 1-3cm, 6>3cm		21	Mild

Study	Allergen	Number of patients in arm	Number of events and Description	% of injections	Events per Patient	Severity
Frew 2006[36]	Timothy grass (100000 SQ-U) Timothy grass (10000 SQ-U) Placebo	410 (reported for all groups)	36 early local reaction 171 delayed local reaction Local reaction defined as redness, swelling and discomfort at injection site	9% 42%	Mild Mild	
Ferrer 2005[53]	Parietaria judaica Placebo	28 (803 injections) 29 (724 injections)	5 local reactions 3 immediate - 2delayed; 3 during buildup and 2 during maintenance. All resolved spontaneously without treatment. No local reactions in the Placebo group	0.6%	0.17	Mild

SCIT CUTANEOUS REACTIONS- Reported as patients

Study	Allergen	Number of Patients in arm	Number of events and Description	% of patients	Severity
Frew 2006[36]	Timothy grass (100000 SQ-U)	203	17 Urticaria	8%	Unspecified
Varney 1991[37] Durham [38]	Timothy grass	21	1 patient: Urticaria	4%	Unspecified
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76]	Timothy grass (Whole pollen allergen) Purified allergen (Ag 19, 25)	20 20	5 Urticaria 5 Urticaria	25% 25%	Moderate Moderate
Garcia-Ortega 1993[6]	Dust mite: Dermatophagoides pteronyssinus (cluster schedule)	18	1 Urticaria	5%	Moderate
McHugh 1986[31] Ewan 1987 [32]	Dermatophagoides pteronyssinus (purified) Placebo	30 (205 injections) 30 (244 injections)	5 patients had erythema 10 patients had generalized pruritus and erythema	16% 33%	Mild Mild
Dreborg 1986[80]	Cladosporium	16	3 patients: urticaria	18%	Unspecified
Prieto 2010[63]	Alternaria Placebo	21 18	2 episodes of general urticaria and pruritus 3 episodes of general urticaria and pruritus	9% 16%	Unspecified Unspecified
Ferrer 2005[53]	Parietaria judaica	28	4 pruritus or urticaria	14%	Unspecified
Cantani 1997[71]	Dermatophagoides pteronyssinus Perennial ryegrass Parietaria officinalis	151	3 patients: urticaria	2%	Unspecified
Nanda 2004[33]	Cat	28 (Total)	1 patient generalized pruritus	3%	Unspecified

SCIT RESPIRATORY REACTIONS - Reported as patients

Study	Allergen	Number of Patients in arm	Number of events and Description	% of patients	Severity
Akmanlar 2000[66]	Both Der P and F (conventional schedule) Both Der P and F (rush schedule)	9 9	3 patients bronchospasm 2 patients bronchospasm	30% 22%	Severe Severe
Altintas 1999[3]	Dust mite: Dermatophagoides pteronyssinus	34	7 patients: late asthmatic symptoms requiring hospitalization	20%	Severe
Garcia-Ortega 1993[6]	Dust mite: Dermatophagoides pteronyssinus (cluster schedule)	18	3 patients had rhinitis, cough, tightness of chest, wheezing 2 patients had wheezing	16% 11%	Mild Moderate
Tabar 2010[89] Tabar 2010[90]	Dust mite SCIT 5 years-SCIT 3 years	142 total	3 patients had rhinoconjunctivitis 2 patients had asthma attacks	3%	unspecified
Varney 2003[68]	Dermatophagoides pteronyssinus	15	7 reactions: cough and rhinorrhea	46%	Mild
McHugh 1986[31] Ewan 1987 [32]	Dermatophagoides pteronyssinus (purified) Placebo	30 (205 injections) 30 (244 injections)	7 patients had asthma-3 patients had rhinitis 1 patient had asthma-2 patients had rhinitis All responded easily to treatment	33% 10%	Mild Mild
Nouri-Aria 2003[59] Walker 2001[42]	Timothy grass Placebo	22 22	1 sneezing, 2 wheezing, 3 rhinitis, 1 mild wheezing	14% 18%	Mild Mild
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76]	Timothy grass (Whole pollen allergen) Purified allergen (Ag 19, 25)	20 20	2 Asthma 1 Rhinitis 1 Asthma 3 Rhinitis, 1 Flu-like symptoms	10% 5% 5% 20%	Moderate Mild Moderate Mild
Frew 2006[36]	Timothy grass (100000 SQ-U) Timothy grass (10000 SQ-U) Placebo	203 104 103	59 nasopharyngitis - 13 wheezing – 12 chest tightness 26 nasopharyngitis – 3 chest tightness 29 nasopharyngitis - 2 chest tightness	41% 27% 31%	Unspecified Unspecified Unspecified
Ferrer 2005[53]	Parietaria Placebo	28 29	7 upper respiratory (rhinitis, rhinoconjunctivitis, sneezing, rhinorrhea and/or nasal congestion) 4 lower respiratory (cough, dyspnea, wheezing and/or chest tightness) 3 upper respiratory (rhinitis, rhinoconjunctivitis, sneezing, rhinorrhea and/or nasal congestion)	39% 10%	Unspecified Unspecified

Study	Allergen	Number of Patients in arm	Number of events and Description	% of patients	Severity
Horst 1989[64]	Alternaria	13	2 patients presented asthmatic reactions	15%	Mild
Leynadier 2000[45]	Multiple: Orchard grass meadow fescue perennial ryegrass sweet vernal grass timothy grass	16	Reversible acute asthma: 2/16 patients	12.5%	Mild
Cantani 1997[71]	Multiple: Dermatophagoides pteronyssinus, Perennial ryegrass, Parietaria officinalis	151	2 patients with wheezing	1%	Unspecified
Varney 1991[37] Durham [38]	Placebo	16	1 patient had shortness of breath-dropped from the study	1%	Unspecified
Kohno 1998[12]	Control (Bronchodilators)	8	2 patients dropped out of the study due to respiratory infection	25%	Unspecified

SCIT RESPIRATORY REACTIONS - Reported as events

Study	Allergen	Number of Patients in arm	Number of events and Description	% of injections	Events per Patient	Severity
Schubert 2009[11]	Dust mites (cluster schedule)	20 (341 injections)	12 reactions: 10 cough-2 dyspnea 2 reactions had bronchial asthma)	3.5% 0.6%	0.7	Mild Moderate
	Dust mites (classic schedule)	10 (151 injections)	7 reactions: 6 cough-1 dyspnea 1 reaction had bronchial asthma)	4.6% 0.7%	0.8	Mild Moderate
Varney 1997[88]	Cats	13(168 injections)	4 mild systemic reactions (cough and itchy nose)	2%	0.3	Mild
	Placebo	15(178 injections)	3 mild systemic reactions (cough and itchy nose)	2%	0.2	Mild
Malling 1986[19]	Cladosporium	11 (212 injections)	32 episodes of mild asthma-5 delayed asthma attacks	NA	2.9	Mild
	Placebo	11 (221 injections)	27 severe asthma attacks-requiring β2 2 episodes of mild asthma		2.45	Moderate Mild
Studies where harms where reported as reactions but total number of injections was not reported						
Prieto 2010[63]	Alternaria	21	15 systemic reactions- 11 respiratory (3 rhinoconjunctivitis, 4 asthma exacerbations, 4 common colds)	NA	0.71	Moderate
	Placebo	18	16 systemic reactions - 11 respiratory (2 rhinoconjunctivitis, 3 asthma exacerbations, 6 common colds)	NA	0.88	Moderate

Study	Allergen	Number of Patients in arm	Number of events and Description	% of injections	Events per Patient	Severity
Arvidsson 2004[56] Arvidsson 2002[57]	White birch	24	76 events in 22 patients (e.g. rhinitis and cough)	27.6%	3.2	Mild
	Placebo	22	81 events in 20 patients (e.g. rhinitis and cough)	19.8%	3.7	Mild

SCIT GASTROINTESTIONAL REACTIONS - Reported as patients

Study	Allergen	Number of Patients in arm	Number of events and Description	% of Patients	Severity
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75] Osterballe 1982[76]	Purified allergen (Ag 19, 25)	20	1 Nausea	5%	Mild

GENERAL SYMPTOMS - Reported as patients

Study	Allergen	Number of Patients in arm	Number of events and Description	% of Patients	Severity
Creticos 1996[1]	Ragweed	30	7 pts presented reactions (14 events) 5 (mild) 9 systemic reactions (severe) rhinitis-urticaria-angioedema: required antihistamines or epi 2 patients dropped out after several systemic reactions	23%	 mild severe
	Placebo	30	1 Bronchospasm + hypotension (Allergen given by mistake)	3%	
Bernstein 1976[35]	All study (Ragweed vs Placebo)	135	4 Systemic reactions: hives and angioedema: discontinued treatment. Only 1 treatment related)	3%	Severe
Dolz 1996[86]	Timothy grass Orchard grass Perennial ryegrass	18	7 patients with nasal and ocular itching, facial reddening, pharyngeal itching, cough and wheezing, and sensation of breathing difficulty	39%	Moderate
Frew 2006[36]	Timothy grass (100000 SQ-U) Timothy grass (10000 SQ-U) Placebo	203 104 103	69 Headache- 16 Fatigue- 12 Flushing 19 Headache- 10 Fatigue- 1 Flushing 36 Headache- 4 Fatigue- 1 Flushing	34% 18% 35%	Unspecified Unspecified Unspecified
Munoz Lejarazu 1993[58]	Timothy grass (seasonal)	18	1 systemic reaction: rash and wheezing: required adrenaline	5%	Moderate
Osterballe 1982[73] Osterballe 1981[74] Osterballe 1980[75]	Timothy (Whole pollen)	20	4 Minor general reactions: 1 Arthralgia, 1 Rhinitis, 2 Fatigue	20%	Mild
Osterballe 1982[76]	Timothy (Purified Ag 19, 25)	20	3 Major general reactions- Angioedema 8 Minor general reactions: 1 Arthralgia, 4 Fatigue, 1 Headache, 2 Conjunctivitis	15% 40%	Moderate Mild

Study	Allergen	Number of Patients in arm	Number of events and Description	% of Patients	Severity
Junqueira de Queiros 2008[30]	Dermatophagoides pteronyssinus	25	6/25 from the Dpt group had hypotension, cough, wheezing and/or dyspnea	24%	Severe
		25	1/25 from the Dpt + MRB group hypotension, cough, wheezing and/or dyspnea	4%	
McHugh 1986[31] Ewan 1987 [32]	Dermatophagoides pteronyssinus (purified)	30 (205 injections)	5 patients had asthma + urticaria or erythema 3 patients had erythema + other symptoms	16% 10%	Unspecified
Ohman 1984[15]			Systemic reactions (rhinoconjunctivitis, asthma, itching and facial swelling and hives)		Unspecified
	Cats	9	4 patients/ 10 reactions in the active group.	44%	
	Placebo	8	1 patient/ 2 reactions in the placebo group	12.5%	
Ferrer 2005[53]	Parietaria judaica	28	1 Unspecific manifestation (cephalea / fever)	3.5%	Unspecified
	Placebo	28	1 Unspecific manifestation (cephalea / fever)	3.5%	Unspecified
Malling 1986[19]	Cladosporium	11	2 patients with general reactions: 1 headache-1 depression	18%	Unspecified
Nouri-Aria 2003[59]	Timothy grass	22	1 itching palms/soles	4.5%	Mild
Walker 2001[42]	Placebo	22	1 conjunctivitis	4.5%	Mild
Zenner 1996[50]	Grass mix Rye- Secale cereale	45	Exacerbations of rhinoconjunctivitis, urticaria, and edema of the eyelid: 9 patients//12 injections	20%	Moderate
			Other: 1 bronchospasm, 1 transient episode of tachycardia, 1 episode of paleness and anxiety	6%	Mild
	Placebo	41	Exacerbations of rhinoconjunctivitis, urticaria, and edema of the eyelid: 5 patients / 7 injections	12%	Moderate
Leynadier 2000[45]	Grass mix:	16	Exacerbations of rhinoconjunctivitis and urticaria: 7/16 patients	44%	Mild
	Placebo	13	Exacerbations of rhinoconjunctivitis and urticaria: 2/13 patients	15%	Mild
			All systemic reactions occurred during the 30 min after injection. No delayed reactions were observed.		

GENERAL SYMPTOMS - Reported as events

Study	Allergen	Number of Patients in arm	Number of events and Description	% of Injections	Events per Patient	Severity
Arvidsson 2004[56] Arvidsson 2002[57]	White birch	24	76 events in 22 patients in the active group general symptoms (e.g. infection symptoms)	40.7%	3.45	Mild
	Placebo	22	81 events in 20 patients in the placebo group. general symptoms (e.g. infection symptoms)	46.7%	4.05	Mild

Klimek 1999[44]	Grass mix	24	Some patients presented nasal/conjunctival symptoms after 5 injections (Number of patients presenting reactions not specified) Other reactions: 1 patient with itching of palms and feet that disappeared without treatment - 1 patient had paleness and anxiety that reversed with antihistamine and diazepam.	NA	NA	Mild

SCIT UNSPECIFIED REACTIONS - Reported as patients

Study	Allergen	Number of Patients in Arm	Number of events and Description of the reaction	% of Patients	Severity
Creticos 1996[1]	Placebo	40	4 patients had unspecified reactions	10%	moderate
Tabar 2010[89] Tabar 2010[90]	Dust mite SCIT 5 years- SCIT 3 years	142 total	3 presented unspecified symptoms	2%	mild
Munoz Lejarazu 1993[58]	Timothy grass (seasonal) Timothy grass (perennial)	18 26	5 patients /6 unspecified reactions 5 patients/8 unspecified reactions	33% 19%	Mild Mild
Nouri-Aria 2003[59] Walker 2001[42]	Timothy grass	22	3 delayed mild systemic unspecified reactions	14%	Mild
Bernstein 1976[35]	Short ragweed Placebo	68 63	23 patients had unspecified systemic reactions: 17 Unspecified /6 severe 8 patients had unspecified systemic reactions: 6 Unspecified /2 Severe	34% 17%	Unspecified Severe Unspecified Severe
Bousquet 1991[83] Bousquet 1991[84]	Grass pollen multiple pollen	16 16	3 patients had a systemic reaction. 4 patients had a systemic reaction	19% 25%	Unspecified Unspecified
Bousquet 1985[4]	Dermatophagoides pteronyssinus	20	4 patients had a systemic reaction 3 patients required adrenaline	20%	Unspecified
Van Metre 1988[16]	Cats	11	2 patients had unspecified systemic reactions that required antihistamines	18%	Mild
Hedlin 1999[70]	Cats Dermatophagoides pteronyssinus White birch Timothy grass (plus pollen extract)	15	5 systemic side effects : 1 patient was excluded due to recurrent asthma and urticaria	33%	Unspecified
Van Metre 1980[24]	Ragweed	15	7 patients had systemic reactions: 10 mild systemic reactions requiring no treatment; 3 mild systemic reactions treated with antihistamines; 6 moderate reactions requiring epinephrine	47%	Mild Moderate
Van Metre 1981[25]	Ragweed (weekly) Ragweed (clustered)	15 18	8 patients had 12 systemic reactions: 9 reactions/6 patients required epinephrine 3 reactions/2 patients were mild, treated with antihistamines 19 systemic reactions: 15 reactions/10 patients required epinephrine 2 reactions/2 patients were mild, treated with antihistamines	53%	 Moderate Mild Moderate Mild

SCIT UNSPECIFIED REACTIONS - Reported as events

Study	Allergen	Number of Patients in Arm	Number of events and Description of the reaction	% of Injections	Events per Patient	Severity
Alvarez-Cuesta 1994[87]	Cats	28	10 patients/14 reactions (1.9 reactions for every 100 injections) had AE 7 patients had local reactions, 3 patients had systemic reactions	1.9%	1.4	Unspecified
Dreborg 1986[80]	Cladosporium	16	45 unspecified systemic reactions	NA	2.8	Unspecified
Reid 1986[29]	SCIT grass	9	All subjects experienced local reactions. SCIT grass Local events: 287 reactions out of 321 injections Systemic events: 4 reactions (3 subjects/321 injections	89% 1.2%	31 4.4	Unspecified
	SCIT non grass	9	SCIT non-grass Local events: 214 out of 325 injections. Systemic events: 1 reaction out of 325 injections.	66% 0.3%	23 1.1	Unspecified

ANAPHYLACTIC REACTIONS

Study	Allergen	Number of Patients in arm	Number of events	Definition of anaphylaxis
Malling 1986[19]	Cladosporium	12	3	Involvement of the skin/mucosal tissue and reduced blood pressure or associated symptoms occurring rapidly after exposure to a likely allergen for that patient 1 Status asthmaticus 1 Angioedema 1 Urticaria with hypotension
McHugh 1986[31] Ewan 1987 [32]	Dermatophagoides pteronyssinus (purified)	30	8	8 reactions(30 patients/205 injections) were considered serious or potentially serious: 'anaphylactic type' reactions: conjunctival flare; intense erythema of the face; angioedema of the face, ear lobes, or neck; acute dyspnea due to asthma, glottal or laryngeal edema
Varney 1991[37] Durham [38]	Timothy grass	21	1	The acute onset of a reaction (within 10 minutes): flushing and chest tightness. Responded to intramuscular adrenaline
Tabar 2010[89] Tabar 2010[90]	Dust mite SCIT 5 years-SCIT 3 years	142 receiving SCIT total	1	Not specified

% of patients calculated, % of injections given in the article, NA Not available: means % is not given and can not be calculated as denominator is not given.

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Appendix E. Evidence Tables for Sublingual Immunotherapy

TABLE E1.- STUDY CHARACTERISTICS SLIT

a) Table E1a. Study Characteristics- SLIT- Asthma

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
D'Ambrosio 1999[1] Italy	Asthma	Seasonal	Single	Weeds: parietaria	No previous immunotherapy Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Industry
Pajno 2000[2] Italy	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: Children No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Industry
Nelson 1993[3] USA	Asthma	Perennial	Single	Animals: cat	Positive specific IgE test	Non-profit
Cortellini 2010[4] Italy	Asthma	Perennial	Single	Mold: Alternaria	No previous immunotherapy Positive skin test Minimum duration of disease: 3 years Pregnant women excluded	Not stated
Stelmach 2009 [5] Penagos 2008[6] Poland	Asthma	Perennial	Multiple	Grass mix	Children: 5-17 years old Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Industry
Lue 2006[7] Taiwan	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: 6-12 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Other (not industry)
Niu 2006[8] Taiwan	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Positive skin test No previous immunotherapy Positive specific IgE test Monosensitized individuals only Minimum duration of disease: 1 year	Not stated
Sambugaro 2003[9] Italy	Asthma	Seasonal and Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae Grass: Grass mix Weeds: Ragweed and Parietaria	Positive skin test Minimum duration of disease: 2 years	Industry

b) **Table E1b. Study Characteristics- SLIT-** Rhinitis

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Horiguchi 2007[10] Japan	Rhinitis	Seasonal	Single	Trees: Japanese cedar	No previous immunotherapy Positive specific IgE test Positive skin test Pregnancy	Government
Okubo 2008[11] Japan	Rhinitis	Seasonal	Single	Trees: Japanese cedar	Positive specific IgE test	Government
Fujimura 2011[12] Japan	Rhinitis	Seasonal	Single	Trees: Japanese cedar	No previous immunotherapy Positive specific IgE test Minimum duration of disease: 2 years Excluded pregnant patients	Government
Hordijk 1998[13] Netherlands	Rhinitis	Seasonal	Multiple	Grass mix	Positive skin test	Industry Government
Tahamiler 2007[14] Turkey	Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 2 years Excluded Pregnancy	Not stated
Tseng 2008[15] Taiwan	Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: 6-18 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Industry Non-profit
deBot 2011[16] Netherlands	Rhinitis	Perennial	Multiple	Dust mite: Dermatophagoides pterynossum and farinae	Age: Children 6-18 years Positive specific IgE test No previous immunotherapy Minimum duration of disease: 1 year	Industry

c) **Table E1c. Study Characteristics- SLIT-** Rhinoconjunctivitis

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
D'Ambrosio 1996 Italy[17]	Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Positive specific IgE test Positive skin test Monosensitized individuals only Excluded Pregnancy	Not stated
la Rosa 1999[18] Leonardi 2009[19] France-Italy	Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Positive specific IgE test Positive skin test Monosensitized individuals only	Industry

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Bowen 2004[20] Canada	Rhinoconjunctivitis	Seasonal	Single	Weeds: Ragweed	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Skoner 2010[21] USA	Rhinoconjunctivitis	Seasonal	Single	Weeds: Ragweed	No previous immunotherapy Positive skin test Minimum duration of disease: 2 years	Industry
Di Rienzo 2006[22] Italy	Rhinoconjunctivitis	Seasonal	Single	Trees: Mountain cedar	Age: 18 – 55 years Positive skin test Minimum duration of disease: 2 years	Not stated
Makino 2010[23] Japan	Rhinoconjunctivitis	Seasonal	Single	Trees: Japanese cedar	Age: adult No previous immunotherapy Positive specific IgE test Minimum duration of disease: 2 years	Government
Horak 1998[24] Austria	Rhinoconjunctivitis	Seasonal	Single	Trees: White Birch	Age: 18-38 years Positive skin test Positive specific IgE test No previous immunotherapy Excluded pregnant women	Not stated
Lima 2002[25] United Kingdom	Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy	Age: adults Positive skin test	Industry Government
Novembre 2004[26] Italy	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Ott 2008[27] Sieber 2012[28] Germany	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Age: 18 – 60 years Positive specific IgE test Positive skin test No previous immunotherapy Minimum duration of disease: 2 years	Industry
Panzer, 2008[29] Czech Republic	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Minimum duration of disease: 2 years	Industry
Roder, 2007[30] Netherlands	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Positive specific IgE test Age: 6-18 years No previous immunotherapy	Industry
Sabbah, 1994[31] France	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Positive specific IgE test Positive skin test	Industry Not stated
Voltolini 2001 [32] Italy	Rhinoconjunctivitis	Seasonal	Single	Trees: Tree mix	Age: 12-65 years old Positive skin test No previous immunotherapy Minimum duration of disease: 2 years Pregnant women excluded	Industry

d) **Table E1d. Study Characteristics- SLIT-** Asthma and Rhinitis

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Marogna 2005[33] Italy	Asthma and Rhinitis	Seasonal	Single	Trees: birch	Age: 18-65 years Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Government Non-profit
Voltolini 2009 [34] Italy	Asthma and Rhinitis	Seasonal	Single	Trees: Birch	Positive specific IgE test Positive skin test	Industry
Marogna 2010[35] Italy	Asthma and Rhinitis	Seasonal	Single	Trees: White birch	Age: 18-65 years No previous immunotherapy Positive skin test Minimum duration of disease: 2 years	Not stated
Amar 2009[36] USA	Asthma and Rhinitis	Seasonal	Multiple	Grass :Timothy grass Trees: Maple, Red/green ash American elm and Cottonwood Weeds: Kochia, Western ragweed, Sagebrush and Russian thistle	Age: 18-70 Positive skin test Minimum duration of disease: 2 years	The Investigators
Marogna 2009[37] Italy	Asthma and Rhinitis	Seasonal	Multiple	Grass: Grass mix	Age: 18-65 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Industry
Stelmach 2011[38] Poland	Asthma and Rhinitis	Seasonal	Multiple	Grass: Grass mix	Age: Children 6-18 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Academia
Marogna 2004[39] Italy	Asthma and Rhinitis	Seasonal	Multiple	Trees: White birch Dust mites: Dermatophagoides pteronyssinus Weeds: Mugwort and Parietaria Grass: Grass mix	Age: 15-65 years No previous immunotherapy Positive skin test Minimum duration of disease: 2 years	Industry Non-profit
Marogna 2006[40] Italy	Asthma and Rhinitis	Seasonal	Multiple	Trees: White birch Grass: Grass mix	Age: >18 years Positive skin test Minimum duration of disease: 2 years	Industry Non-profit

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Marogna 2008[41] Italy	Asthma and Rhinitis	Seasonal	Multiple	Trees: White birch Grass: Grass mix	Age: 5-17 years No previous immunotherapy Positive skin test Minimum duration of disease: 2 years	Industry
Moreno-Ancillo 2007[42] Spain	Asthma and Rhinitis	Seasonal	Multiple	Grass: Grass mix Trees: Olive	Age: 18-65 years Positive specific IgE test Monosensitized individuals only Minimum duration of disease: 2 years	Industry
Hirsch, 1997[43] Germany	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: children No previous immunotherapy Positive specific IgE test Positive skin test	Not stated
O'Hehir 2009[44] O'Hehir 2009[44]	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: 15 – 55 years Positive specific IgE test Positive skin test Monosensitized individuals only	Government Non-profit
Bush, 2011[45] USA	Asthma/ Rhinitis	Perennial	Single	Dust mite: Dermatophagoides farinae	Age: 18-50 years Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Industry
Tari, 1990[46] Italy	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Minimum duration of disease: 3 years	Not stated
Bahceciler, 2001[47] Turkey	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: children >7 years old No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Guez, 2000[48] France	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Positive skin test	Industry
Marogna, 2010[49] Italy	Asthma/ Rhinitis	Perennial	Single	Dust mite: Dermatophagoides pterynossum and farinae	Age: 18-65 years No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 2 years Excluded pregnant patients	Industry

e) **Table E1e. Study Characteristics- SLIT-** Asthma and Rhinoconjunctivitis

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Pajno, 2003[50], Pajno, 2004[51] Italy	Asthma and Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Age: children Positive skin test	Industry
Passalacqua 1999[52] Italy	Asthma and Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	No previous immunotherapy Monosensitized individuals only Minimum duration of disease:2 years	Industry Government
Vervloet, 2007[53] France	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Bald-cypress	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Vourdas, 1998 France-Greece[54]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Olive	Positive specific IgE test Positive skin test	50% of authors are industry
Pajno 2011[55] Italy	Asthma/ Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy	No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Not stated
Feliziani 1995[56] Italy	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass Mix	Age: 14 – 48 years No previous immunotherapy Positive skin test Minimum duration of disease Minimum duration of disease: 2 years Excluded Pregnancy	Industry
Pfaar 2007[57] Multiple European countries	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Industry
Pradalier 1999[58] France	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Positive specific IgE test Positive skin test	Industry
Valovirta 2006[59] Savolainen 2006[60] Finland	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Trees: Tree mix	Age: 5-14 years No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Industry
de Blay 2007[61] France	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Orchard grass, Timothy grass and Perennial ryegrass	Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Industry

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Pozzan 2010[62] Italy	Asthma/ Rhinoconjunctivitis	Perennial	Single	Mold: Alternaria	Age: 10-65 years Positive skin test Minimum duration of disease: 2 years Excluded pregnant patients	Industry
Alvarez-Cuesta 2007[63] Spain	Asthma and Rhinoconjunctivitis	Perennial	Single	Animals: cats	Age: 14-55 years Positive specific IgE test Positive skin test Minimum duration of disease:1 year	Industry
Ippoliti 2003[64] Italy	Asthma and Rhinoconjunctivitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: children No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Government
Rodriguez 2006[65] Spain	Asthma Rhinoconjunctivitis	Seasonal and Perennial	Multiple	Grass: Unspecified grass Dust mites: Unspecified dust mites	No previous immunotherapy Positive specific IgE test Positive skin test	Industry

TABLE E2.- PATIENT CHARACTERISTICS- SLIT

a) Table E2a. Patient Characteristics- SLIT- Asthma

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
D'Ambrosio, 1999 [1]	30	SLIT Placebo	32 +/- 17 32 +/- 18	50/50 43/57	14/0 16/0	NR
Pajno, 2000 [2]	24	SLIT Placebo	11(Range 8-15) 12 (Range 8-15)	58/42 50/50	12/0 12/3	5
Nelson, 1993 [3]	44	SLIT Placebo	Range: 20-74; males 18-46: females Range: 25-48: males 19-40: females	35/65 29/71	20/2 21/1	NR
Cortellini 2010 [4]	27	SLIT Placebo	19 +/- 7 (Range 16-42) 24 +/- 7 (Range 14-44)	53/47 58/42	15/0 12/1	4.4 years 5.2 years
Stelmach, 2009 [5] Penagos 2008[6]	50	SLIT Placebo	9 +/- 2 8 +/- 2	60/40 70/30	25/5 25/10	NR
Lue, 2006 [7]	20	SLIT Placebo	8 +/- 2 9 +/- 2	40/60 40/60	10/0 10/0	1

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Niu, 2006 [8]	110	SLIT Placebo	8 +/- 2 (Range 5-11) 8+/- 2 (Range 5-12)	61/39 58/42	56/7 54/6	1
Sambugaro, 2003 [9]	58	8-day induction 15-day induction 20-day induction Untreated	19 (Range 4-43) 26 (Range 5-42) 17 (Range 6-41) 23 (Range 10-37)	56/44 39/61 58/42 60/40	18/0 18/0 12/0 10/0	NR

b) Table E2b. Patient Characteristics- SLIT- Asthma Rhinitis

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Horiguchi, 2007 [10]	67	SLIT Placebo	27 +/- 5 26 +/- 6	51/49 46/54	43/2 24/2	9
Okubo, 2008[11]	61	SLIT Placebo	41/- 15 40+/- 15	49/51 32/68	37/0 22/0 2 dropouts before arm allocation	NR
Fujimura 2011 [12]	103	SLIT Placebo	44.4 (Range 16-73) 42.3 (Range 19-70)	34/66 22/78	51/15 37/10	NR
Hordijk, 1998[13]	69	SLIT Placebo	28 28	52/48 43/57	27/8 30/6 Numbers as reported	NR
Tahamiler, 2007[14]	NR	SLIT /placebo SLIT alone	28+/- 10 (Range 12-51) 26+/- 8 (Range 10-49)	54/46 54/46	67/NR 70/NR	2 3
Tseng, 2008[15]	63	SLIT Placebo	10 +/- 3 10 +/- 3	73/27 70/30	30/2 33/2	63%: 2-5, 33%: 6-10, 3%: 13 52%:2-5 ,48%: 6-10,0% :13
deBot 2011[16]	257	SLIT Placebo	11.8 +/- 3.1 11.7 +/- 2.9	61/39 59/41	125/17 126/15 6 withdrew consent before arm allocation	1 year

c)Table E2c. Patient Characteristics- SLIT- Asthma Rhinoconjunctivitis

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
D'Ambrosio, 1996[17]	40	SLIT Pharmacotherapy	30 (Range 18-41) 34 (Range 19-67)	47/53 33/67	15/5 15/5	2 or more
la Rosa, 1999[18] Leonardi, 2009[19]	41	SLIT Placebo	10 (Range 6-14) 10 (Range 7-13)	65/35 57/43	20/5 21/4	3 4
Bowen, 2004[20]	83	SLIT Placebo	38 (Range 14-58) 35 (Range 16-56)	NR NR	43/15 40/11	19 17
Skoner, 2010[21]	115	High dose SLIT Medium dose SLIT Placebo	34 (Range 20-49) 34 (Range 19-49) 35 (Range 20-50)	33/67 26/74 48/53	36/5 39/8 40/5	NR
Di Rienzo, 2006[22]	34	SLIT Placebo	34+/- 10 (Range 18-55) Entire Study	47/53 Entire Study	19/1 15/1	NR
Makino, 2010[23]	25	SLIT Placebo	49+/- 15 48 +/- 13	67/34 69/31	9/0 15/1	2
Horak, 1998 Austria [24]	41	SLIT Placebo	33+/- 15 (Range 18-38) 32 +/-16 (Range 18-38)	36/64 (Entire study)	20 21 (7 dropouts entire study)	9 years
Lima 2002[25]	56	SLIT Placebo	34 (Range 21-53) 34 (Range 21-55)	54/47 32/68	28/2 28/5	2
Novembre, 2004[26]	113	SLIT Control	9 (Range 5-14) 8 (Range 4-16)	70/30 70/30	54/6 59/10	NR
Ott, 2008[27] Sieber 2012[28]	213	SLIT followed by placebo Placebo	33+/- 11 7.9- 64.7 34+/- 9 Range 7.9- 64.7	46/54 54/46	142/10 67/4	13
Panzer, 2008[29]	35	SLIT Placebo-SLIT	17 +/- 9 (Range 7-50) 24 +/- 12 (Range 7-50)	55/45 60/40	20/0 15/0	NR
Roder, 2007[30]	204	SLIT Placebo	13+/- 7 (Range 7-17) 13+/- 3 (Range 6-17)	67/33 44/56	108/26 96/24	NR
Sabbah, 1994[31]	58	SLIT Placebo	23 +/- 10 (Range 13-43) 27 +/- 12 (Range 13-51)	59/41 48/52	29/0 29/0	11 10

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Voltolini 2001 [32]	30	SLIT Placebo	38 (Range 17-63) 39 (Range 24-64)	47/53 27/73	15/1 15/2	NR

d) Table E2d. Patient Characteristics- SLIT- Asthma Asthma and Rhinitis

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Marogna, 2005[33]	79	SLIT Placebo	28 (Range 18-43) 29 (Range 19-45)	55/45 57/44	39/10 40/17	NR
Voltolini, 2009[34]	24	SLIT Placebo	44+/- 9 40 +/- 7	50/50 30/70	14/1 10/1	NR
Marogna 2010[35]	33	SLIT Montelukast	NR	NR	17/1 16/3	2 years
Amar, 2009[36]	58	SLIT Monotherapy SLIT Multiple allergen Placebo	39 36 39	26/74 41/59 47/53	19/0 17/3 17/2	2 years
Marogna, 2009[37]	51	SLIT Budesonide	27 +/- 1 (Range 17-41) 27 +/- 1 (Range 19-41)	44/56 46/54	25/2 26/3	8 7
Stelmach 2011[38]	60	SLIT pre-coseasonal SLIT continuous Placebo	8.3 Range 5-17	65/35 74/26 61/39	20/3 20/1 20/2	2 years
Marogna, 2004[39]	511	SLIT Control	23 (Range 5-60) 22 (Range 5-58)	56/44 63/37	319/48 192/22	NR
Marogna, 2006[40]	48	SLIT - birch SLIT - grass SLIT - birch + grass Control	28 27 26 27	NR NR NR NR	12/0 11/0 12/0 13/0	NR
Marogna, 2008[41]	216	SLIT Control	11+/- 0 10 +/- 0	72/38 60/40	144/14 72/6	2 years
Moreno-Ancillo, 2007[42]	105	SLIT Placebo	29+/-10 (Range: 14-55) 26 +/- 8 (Range: 14-55)	54/46 57/43	52/11 53/9	7
Hirsch, 1997[43]	30	SLIT Placebo	11 (Range 6-15) 10 (Range 6-14)	67/34 67/33	15/1 15/0	5 (asthma), 5 (rhinitis) 3 (asthma), 3 (rhinitis)

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
O'Hehir, 2009[44] O'Hehir, 2009[44]	30	SLIT Placebo	29+/- 8 38+/- 11	NR NR	15/2 15/1	Minimum 2
Bush 2011[45]	31	SLIT high dose SLIT Low dose Placebo	30.6	50/50 10/90 27/73	10/1 10/3 11/6	2 years
Tari, 1990[46]	66	SLIT Placebo	Range 5-12 Range 5-12	Entire study 64/36	34/4 32/4	3 years
Bahceciler, 2001[47]	15	SLIT Placebo	Median 12 (Range 8-18) Median 12 (Range 7-15)	50/50 58/43	8/0 7/0	Median 1.5 Median 3
Guez, 2000[48]	72	SLIT Placebo	30+/- 12 (Range 12-51) 23 +/- 11 (Range 6-47)	39/61 42/58	36/11 36/22	10 8
Marogna 2010[49]	78	SLIT 3 yrs SLIT 4 yrs SLIT 5 yrs	21.1 +/- 1.4 Range 15-34	NR	19/5 21/5 17/0 21/9	2 years

e)Table E2e. Patient Characteristics- SLIT- Asthma Asthma and Rhinoconjunctivitis

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Pajno 2003[50,] Pajno 2004[51]	30	SLIT+ fluticasone Placebo+fluticasone	11 (Range 8-14) 11 (Range 8-14)	47/53 40/60	15/1 15/2	5 3
Passalacqua, 1999[52]	30	SLIT Placebo	33 (Range 22-47) 30 (Range 19-36)	67/34 33/67	15/1 15/2	3 4
Vervloet, 2007[53]	76	SLIT Placebo	39 (Range 22-60) 39 (Range 19-60)	58/42 45/55	38/2 38/4	8 8
Vourdas, 1998[54]	69	SLIT Placebo	12 (Range 8-17) 12 (Range 7-17)	74/37 67/34	34/1 32/1 3 dropouts before arm allocation	4 4
Pajno 2011[55]	80	SLIT continuous; SLIT co-seasonal	11 (Range 8-16) 12 (Range 8-16)	60/40 47/53	40/3 40/5	5.2 years 4.1 years
Feliziani, 1995[56]	34	SLIT Placebo	NR	NR NR	18/0 16/0	Minimum 2

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Pfaar, 2007[57]	185	SLIT Placebo	33 (Range 18-59) 34 (Range 17-55)	66/34 59/41	94/45 91/36	NR
Pradalier, 1999[58]	126	SLIT Placebo	28+/- 11 (Range 8-50) 30 +/- 12 (Range 7-58)	47/53 59/41	62/3 61/4	9 5
Valovirta, 2006[59] Savolainen, 2006[60]	98	SLIT High dose SLIT Low dose Placebo	9 +/- 3 10 +/- 3 10 +/- 3	49/52 61/39 62/38	32/7 33/1 33/6	4 5 5
de Blay, 2007[61]	118	SLIT Placebo	24+/- 7 (Range 12 -41) 27 +/- 8 (Range 12 -41)	56/44 61/39	61/9 57/8	6 6
Pozzan 2010[62]	52	SLIT Placebo	18 +/- 9 19+/-10	67/33 55/45	34/1 18/0	2 years
Alvarez-Cuesta, 2007[63]	50	SLIT Placebo	35 (Range 14-55) Entire study	NR NR	25/8 25/9	NR NR
Ippoliti, 2003[64]	86	SLIT Placebo	Median;9 (Range 5-12) Median;9 , (Range 7-11)	60/41 56/44	47/0 39/0	2 2
Rodriguez, 2006[65]	135	SLIT SLIT no 30d updosing	23+/- 11 (Range 7-55) 22 +/- 10 (Range 7-55)	55/45 47/53	69/6 66/6	NR NR

TABLE E3.- INTERVENTION CHARACTERISTICS-SLIT

a) **Table E3a. Intervention Characteristics- SLIT- Asthma**

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Purello-D'Ambrosio, 1999[1]	SLIT Parietaria Placebo	Conventional therapy	5 drops of 0.6 µg /ml	199.5 BU	3 times a week,rush	12.77 Par j1 (cumulative)	9 months
Pajno, 2000[2]	SLIT Dust mite Placebo	ONLY rescue medication	5 drops of 10 BU/ml	NR	3 times a week	2.4 Der p1, 1.2 Der p 2 (per week)	2 years
Nelson, 1993[3]	SLIT Cat Placebo	ONLY rescue medication	20 drops of 100,000 AU/ml	4,500,000 AU	3 times a week	45- 900 Fel d 1 (cumulative)	105 days

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Cortellini 2010 [4]	SLIT Placebo	Rescue	10,000 RU	60 µg Alt a1	Every other day	1.5 µg Alt a1 (maintenance)	10 months
Stelmach2009 [5] Penagos 2008[6]	SLIT Placebo	Conventional therapy	120 IR	43800 IR	Daily	25 µg/ml	2 years
Lue, 2006[7]	SLIT Dust mite Placebo	Conventional therapy	20 drops of 300 IR/mL	41824 IR	Daily	3000 Der F , 1700 Der P (cumulative)	6 months
Niu, 2006[8]	SLIT Dust mite Placebo	ONLY rescue medication	20 drops of 300 IR/ml	41824 IR	Daily	3000 Der F , 1700 Der P (cumulative)	24 weeks
Sambugaro, 2003[9]	SLIT/ 8-d induction Dust mite-grass mix-ragweed and parietaria SLIT/ 15-d induction Dust mite-grass mix-ragweed and Parietaria SLIT/ 20-d induction Dust mite-grass mix-ragweed and Parietaria	Conventional therapy	1000 STU	NR	Daily	115.2 Der p1, 57.6 Der p2, 72 Group V grass, 648 Bet v 1,16.8 Par j 1 (cumulative) 115.2 Der p1, 57.6 Der p2, 72 Group V grass, 648 Bet v 1, 16.8 Par j 1 (cumulative) 115.2 Der p1, 57.6 Der p2, 72 Group V grass, 648 Bet v1, 16.8 Par j 1 (cumulative)	2 years

b) **Table E3b. Intervention Characteristics- SLIT-**Rhinitis

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Horiguchi, 2007[10]	SLIT Japanese cedar Placebo	Conventional therapy	1 mL of 1000 JAU	NR	Weekly	1.5 Cry j1 (maintenance)	7 months
Okubo, 2008[11]	SLIT Japanese cedar Placebo	Conventional therapy	1 ml of 2000 JAU/ml	NR	Weekly	NR	6 months
Fujimura 2011[12]	SLIT Japanese Cedar placebo	Conventional therapy	2000 JAU		Once a week	1.5-4.2 µg Cry j 1 (maintenance dose)	20 months

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Hordijk, 1998[13]	SLIT Grass mix Placebo	Conventional therapy	9500 BU	NR	2 times a week	NR	10 months
Tahamiler, 2007[14]	SLIT Dust mite 2 years SLIT Dust mite 3 years	ONLY rescue medication	5 drops of 1000 STU/mL 5 drops of 1000 STU/mL	NR	3 times per week	NR	3 years after discontinuation of therapy
Tseng, 2008[15]	SLIT Dust Mite Placebo	ONLY rescue medication	20 drops 300 IR/mL	37,312 IR	Daily	1560 Der P 2710 Der f (cumulative)	3 weeks induction therapy, 21 weeks maintenance
deBot 2011[16]	SLIT Dust mite (DP); placebo	Conventional therapy	20 drops =700 BU	435 µg Der p 1	2 times a week	2.03 µg Der p 1 (maintenance dose)	2 years

c) **Table E3c. Intervention Characteristics- SLIT-**Rhinoconjunctivitis

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
D'Ambrosio 1996 [17]	SLIT Parietaria Medication	Conventional therapy	5 drops of10 BU/ml	13 µg	every other day	0.12 Par j 1 (maintenance)	8 months (mid Jan to end Sep)
La Rosa 1999[18] Leonardi 2009[19]	SLIT Parietaria Placebo	Conventional therapy	20 drops of 300 IR/ml	75,000 IR per year	3 times a week	52.5 Par j 1 (cumulative)	2 years
Bowen 2004[20]	SLIT Ragweed Placebo	Conventional therapy	100 - 300 IR/ml	NR	Daily	116 Amb a 315 (per day)	3 months (estimated duration)
Skoner 2010[21]	SLIT Ragweed High dose SLIT Ragweed Medium dose	ONLY rescue medication	48 µg 4.8 µg	4981 +/- 1487 µg Amb a 1 498 +/- 185 µg Amb a 1	Daily	48Amb a1 (maintenance) 4.8Amb a1 (maintenance)	17 +/- 3 weeks
Di Rienzo 2006[22]	SLIT Mountain cedar Placebo	Conventional therapy	8 drops of 300 IR/ml	NR	Daily	NR	4 to 5 months (Preseasonal December - April) Follow-up +/- 5 months (unclear)

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Makino 2010[23]	SLIT Japanese cedar Placebo	Conventional therapy	1 mL of 2000 JAU/mL	NR	Weekly	15 Cr j1, 2-5 Cr j2 (maintenance)	5 months
Horak 1998[24]	SLIT Birch Placebo	Conventional therapy	10 drops (500 STU/ml)	225 STU	3 times a week	NR	3 months
Lima 2002[25]	SLIT Timothy Placebo	Conventional therapy	6 drops of 1 mg/ml	NR	Daily	900 Phl p5 (per month)	12-18 months 18 months
Novembre 2004[26]	SLIT Grass mix symptomatic therapy	ONLY rescue medication	5 drops of 25 BU/ml	120 µg	Daily	0.5 Group V major grass (maintenance)	3 years
Ott 2008[27] Sieber 2012[28]	SLIT grass mix followed by placebo placebo	ONLY rescue medication	300 IR maintenance dose (escalation from 30 IR to 300 IR in one hour)	22000 IR per season 66000 IR total over 3 seasons	Ultrarush, then daily for 3 seasons	1500 µg Grp V major allergen per season, or 4500 total over study	Co-seasonal for 3 years (3 seasons); follow-up season at year 4 where everyone had placebo
Panzer 2008[29]	SLIT Grass mix Placebo	ONLY rescue medication	10 drops of 10000 JSK/ml (jednotkastandardnikvality- standard quality unit)	>580000 JSK	3 times a week	NR	1 year
Roder 2007[30]	SLIT Grass mix Placebo	Conventional therapy	9500 BU	1976000 BU 4.5 mg Lol p5	2 times a week	21 Lol p5 (maintenance)	2 years
Sabbah 1994[31]	SLIT Grass mix or dust mite Placebo	ONLY rescue medication	20 drops of 100 IR/ml	4500 IR	Daily for one month, Then alternating daily for one month	NR	120 days
Voltolini 2001 [32]	Co-seasonal SLIT Conventional meds	conventional	5 drops 25 BU/ml	819 BU/5months= 445 mg Bet v1	3 times a week	445 milligram Bet v1 (cumulative)	5 months per yr for 2 years (co-seasonal)

d) **Table E3d. Intervention Characteristics- SLIT-**Asthma and Rhinitis

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Marogna 2005[33]	SLIT Birch Placebo	Conventional therapy	102 µg per year	NR	Daily	102 Bet v1 (per year)	3.5 years
Voltolini 2009[34]	SLIT Birch Placebo	Conventional therapy	300	13.8 IR per season	Daily	13.8 IR (6.9 µgBet v1 per season)	4 months
Marogna 2010[35]	SLIT birch; Monteleukast	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
Amar 2009[36]	SLIT Timothy-Monotherapy SLIT Timothy-Multiallergen therapy	Conventional therapy	19 µg	571 µg per month	Daily	19Phl p5 (maintenance)	15 months
Marogna 2009[37]	SLIT Grass mix Inhaled Corticosteroids	Conventional therapy	5 drops of 10,000 RU/ml	70 µg (yearly)	3 times a week	70 Phl p1 (per year)	5 years
Stelmach 2011[38]	SLIT pre-coseasonal - grass mix SLIT continuous – grass mix placebo	ONLY rescue medication	300IR	3.6 mg 7.3 mg (of major allergen)	Arm 1:Daily for 6 of 12 months Arm 2: daily for 12 of 12 months	10 µg of major allergens (maintenance dose) Dact g 5, Antx 0 5, Lol p 5, Poa p 5, Phl p 5	12 months
Marogna 2004[39]	SLIT Dust mite, birch, grass mix, parietaria, mugwort Pharmacotherapy	Conventional therapy	5 drops of 10,000 RU/ml	390 µg Der p1/ Der p2,70 µg Phl p1, 70 µg Par j1, 100 µg Bet v1 (per year)	3 times a week	390 µg Der p 1/Der p 2, 70 µg Phl p 1, 70 µg Par j 1, 100 µg Bet v 1 (per year)	3 years
Marogna 2006[40]	SLIT Birch alone SLIT Birch and Grass	Conventional therapy	100 µg (monthly) 70 µg (monthly)	NR	every other day	100 µg (per month) 70 µg (per month)	4 years
Marogna 2008[41]	SLIT Birch-Grass-Dust mite and Parietaria Conventional therapy	Conventional therapy	5 drops of 10,000 RU/ml	480 µg of Der p1, 480 µg Der p2, 40 µg of Phl p 1,40 µg Par j 1, 100 µg of Bet v 1 (per year)	3 times a week	480 µg of Der p1, 480 µg Der p2, 40 µg of Phl p 1,40 µg Par j 1, 100 µg of Bet v 1 (per year)	3 years

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Moreno-Ancillo 2007[42]	SLIT Grass mix and olive Placebo	NR	2 µg grass, 3 µg olive	NR	Daily	2 Group V major grass, 3 Oeuropaea Ole e1 (maintenance)	10 months
Hirsch 1997[43]	SLIT Dust mite Placebo	Conventional therapy	7 drops of 11.9 µg /ml=3.75 µg	570 µg (per year)	3 times a week	570 Dep p1 (per year)	1 year
O'Hehir 2009[44] O'Hehir 2009[44]	SLIT Dust mite Placebo	ONLY rescue medication	8 drops	85621 IR		17100 mg Der p 1; 3400 mg Der p 2 (per year)	1 year
Bush 2011[45]	SLIT high dose Dust mite (Der F) SLIT Low dose Dust Mite Placebo	Conventional therapy	4200 AU/day =70 µg Der f 1/day 60 AU/day=1 µg Der f 1/day	NR	Once a day	70 µg Def f 1 per day	12-18 months
Tari 1990[46]	SLIT Placebo	ONLY rescue medication	15 drops of 500 STU/ml	NR	3 times per week		18 months
Bahceciler 2001[47]	SLIT Dust mite 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
Guez 2000[48]	SLIT Dust mite Placebo	Conventional therapy	20 drops of 300 IR/ml	90,000 IR	3 times a week	2200 Der p1, 1700 µg Der f1 (cumulative)	24 months
Marogna 2010[49]	SLIT 3 yrs; SLIT 4 yrs; SLIT 5 yrs. Dust mite (DP) (Other group excluded as not randomized)	Conventional therapy	5 drops of 10,000RAST units/ml	390 µg Der p1/Derp2	3 times a week		3, 4, or 5 years.

e) **Table E3e. Intervention Characteristics- SLIT-**Asthma and Rhinoconjunctivitis

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Pajno 2003[50,] Pajno 2004[51]	SLIT Parietaria Placebo	Conventional therapy	5 drops of 10BU/ml	20.3 µg	every other day	20.3 Par j1 (cumulative)	13 months

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Passalacqua 1999[52]	SLIT Parietaria Placebo	ONLY rescue medication	5 drops of 10 BU/ml =12 µg	256 BU	Daily	16 Par j1 (cumulative)	6 months
Vervloet 2007[53]	SLIT Bald-cypress Placebo	ONLY rescue medication	300 IR	NR	Rush, Then daily	228 Jun a1 (maintenance)	120 days
Vourdas 1998[54]	SLIT Olive Placebo	Conventional therapy	20 drops of 300 IR/ml	30000 IR/year	Daily	4050 Ole e 1 (per year)	Seasonal (6 months each year) for 2 years
Pajno 2011[55]	continous SLIT co-seasonal SLIT Grass mix	Conventional therapy	6 drops of 300 IR/ml	NR	5 days per week	6 drops of 14 µg /ml Phl p 5 (maintenance dose)	32 months 4 months/year during season, total of 2 years of treatment
Feliziani 1995[56]	SLIT Grass mix Placebo	Conventional therapy	5 drops of 100 BU/ml =20 BU	NR	3 times a week	NR	Until end of pollen season
Pfaar 2007[57]	SLIT Grass mix Placebo	ONLY rescue medication	40 µg (of group 5 grass allergen)	NR	Daily	40 Group V major grass (maintenance)	2 years
Pradalier 1999[58]	SLIT Grass mix or dust mite (updosing) SLIT Grass mix or dust mite (No updosing)	Conventional therapy	2 µg GroupV major grass, or 0.8/0.4 µg Der p1/Der p2 2 µg GroupV major grass, or 0.8/0.4 µg Der p1/Der p2	NR	Daily	2 µg Group V major grass, or 0.8/0.4 µg Der p1/Der p2	3 months 2 months
Valovirta 2006[59] Savolainen 2006[60]	SLIT Tree mix high dose SLIT Tree mix low dose Placebo	Conventional therapy	100,000 SQ-U/ml (per week) 12,000 SQ-U/ml (per week)	200,000 SQ-U per week =30 µg 24,000 SQ-U per week or 3.6 µg	5 times a week	30 Bet v1/Aln g 1/Cor a1 (per week) 3.6 Bet v1/Aln g 1/Cor a1 (per week)	5 weeks build-up, up to 18 months maintenance
De Blay 2007[61]	SLIT Grass mix Placebo	ONLY rescue medication	300 IR	31800 IR	3 times a week	2750 Group 3 major grass (cumulative)	10 months

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Pozzan 2010[62]	SLIT Alternaria placebo	ONLY rescue medication	0.12 µg Alt a 1 per day	NR	Daily	3.6 µg Alt a 1 per month	3 years
Alvarez-Cuesta 2007[63]	SLIT Cat Placebo	Conventional therapy	5 drops of 0.51 µg /ml	17.1 µg Fel d 1.	Daily	0.51 Fel d1 (maintenance)	12 months
Ippoliti 2003[64]	SLIT Dust mite 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
Rodriguez 2006[65]	SLIT Dust mite Placebo	Conventional therapy	1.0 ml of 0.5 µg /ml 2.0 Der f1	NR	Weekly	0.5 Der f1 (maintenance)	10 months

TABLE E4.- QUALITY ASSESSMENT-SLIT

a) **Table E4a. Quality aseessment -SLIT-**Asthma

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
D'Ambrosio, 1999 [1]	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
Pajno, 2000 [2]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Nelson, 1993 [3]	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
Cortellini 2010 [4]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High
Stelmach 2009[5] Penagos 2008[6]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Lue, 2006 [7]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Niu, 2006 [8]	Low risk	Low risk	Low risk	High risk	High risk	No	Medium risk
Sambugaro 2003 [9]	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk

b) **Table E4b. Quality aseessment -SLIT-**Rhinitis

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Horiguchi, 2007 [10]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Okubo, 2008[11]	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
Fujimura 2011 [12]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Hordijk, 1998[13]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Tahamiler, 2007[14]	Low risk	Low risk	High risk	High risk	Low risk	No	Medium risk
Tseng, 2008[15]	Low risk	Low risk	Low risk	High risk	Low risk	No	Medium risk
deBot 2011[16]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk

c) **Table E4c. Quality aseessment -SLIT-**Rhinoconjunctivitis

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
D'Ambrosio, 1996 [17]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
La Rosa 1999[18] Leonardi, 2009[19]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Bowen 2004[20]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Skoner, 2010[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Di Rienz, 2006[22]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Makino 2010[23]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
Horak, 1998[24]	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
Lima 2002[25]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Novembre, 2004[26]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Ott, 2008[27] Sieber 2012[28]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Panzer, 2008[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Roder, 2007[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Sabbah, 1994[31]	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Voltolini 2001 [32]	Low	Low	High	Low	High	High	Medium

d) **Table E4d. Quality aseessment -SLIT-**Asthma and Rhinitis

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Marogna, 2005[33]	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
Voltolini, 2009[34]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Marogna 2010[35]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Amar, 2009[36]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Marogna, 2009[37]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Stelmach 2011[38]	Low risk	Low risk	Low risk	Low risk	High risk	No	Low risk
Marogna, 2004[39]	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
Marogna, 2006[40]	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
Marogna, 2008[41]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
Moreno-Ancillo 2007[42]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Hirsch, 1997[43]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
O'Hehir, 2009[44] O'Hehir, 2009[44]	Low risk	Low risk	High risk	High risk	High risk	Yes or unclear	High risk

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Bush 2011[45]	Low risk	High risk	Low risk	Low risk	High risk	Yes or unclear	Medium risk
Tari, 1990[46]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Bahceciler, 2001[47]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Guez, 2000[48]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Marogna 2010[49]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk

e) **Table E4e. Quality aseessment -SLIT-**Asthma Rhinoconjunctivitis

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Pajno 2003[50,] Pajno 2004[51]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Passalacqua, 1999[52]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Vervloet, 2007[53]	Low risk	Low risk	High risk	Low risk	High risk	Yes or unclear	Medium risk
Vourdas, 1998[54]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Pajno 2011[55]	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
Feliziani, 1995[56]	Low risk	Low risk	High risk	High risk	Low risk	No	Medium risk
Pfaar, 2007[57]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Pradalier, 1999[58]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Valovirta, 2006[59] Savolainen, 2006[60]	Low risk	High risk	Low risk	Low risk	Low risk	Yes or unclear	Medium risk
De Blay, 2007[61]	Low risk	Low risk	High risk	Low risk	High risk	Yes or unclear	Medium risk
Pozzan 2010[62]	Low risk	High risk	Low risk	Low risk	High risk	Yes or unclear	Medium risk
Alvarez-Cuesta 2007[63]	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
Ippoliti, 2003[64]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Rodriguez, 2006[65]	Low risk	High risk	Low risk	Low risk	Low risk	Yes or unclear	Medium risk

TABLE E5.- ASTHMA AND ASTHMA COMBINED SCORES -SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Pajno 2000 [2]	Dust mite	SLIT Placebo	2 years	Mean score for nighttime symptoms per month	0-90 per month	14 15	6 13.2	SLIT pre vs post p = 0.001 Placebo pre vs post p= 0.439 SLIT vs Placebo p <0.0001
Pajno 2000 [2]	Dust mite	SLIT Placebo	2 years	VAS Asthma Symptoms	0-10/day	5.1 5.3	2.5 6.6	SLIT pre vs post p = 0.001
Cortellini 2010 [4]	Alternaria	SLIT Placebo	10 months	Asthma, Rhinitis, Conjunctivitis score		421(102) 305	182(67) 315(115)	SLIT pre vs post p<0.001 Placebo pre vs post NS SLIT vs Placebo p=0.02
Lue 2006 [7]	Dust mite	SLIT Placebo	6 months	night time asthma score	0-3/day	0.51 +/- 0.24 0.5 +/- 0.38	0.16 +/- 0.15 0.5 +/- 0.47	SLIT pre vs post p< 0.001 Placebo pre vs post p=0. 996 SLIT vs Placebo p = 0.047
Niu 2006[8]	Dust mite	SLIT Placebo	24 weeks	daily asthma symptoms	0-3/day	0.11 0.05	0.04 0.06	SLIT vs Placebo p= 0.028
Hirsch 1997[43]	Dust mite	SLIT Placebo	1 year	Mean daily pulmonary symptoms	0-3	0.36 0.07	0.07 0.28	Placebo pre vs post p=1545 SLIT vs Placebo p< 0.05
Tari 1990[46]	Dust mite	SLIT Placebo	18 months	Daily Lung symptom score (sum of individual sx scores)	0-3/sx	10 10	6 9.5	SLIT pre vs post p 0.001 SLIT vs Placebo NS
Bahceciler 2001[47]	Dust mite	SLIT placebo	6 months	Asthma symptoms	0-3	0.64 0.33	0.3 0.26	SLIT pre vs post p <0.05
Ippoliti 2003[64]	Dust mite	SLIT Placebo	6 months	asthma symptom score		3.28 3.08	1.28 3.15	SLIT pre vs post p <0.001 Placebo pre vs post p NS
deBot 2011[16]*	Dust mite	SLIT placebo	2 years	Dyspnea/wheeze score		NR	0.21 0.11	SLIT vs Placebo p=0.01

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
D'Ambrosio1996 [17]	Parietaria	SLIT Placebo	5 months	Rhinoconjunctivitis plus asthma symptom scores	0 = none	NR NR	4352 6134	SLIT vs Placebo p <0.05
Purello-D'Ambrosio1999[1]	Parietaria	SLIT Placebo	10 months	Unspecified Asthma plus rhinoconjunctivitis score	0-3	NR NR	NR NR	SLIT pre vs post p=0.001
Pajno 2003[50], Pajno 2004[51]	Parietaria	SLIT Placebo	Pollen season (April-June)	Chest symptom score	0-21/ week		16 median weekly score 18 median weekly score	SLIT vs Placebo p =0.191
Pajno 2003[50], Pajno 2004[51]	Parietaria	SLIT Placebo	Pollen season (April-June)	VAS Chest symptoms	0-10/ day		1.5 median weekly score 2.0 median weekly score	SLIT vs Placebo p =0.037
Lima 2002[25]	Timothy	SLIT Placebo	18 months	Overall chest symptom scores	0-12/ day	NR NR	117 32	SLIT vs Placebo p= 0.64
Lima 2002[25]	Timothy	SLIT Placebo	18 months	Overall improvement compared to previous years	-3 to +3	NR NR	77% better than prior years 39% better than prior years	SLIT vs Placebo p<0.05
Marogna 2005[33]	Birch	SLIT Placebo	3.5 years	Lung, nasal, eye symptoms	0-360	290 300	50 150	SLIT vs Placebo p<0.001
Voltolini 2010[34]	Birch	SLIT Placebo	18 months; at peak season	number of days with asthma	# of days with asthma	10 13	2 7	SLIT vs Placebo p< 0.05
Marogna 2010[35]	Birch (GINA criteria asthma dx)	SLIT Montelukast	5 years	0-3 per lower airway symptom	0-12/day	186.1 (10.3 SEM) 166.4 (7.9 SEM)	39.4(5.6) 158.9(7.6)	SLIT pre vs post p<0.001; Montelukast pre vs post NS; SLIT vs Montelukast p<0.0001
Panzner 2008[29]	Grass mix	SLIT Placebo	End of pollen season (September 2004)	bronchial symptoms score	0-12/ day	NR NR	31.95 103.8	SLIT vs Placebo p= 0. 0299

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Panzner 2008[29]	Grass mix	SLIT Placebo	End of pollen season (September 2004)	Total symptoms score Bronchial, nasal , ocular	0-48/ day		204 611	SLIT vs Placebo 2 p= 0.02
Marogna 2009[37]	Grass mix	SLIT Inhaled corticosteroid	5 years	lower airway score	0-12/ day	176.0 +/- 6.2 162.2 +/- 4.9	52.1 +/- 12.5 110.2 +/- 5.3	SLIT pre vs post p< 0.001 Placebo pre vs post p< 0.001 SLIT vs Placebo p< 0.001
Moreno-Ancillo 2007[42]	Grass mix Olive tree	SLIT Placebo	10 months	Pulmonary symptoms	0-9	0.3 +/- 0.43 0.28 +/- 0.35	0.16 +/- 0.21 0.14 +/- 0.22	SLIT pre vs post p =0.016 SLIT vs Placebo p= 0.16 Placebo pre vs post p= 0.1545
Marogna 2007[40]	Birch and Grass	SLIT Birch alone SLIT Grass alone SLIT Birch +Grass Pharmacotherapy	4 years	Combined asthma and rhinitis symptom score for Birch pollen season	0-21/ day	340 340 340 290	70 150 50 290	Birch vs Pharm p< 0.001 Grass vs Pharm p< 0.001 Birch+Grass vs Pharm p< 0.001
Marogna 2007[40]	Birch and Grass	SLIT Birch alone SLIT Grass alone SLIT Birch +Grass Pharmacotherapy	4 years	Combined asthma and rhinitis symptom score for grass pollen season	0-21/ day	300 320 320 275	120 50 20 300	Birch vs Pharm p< 0.01 Grass vs Pharm p< 0.001 Birch+Grass vs Pharm p< 0.001
Bush 2011[45]	Dust Mite (NHLB criteria for asthma)	High dose Low Dose placebo	12-18 months	0-3 per symptom, asthma and nasal, 0-24/day		NR	NR	High dose vs placebo NS Low dose vs placebo NS
Pajno* 2011[55]	Grass Mix (peds)	Cont SLIT Co-seasonal SLIT	3 yrs	0-3 per Chest symptom, 0-12 per day.	% reduction from baseline	NR	80% reduction 50% reduction	Continuous vs Seasonal NS
Pajno 2011[55]	Grass mix (peds)	Cont SLIT; Co seasonal SLIT	3 years	0-3 per symptom per day. Nasal, chest, eye symptoms	Reported as % reduction from baseline		60% reduction 50% reduction	Continuous vs Seasonal NS. Comparing the difference in percent reduction in symptoms between the 2 groups

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Valovirta, 2006[59] Savolainen 2006[60]	Tree mix	SLIT high dose SLIT low dose Placebo	Whole pollen season	Asthma symptoms	0-3/ day	NR NR NR	0.6 0.5 0.9	High dose vs placebo p=0.02 Low dose vs placebo NS
Valovirta, 2006[59] Savolainen 2006[60]	Tree mix	SLIT high dose SLIT low dose Placebo	Whole pollen season	Asthma and rhinoconjunctivitis symptoms	0-9/ day	NR NR NR	2.9 2.9	High dose vs placebo p=0.01, Low dose vs placebo p =0.03,
Pozzan 2010[62]	Alternaria (GINA criteria used for asthma dx)	SLIT placebo	3 years	Clinical improvement 6-0 VAS		NR	4.7±0.8 2.0 ±1.6	SLIT vs Placebo p =0.002
Marogna, 2004[39]	Dust mite, birch, grass mix, parietaria, mugwort	SLIT Placebo	3 years	Combined asthma and rhinitis symptom score	0-21/ day	147 +/- 3.3 138 +/- 2.3	54.7 +/- 2.8 121 +/- 3.8	SLIT pre vs post p< 0.0001 Placebo pre vs post p NS SLIT vs Placebo p< 0.0001

*Reported only asthma scores

TABLE E6.- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES -SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Purello-D'Ambrosio 1999[1]	Parietaria	SLIT Placebo	10 months	Unspecified rhinitis symptom scores	0-12	NR NR	NR NR	SLIT pre vs post p= 0.04
Nelson 1993[3]	Cat	SLIT Placebo	7 months	nasal blockage index after exposure to cat room	(Oral minus nasal peak flow)/oral flow	mean: 6.6 SEM 3.56 mean: 6.33 SEM 4.96	mean: 0.95 SEM 1.75 mean: 5.00 SEM 4.09	SLIT pre vs post p<0.001 SLIT vs Placebo p= NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Nelson 1993[3]	Cat	SLIT Placebo	7 months	Unspecified rhinitis symptom scores		Mean 29.10 SEM: 4.02 mean: 35.53 SEM: 5.68	Mean 12.15 SEM 1.94 % improv58.25 mean: 18.67 SEM: 2.96 % improv47.17	SLIT pre vs post p<0.001 SLIT vs Placebo <0.01
Hordijk 1998[13]	Grass Mix	SLIT Placebo	3 months (end of pollen season)	Mean peak pollen patient reported rhinitis daily scores	0-63/day	2.16 1.27	3.21 5.12	SLIT vs Placebo p= 0.03 peak season
Hordijk 1998[13]	Grass mix	SLIT Placebo	10 months	investigator rhinoconjunctivitis assessment	NS		3.21+/- 3.05 5.13+/- 3.6	SLIT vs Placebo p = 0.03
Horiguchi 2008[10]	Japanese cedar	SLIT Placebo	7 months	sneezing	0-4	NR NR	0.98 1.2	SLIT vs Placebo p <0.0001
Horiguchi 2008[10]	Japanese cedar	SLIT Placebo	7 months	Nasal secretion	0-4	NR NR	0.95 1.24	SLIT vs Placebo p <0.0001
Horiguchi 2008[10]	Japanese cedar	SLIT Placebo	7 months	Nasal obstruction	0-4	NR NR	0.43 0.52	SLIT vs Placebo p =0.0028
Okubo 2008[11]	Japanese cedar	SLIT Placebo	end of cedar season, (April 5th)	total rhinitis symptom score; every day, between Feb 2 -Apr 5	0-9		5.1 5.9	SLIT pre vs post p= NS SLIT vs Placebo p= NS
Stevens 1984[66]	Parietaria	SLIT Placebo	10 months	Nasal symptoms	0-12	64.1 64.7	42 76	SLIT vs Placebo NS
Tahamiler 2007[14]	Dust mite	SLIT 2 years SLIT 3 years	6 years after start; year 2, and year 3	Nasal symptoms	0-3	2.304 +/-0.3 2.366 +/-0.4	0.8701 +/- 0.9706 0.3723+/- 0.5383	SLIT 2y pre vs post p<.05 SLIT 3y pre vs post p<.05 2y Vs. 3y p< 0.001
deBot 2011[16]	Dust Mite	SLIT placebo	2 years	0-3/nasal symptom score of 0-12/day		3.25 3.25	2.26 (26% decrease) 2.01 (37%decrease)	SLIT vs Placebo NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Marogna 2010[35]	Birch	SLIT birch Monteleukast	5 years	0-3/upper airway symptom. 0-12/day		82.0 93.6	26.8 86.4	SLIT pre vs Post P<0.05; Montelukast pre vs post NS. SLIT vs Placebo p <0.05
Tseng 2008[15]	Dust mite	SLIT Placebo	24 weeks	Unspecified rhinitis symptom scores	0-3	1.79 +/- 1.13 2.33 +/-1.62	1.72+/- 1.78 1.89 +/-1.9	SLIT pre vs post p= 0.826 Placebo pre vs post p= 0.095 SLIT vs Placebo p= 0.6
La Rosa 1999[18] Leonardi 2009[19]	Parietaria	SLIT Placebo	2 years	Unspecified rhinitis symptom scores	0-12	NR NR	NR NR	SLIT vs Placebo p= 0.02 >30% reduction in rhinitis symptom
Bowen 2004[20]	Ragweed	SLIT Placebo	3 months (end of pollen season)	Sneezing score	0-3	NR NR	0.99 +/- 0.64 1.34 +/- 0.67	SLIT vs Placebo p= 0.04
Bowen, 2004[20]	Ragweed	SLIT Placebo	3 months (end of pollen season)	total rhinitis score	0-12	NR NR	3.95 +/- 2.45 5.03 +/- 2.54	SLIT vs Placebo p= 0.09
Bowen 2004[20]	Ragweed	SLIT Placebo	3 months (end of pollen season)	Rhinorrhea score	0-3	NR	1.10+/-0.81 1.36+/-0.67	SLIT vs Placebo NS
Bowen 2004[20]	Ragweed	SLIT Placebo	3 months (end of pollen season)	Nasal obstruction score	0-3	NR	1.07 +/-0.79 1.19 +/- 0.90	SLIT vs Placebo NS
Bowen 2004[20]	Ragweed	SLIT Placebo	3 months (end of pollen season)	Nasal pruritis score	0-3	NR	0.79 +/- 0.65 1.15 +/- 0.73	SLIT vs Placebo p=0.04
Lima 2002[25]	Timothy	SLIT Placebo	18 months; at peak season	Unspecified rhinitis symptom scores	NR	NR NR	742 1288	SLIT vs Placebo p= 0.37 CI -191
Panzner 2008[29]	Grass mix	SLIT Placebo	End of pollen season (September 2004)	nasal symptoms score	NR	NR NR	111.35 321.6	SLIT vs Placebo p= 0.0017
Panzner 2008[29]	Grass mix	SLIT Placebo	10 months	Rhinoconjunctivitis total symptoms score	NR	NR NR	111.35 321.6	SLIT pre vs post p = 0.0076 Placebo pre vs post p = 0.293

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Roder 2007[30]	Grass mix	SLIT Placebo	2 years	mean daily total of all rhinitis symptoms	0-15	5.6 9.0	3.1 3.4	SLIT vs Placebo NS CI -0.66 - 0.5
Sabbah 1994[31]	Grass mix	SLIT Placebo	17 weeks	Nasal symptom scores	0-7	NR NR	NR NR	SLIT vs Placebo p NS
Voltolini 2010[34]	Birch	SLIT Placebo	1 year	Nasal obstruction score	0-3	2 2	1.5 2	SLIT vs Placebo p <0.05
Voltolini 2010[34]	Birch	SLIT Placebo	1 year	Rhinorrhea symptom score	0-3	2 2	1 1.5	SLIT vs Placebo p <0.05
Marogna 2009[37]	Grass mix	SLIT Inhaled corticosteroid	5 years	Upper airway score	NR	116.2 +/- 12.3 89.8 +/- 10.4	33.0 +/- 5.2 108.3 +/- 11.4	SLIT pre vs post p <0.001 Steroids pre vs post p NS SLIT Vs. Steroids p = 0.001
Moreno-Ancillo 2007[42]	Grass mix and Olive	SLIT Placebo	10 months	Unspecified rhinitis symptom scores		0.88 +/- 0.53 0.74 +/- 0.44	0.55 +/- 0.35 0.56 +/- 0.41	SLIT pre vs post p = 0.0076 Placebo pre vs post p = 0.293
Hirsch, 1997[43]	Dust mite	SLIT Placebo	1 year	nasal symptom score	0-3	1.4 0.48	0.84 0.34	SLIT vs Placebo p NS
O'Hehir, 2009[44] O'Hehir 2009[44]	Dust mite	SLIT Placebo	1 year	rhinitis symptom score	0-3	60 60	35 40	SLIT pre vs post p <0.05 Placebo pre vs post NS
Bahceciler, 2001[47]	Dust mite	SLIT Placebo	6 months	Rhinitis score	0-2	1 (median) 0.64 (median)	0.4 (median) 0.38 (median)	SLIT vs Placebo p=0.56, NS
Guez, 2000[48]	Dust mite	SLIT Placebo	24 months	Unspecified rhinitis symptom scores	0-3	3.8 4	2.3 (1.9) 3.2 (2.4)	SLIT vs Placebo p NS, SLIT pre vs post p<0.05
Pajno 2003[50,] Pajno 2004[51]	Parietaria	SLIT Placebo	13 months	Nasal symptoms	0-3	NR	NR	SLIT vs Placebo NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Vervloet, 2007[53]	Mountain cedar	SLIT Placebo	120 days	Rhinitis total score	0-12		2.68 +/- 1.64 2.44 +/- 2.06	SLIT vs Placebo p=0.68
Vourdas, 1998[54]	Olive	SLIT Placebo	pollen season Year 2	Rhinitis score	0-4		0.72 1.22	SLIT vs Placebo p NS
Pradalier, 1999[58]	grass mix	SLIT Placebo	4 months (scores are reported for the entire pollen season	total rhinitis score	0-12		2.33 +/- 1.61 2.65 +/- 1.97	SLIT vs Placebo p NS
Valovirta, 2006[59] Savolainen 2006[60]	Tree mix	SLIT high dose SLIT low dose Placebo	Peak season	Nasal symptoms	0-3	NR NR NR	1.5 1.6 2.2	High dose vs Placebo p=0.04 Low dose vs Placebo p =0.04
De Blay, 2007[61]	Grass: Orchard, Timothy and ryegrass	SLIT Placebo	10 months	4-point scale rhinitis symptom scores	0-30		22.26 +/- 16.55 23.12 +/- 17.50	SLIT vs Placebo p = 0.67
Ippoliti, 2003[64]	Dust mite	SLIT Placebo	6 months	Rhinitis symptom score	0-3	0.84 0.91	0.39 0.82	SLIT pre vs post p <0.001 Placebo pre vs post p NS
Yonekura, 2010[67]	Dust mite	SLIT Placebo	1 year	Unspecified rhinitis symptom scores `		1.65 1.75	1.2 1.6	SLIT pre vs post p <0.05 Placebo pre vs post p NS
Skoner, 2010[21]	Birch	SLIT high dose SLIT medium dose Placebo	Weeks 10 – 18	Unspecified Rhinoconjunctivitis Symptom score	0-3		0.19 +/-1.16 0.46 +/- 1.4	High Vs. Placebo p = 0.005 Medium Vs. Placebo p =0.19 High Vs. Medium p =0.51 (values are average for entire pollen season)
Novembre, 2004[26]	Grass mix	SLIT Placebo	3 years	Unspecified Rhinoconjunctivitis Symptom score				SLIT vs Placebo NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Ott, 2008[27] Sieber 2012[28]	Grass mix	SLIT Placebo	3 years	VAS Rhinoconjunctivitis Symptom score		0.0 0.0	-1.94 -0.3	SLIT vs Placebo p = 0.015
Amar, 2009[36]	Timothy	SLIT-mono SLIT-Multi Placebo	15 months	Rhinoconjunctivitis Symptom score	0-3	6.3 8.1 6.4	4.0 5.4 3.9	Mono vs Placebo NS Multi vs Placebo NS
Feliziani, 1995[56]	Grass mix	SLIT Placebo	End of pollen season	Rhinoconjunctivitis Symptom score	0-2	7.1 10.5	2.4 8.0	SLIT vs Placebo p=0.01
Tari 1990[46]	Dust mite	SLIT Placebo	18 months	Combined nasal and respiratory symptoms	0-3	14.5 13.5	8.0 12.0	SLIT vs Placebo p<0.05 at 12 months SLIT vs Placebo p<0.001 at 18 months

NS: Not significant

TABLE E7.- CONJUNCTIVITIS SYMPTOM SCORES -SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
deBot 2011[16]	Dust mite	SLIT placebo	2 years	0-3/eye score, 0-9 /day		NR	SLIT 0.49, placebo 0.57	SLIT vs Placebo NS
Moreno-Ancillo 2007[42]	Grass mix and Olive tree	SLIT Placebo	10 months	Ocular symptoms	0-3	0.89 +/- 0.63 0.64 +/- 0.5	0.48 +/- 0.39 0.46 +/- 0.31	SLIT pre vs post p = 0.0092 Placebo pre vs post p = 0.1401
Vervloet, 2007[53]	Mountain cedar	SLIT Placebo	120 days	Conjunctivitis total score	0-9	0.02 0	1.14 +/- 1.14 1.24+/-1.40	SLIT vs Placebo p = 0.95 Peak season

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Vourdas, 1998[54]	Olive	SLIT Placebo	End of pollen season Year 2	4-point scale	0-4	NR NR	0.04 0.23	SLIT vs Placebo p <0.05; only significant week 19
Sabbah, 1994[31]	Grass mix	SLIT Placebo	17 weeks	Ocular redness	0-6	0 0.4	1.5 4.5	SLIT vs Placebo p <0.05 Peak season
Sabbah, 1994[31]	Grass mix	SLIT Placebo	17 weeks	Ocular pruritus	0-7	0.5 0.5	2.5 4.5	SLIT vs Placebo p NS
Bowen, 2004[20]	Ragweed	SLIT Placebo	3 months (end of pollen season)	total conjunctivitis score	0-9	NR NR	1.96 +/- 1.9 2.38+/- 1.92	SLIT vs Placebo p= 0.35
Lima, 2002[25]	Timothy	SLIT Placebo	18 months; at peak season	unspecified		NR NR	462 550	SLIT vs Placebo p= 0.86 CI -18
Panzner, 2008[29]	Grass mix	SLIT Placebo	End of pollen season (September 2004)	ocular symptoms score	0-16/day	NR	60.20 185.67	SLIT vs Placebo p= 0.013
De Blay, 2007[61]	Orchard, Timothy and Regrass	SLIT Placebo	10 months	4-point scale	0-30	NR	7.79 11.18	SLIT vs Placebo p = 0.08
Purello-D'Ambrosio, 1999[1]	Parietaria	SLIT Placebo	10 months	unspecified	0-6	NR	NR	SLIT pre vs post p= 0.04
Valovirta, 2006[59] Savolainen 2006[60]	Tree Mix	SLIT HighDose SLIT LowDose Placebo	Whole pollen season	Total eye symptoms	0-9/day	NR	0.8 0.9 1.1	High vs Placebo, p=0.04, Low vs Placebo NS
Tari, 1990[46]	Dust mite	SLIT Placebo	18 months	Ocular symptoms				SLIT vs Placebo p NS

NS: Not significant

TABLE E8.- MEDICATION SCORES - SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Purello-D'Ambrosio 1999[1]	Parietaria	SLIT Placebo	10 months	Unspecified		NR NR	NR NR	SLIT pre vs post p<0.05 60% Percentage improvement
Pajno, 2000[2]	Dust mite	SLIT Placebo	2 years	Unspecified		259.7 296	82.7 205.2	SLIT vs Placebo p <0.0001
Cortellini 2010 [4]	Alternaria	SLIT Placebo	10 months	Medication score	0-2 per medication per day	97 83	40 94	SLIT vs Placebo p=0.02
Lue, 2006[7]	Dust mite	SLIT Placebo	6 months	Unspecified		1.7 +/- 1.08 1.25 +/- 0.72	1.0 +/- 0.94 1.1 +/- 1.15	SLIT pre vs Post p = 0.034 Placebo pre vs Post p= 0.432 SLIT vs Placebo p = 0.366
Niu, 2006[8]	Dust mite	SLIT Placebo	24 weeks	Medication scores antihistamines and oral corticosteroids				SLIT vs Placebo p No significant change
Okubo, 2008[11]	Japanese Cedar	SLIT Placebo	End of season (april)	Medication score			0.44 0.36	SLIT pre vs Post p NS Placebo pre vs Post p NS
Troise, 1995[68]	Parietaria	SLIT Placebo	Peak season (4 months)	0 to 3 grading the medications required	1-3	NR NR	25.6 250.2	SLIT vs Placebo P<0.05 during peak season
Tseng, 2008[15]	Dust mite	SLIT Placebo	24 weeks	Need of antihistimine tablets		0.38 +/- 0.44 0.62 +/- 0.65	0.25 +/- 0.51 0.53 +/- 0.69	SLIT pre vs Post p = 0.826 Placebo pre vs Post p = 0.312
Tseng, 2008[15]	Dust mite	SLIT Placebo	24 weeks	beta-2 agonist puffs per day		0.04 +/- 0.13 0.05 +/- 0.17	0.04 +/- 0.12 0.04 +/- 0.15 1024	SLIT pre vs Post p = 0 .932 Placebo pre vs Post p = 0.843 SLIT vs Placebo p= 0.74
deBot 2011[16]	Dust mite	SLIT placebo	2 years	Proportion of days with rescue meds		NR	0.21 0.26	SLIT vs Placebo NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
La Rosa 1999[18] Leonardi 2009[19]	Parietaria	SLIT Placebo	2 years	Anti-rhinitis medication score				SLIT vs Placebo p NS
Bowen, 2004[20]	Ragweed	SLIT Placebo	3 months (end of pollen season)	Unspecified			1.05 +/- 1.60 1.26 +/- 1.24	SLIT vs Placebo p = 0.36
Skoner, 2010[21]	Short Ragweed	SLIT- high dose SLIT- medium dose Placebo	Weeks 10-18	Total medication score	0-3	NR NR NR	0.0003+/- 1.64 0.16 +/- 0.92 0.63 +/- 1.06	High vs Medium p= 0.59 High vs Placebo p= 0.004 Medium vs Placebo p = 0.12
Makino, 2010[23]	Japanese Cedar	SLIT Placebo	5 months	Unspecified			39.4 +/- 12.5 56.0 +/- 16.1	SLIT vs Placebo p= 0.42
Lima, 2002[25]	Timothy	SLIT Placebo	18 months	rescue medication use			1418 2569	SLIT vs Placebo p= 0.19 45% improvement SLIT
Ott, 2008[27] Sieber 2012[28]	Grass mix	SLIT Placebo	End of season 4	unspecified			0.07+/- 11.69 -0.98 +/- 2.61	SLIT vs Placebo p= 0.8397
Panzner, 2008[29]	Grass mix	SLIT Placebo	End of pollen season (September 2004)	rescue medication intake score		NR NR	4.60 13.93	SLIT vs Placebo p= 0.036
Voltolini 2001 [32]	Alder, birch, hazel	SLIT medication	2 yrs	Medication score	0-3 per med per day	87.86 61.62	29.09 66.7	SLIT pre vs post p=0.0076 SLIT vs Meds p=0.0097 Mag of effect =39%
Roder, 2007[30]	Grass mix	SLIT Placebo	2 years	% rescue med free days			69.3 (3.4) 74.2 (3.2)	SLIT vs Placebo p=0.67
Marogna, 2005[33]	White Birch	SLIT Placebo	3 years	Doses of Salbutamol used per month		9 10	1.9 10.4	SLIT vs Placebo p< 0.001

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Marogna 2010[35]	Birch	SLIT monteleukast	5 years	1 point per nasal corticosteroid (NCS) or Beta agonist use.	NCS score; Beta agonist score	NCS 15.8 (1.1 SEM) Beta 20.1 (0.7) NCS 16.6(1.0) Beta 19.4 (0.9)	NCS 4.3(0.7) Beta 4.0(0.9) NCS 15.0(1.0) Beta 15.8(1.0)	NCS SLIT vs Montelukast p <0.05 Beta agonists: SLIT pre vs post p<0.01, Montelukast pre vs post p =0.019 SLIT vs Montelukast p<0.0001
Amar, 2009[36]	Timothy	SLIT mono SLIT multi Placebo	15 months	Medication scores. 0-8 points per dose		0.19 0.17 0.11	0.10 0.07 0.05	P=0.7 comparison of the 3 arms
Marogna, 2009 [37]	Grass mix	SLIT Placebo	5 years	Bronchodilators use		23.0 +/- 1.5 22.4 +/- 0.9	5.1 +/- 1.4 13.0 +/- 1.2	SLIT pre vs post p= 0.001 Placebo pre vs post p= 0.001 SLIT vs Placebo p= 0.01
Marogna, 2009[37]	Grass mix	SLIT Placebo	5 years	Nasal corticosteroids use	NS	19.1 +/- 2.2 24.8 +/- 3.1	6.0 +/- 0.9 26.0 +/- 2.3	SLIT vs Placebo p< 0.001
Marogna, 2007[40]	Birch and Grass	SLIT Birch alone SLIT Grass alone SLIT Birch + Grass Pharmacotherapy	4 years	Drug score during birch pollen season		70 68 70 60	15 30 10 62	Birch Vs. Pharm p< 0.001 Grass Vs. Pharm p< 0.001 Mix Vs. Pharm p< 0.001
Marogna, 2007[40]	Birch and Grass	SLIT Birch alone SLIT Grass alone SLIT Birch + Grass Pharmacotherapy	4 years	drug score for grass pollen season		70 65 68 65	30 10 10 65	Birch Vs. Pharm p< 0.001 Grass Vs. Pharm p< 0.001 Mix Vs. Pharm p< 0.001
Marogna, 2007[42]	Grass mix Olive tree	SLIT Placebo	10 months	total medication scores		2.44 +/- 3.13 2.41+/- 2.49	1.68+/- 2.16 1.41+/- 1.48	SLIT pre vs post p =0.55 Placebo pre vs post p= 0.118
Hirsch, 1997[43]	Dust mite	SLIT Placebo	1 year	pulmonary symptom relief medication			5 8	SLIT vs Placebo p NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Hirsch, 1997[43]	Dust mite	SLIT Placebo	1 year	nasal symptom relief medication			3 1	SLIT vs Placebo p NS
Bush 2011[45]	Dust mite	High dose; low dose; placebo	12-18 months	Reported as albuterol use per day, another score for antihistamine use per day	1 point for loratadine/ alberterol, 2 points for azalastine;	Albuterol/ Antihistamine 0.0/0.0 0.0/0.03 0.01/0.21	Albuterol/ Antihistamine 0.0/0.02 0.0/0.0 0.0/0.57	No significant difference when compared to placebo either albuterol or antihistamine use when compared to placebo
Bahceciler, 2001[47]	Dust mite	SLIT Placebo	6 months	Beta-2 mimetic (agonist) use; 2-point scale	0-1	median: 0.17 range: 0-0.77 median: 0.17 range: 0-1	median: 0.03 range: 0-0.48 median: 0.08 range: 0-0.29	SLIT vs Placebo p=0.028
Bahceciler, 2001[47]	Dust mite	SLIT Placebo	6 months	Inhaled corticosteroid (ICS) dose; 6-point scale	0-5	median: 3.5 range; 2-4 median: 3 range; 2-5	median: 2 range; 1-3 median: 3 range; 0-5	SLIT pre vs post p = 0.6 SLIT vs Placebo p = 0.67
Guez, 2000[48]	Dust mite	SLIT Placebo	24 months	Unspecified	1- no max	9.2 10.2	4.1 (5.5) 6.1 (6.8)	SLIT vs Placebo p NS
Marogna 2010[49]	Dust mite (PD20 is inclusion criteria)	SLIT 3 yrs; SLIT 4 yrs; SLIT 5 yrs.	15 years	1 point per med		79 70 67	5 yr: , 20 yr: 9, 50 15,12 11,10	P values not reported (Note: values abstracted at of 5 years, then at year 20 before 2nd course of SLIT started in some groups)
Pajno 2003[50,] Pajno 2004[51]	Parietaria	SLIT Placebo	Pollen season (April-June)	Drug scores			0 2	SLIT vs Placebo p =0.192
Passalacqua 1999[52]	Parietaria	SLIT Placebo	End of pollen season (8 months)	Drug intake scores means		115.5 137.4	42.3 83	SLIT pre vs post p =0.008 Placebo pre vs post p NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Vervloet, 2007[53]	Mountain cedar	SLIT Placebo	4 months	Total medication score		NR NR	3.39 +/- 3.94 4.71+/- 5.0	SLIT vs Placebo p = 0.03
Vourdas, 1998[54]	Olive	SLIT Placebo	Pollen season Year 2	Unspecified				SLIT vs Placebo p NS
Sabbah, 1994[31]	Grass mix	SLIT Placebo	17 weeks	Consumption of specific medications				Nasal and eye drops Cromoglycate / terfenadine SLIT vs Placebo p<0.005 Betamethasone and dexchlopheniramine SLIT vs Placebo p<0.005
Pajno 2011[55]	Grass mix	Continous SLIT Co-seasonal SLIT	3 years	Percent reduction from baseline	1 topical med; 2 systemic meds	NR	70% reduction 50% reduction	Cont vs coseasonal: NS difference in amount of reduction of medication use
Feliziani, 1995[56]	Grass mix	SLIT Placebo	End of pollen season	medications for rhinoconjunctivitis symptoms		NR NR	24.05 76	SLIT vs Placebo p=0.002
Pradalier, 1999[58]	Grass mix	SLIT Placebo	4 months (Scores for the entire pollen season)	Global medication score (cortisone and short acting beta agonists)			1.77 +/- 2.27 2.13 +/- 2.74	SLIT vs Placebo p NS
Valovirta, 2006[59] Savolainen 2006[60]	Tree mix	SLIT high dose SLIT low dose Placebo	Peak season	Unspecified	0-8		4.5 5.5 6.5	SLIT high vs placebo p=0.06 whole season, p=0.04 during peak season; SLIT low vs placebo p=0.72 whole season, p=0.83 during peak season
De Blay, 2007[61]	Grass mix	SLIT Placebo	10 months	Medication scores. 0-5 points per dose	0-66		7.18 +/- 11.6 9.15 +/- 10.8	SLIT vs Placebo p=0.11

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Novembre, 2004[26]	Grass Mix	SLIT Conventional ther	3 years	Medication score	1 per medication	NR	NR	SLIT vs Conventional p=0.02
Tari, 1990[46]	Dust mite	SLIT Placebo	18 months	Medication score				20% reduction of in medicine consumption in active group No changes in placebo
Pozzan 2010[62]	Alternaria	SLIT; placebo	3 years	1 point per med use, except 2 points for oral corticosteroid/ per day. One extra point added if meds used >20 days during peak exposure		4.3 3.5	1.7 4.0	SLIT vs Placebo p=0.0001

NS: Not significant

TABLE E9.- COMBINED SYMPTOM AND MEDICATION SYMPTOM SCORES -SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Purello-D'Ambrosio 1999[1]	Parietaria	SLIT Placebo	10 months	Nasal, eye, bronchial symptoms plus medication	0-27	NR NR	NR NR	SLIT vs Placebo p=0.04 45% improvement over placebo
Cortellini 2010 [4]	Alternaria	SLIT placebo	10 months	Eye, nose, asthma symptoms plus medication		NR	NR	SLIT vs Placebo p=0.01
Sambugaro 2003[9]	Dust mite, grass mix, ragweed, parietaria	SLIT 8 day induction SLIT 15 day SLIT 20 day Conventional therapy	2 years	Allergic symptoms, plus amount of medication	0-6	5 5 5 5	3.1 2.1 1.9 5.25	All SLIT arms pre/post treatment p<0.0001 (48-50% reduction), All SLIT arms vs placebo p=0.0001 (51-55% reduction)

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Horiguchi, 2008[10]	Japanese Cedar	SLIT placebo	7 months	Nasal symptoms plus medication	NR	NR NR	1.2 1.7	SLIT vs Placebo p<0.001
Okubo, 2008[11]	Japanese cedar	SLIT placebo	End of season (april)	Nasal symptoms plus medication	NR	NR NR	NR NR	SLIT vs Placebo NS
Fujimura 2011[12]	Japanese Cedar	SLIT placebo	20 months	0-4 nasal sx plus 0-2 per medication used per day	NR	NR	NR	Total SMS: SLIT vs Placebo NS (exact p value is not given, only NS) Peak season: SLIT vs Placebo p=0.02
D'Ambrosio, 1996[17]	Parietaria	SLIT Conventional therapy	8 months	Nasal, eye, bronchial symptoms plus medication	NR	NR NR	5247 7158	SLIT vs conventional P=0.037 during peak season
Skoner, 2010[21]	Ragweed	SLIT –high dose SLIT-medium does Placebo	17 weeks	Nasal, ocular symptoms plus medication		NR NR NR	0.19 +/- 2.32 0.63 +/- 2.02 1.63 +/- 2.99	SLIT high vs Placebo p =0.02, SLIT low vs Placebo NS
Di Rienzo, 2006[22]	Mountain Cedar	SLIT Placebo	0-12	Nasal, ocular symptoms plus medication		NR NR	NR NR	SLIT vs Placebo NS
Makino, 2010[23]	Japanese Cedar	SLIT Placebo	5 months	Nasal symptoms plus medications	NR	NR NR	122 166	SLIT vs Placebo NS
Novembre, 2004[26]	Grass Mix	SLIT Conventional therapy	3 years	Nasal, eye, bronchial symptoms plus medication	NR	NR NR	NR NR	SLIT vs Conventional NS
Ott, 2008[27] Sieber 2012[28]	Grass mix	Placebo SLIT	18 months	Nasal, eye, bronchial symptoms, plus medications		0.97 1.28	-1.76 -1.19	SLIT vs Placebo NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Marogna, 2007[40]	Birch, Grass, Birch plus Grass	SLIT Birch SLIT Grass SLIT Birch + Grass Conventional Therapy	End of season 4	Nasal, eye, bronchial symptoms, plus medications				All SLIT Arms: pre versus post–treatment intra-group comparison, p <0.05
Marogna, 2008[41]	Dust mite, birch, grass mix, parieteria	SLIT Placebo	3 years	Nasal, eye, bronchial symptoms, plus medications	0-750	140 145	40 100	SLIT vs Placebo P<0.001
Moreno-Ancillo, 2007[42]	Grass Mix and Olive	SLIT Placebo	10 months	Nasal, eye, bronchial symptoms plus medication	NR	1.89 1.76	1.23 1.10	SLIT vs Placebo NS
Guez, 2000[48]	Dust mite	SLIT Placebo	2 years	Nasal symptoms plus medications		13.0 14.3	6.4 9.2	SLIT pre vs post p <0.01 Placebo pre vs post p< 0.01
Marogna 2010[49]	Dust mite (PD20 is inclusion criteria)	SLIT 3 yrs; SLIT 4 yrs; SLIT 5 yrs.	15 years	Nasal, chest, eye, 0-3 per symptoms; 0-1 per med		417 383 412	<u>5 yr, 20 yr:</u> 100, 250 125, 80 140, 40	P values not reported (Note: values abstracted at of 5 years, then at year 20 before 2nd course of SLIT started in some groups)
Passalacqua 1999[52]	Parietaria	SLIT Placebo	8 months	Nasal, eye, bronchial symptoms plus medication		417.1 403.5	231.5 274.3	SLIT pre vs post p =0.006, Placebo pre vs post p›0.046
Voltolini 2001 [32]	Alder, birch, hazel	SLIT medications	2 yrs	Medication, eye, nasal, chest symptoms		NR NR	134.04 272.2	SLIT vs Meds p›0.002
Pajno 2011[55]	Grass Mix	Cont SLIT Co-seasonal SLIT	3 yrs	0-3 per symptom (nose, chest, eye), 1 point topical med, 2 point systemic med per day	% reduction from baseline	NR	70% reduction 55% reduction	Cont vs coseasonal NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Pfaar, 2008[57]	Grass mix	Placebo SLIT	1.5 years	Nasal, eye, bronchial symptoms plus medication		527 442	214 453 9.15 +/- 10.8	SLIT vs Placebo p= 0.002

TABLE E10.- ALLERGY CHALLENGES AND FUNCTIONAL OUTCOMES: PFT -SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Tahamiler, 2007[14]	Dust mite	SLIT 2 years SLIT 3 years	6 years after start; end of second year, end of 3rd year	nasal provocation modified form of the end-point titration method described by Gerth van Wijk	0-3	1.8806 +/- 0.99 1.9515 +/- 0.85	0.4925 +/- 0.92 0.1702 +/- 0.59	SLIT pre vs post p<0.05 Placebo pre vs post p<.005
Amar, 2009[36]	Timothy	SLIT mono SLIT multi Placebo	15 months	nasal provocation	0-5	1.9 1.7 2.3	2.5 2.2 2.1	SLIT mono vs Placebo p =0.03 SLIT multi vs Placebo p=0.11
Hirsch, 1997[43]	Dust mite	SLIT Placebo	1 year	nasal provocation (acoustic rhinometry)	SBU/ml 40% reduction nasal flow	1240 470	1380 1790	SLIT pre vs post p <0.001 Placebo pre vs post NS SLIT vs Placebo NS
Passalacqua 1999[52]	Parietaria	SLIT Placebo	End of pollen season (8 months)	nasal provocation ASNC	0-12	8 8	4 6.5	SLIT pre vs post p<0.001 Placebo pre vs post p <0.01 SLIT vs Placebo p =0.0001
Alvarez-Cuesta, 2007[63]	cat	SLIT Placebo	1 year	nasal provocation natural challenge test (cat room), 5 assessments in 90 minutes	0-9	317.06 312.50	151.62 52% improvement 317.97	Arm 1 Vs. Arm 1 p =0.002 Arm 2 Vs. Arm 2 p =0.959 SLIT vs Placebo p =0.002

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
La Rosa 1999[18] Leonardi 2009[19]	Parietaria	SLIT Placebo	2 years	ocular conjunctival provocation test	0-3	NR NR	NR NR	SLIT vs Placebo p =0.02
Lima, 2002[25]	Timothy	SLIT Placebo	18 months; at peak season	ocular provocation challenge scores		NR NRl	3200 3200	SLIT vs Placebo p=0.18
Alvarez-Cuesta, 2007[63]	cat	SLIT Placebo	1 year	ocular provocation challenge natural challenge test (cat room) at 5 times in 90 minutes	0-6	91.91 93.44	19.71 71% improvement 68.13	SLIT pre vs post p < 0.001 Placebo pre vs post p =0.33 SLIT vs Placebo p =0.118
Alvarez-Cuesta, 2007[63]	cat	SLIT Placebo	1 year	Bronchial symptoms challenge test (cat room) at 5 times in 90 minutes	0-9	174.41 160.00	45.74 68% improvement 143.44	SLIT pre vs post p=0.003 Placebopre vs post p=0.263 SLIT vs Placebo p=0.118
Lue, 2006[7]	Dust mite	SLIT Placebo	6 months	FEV1		75 (graph) 80 (graph)	90 (graph) 82 (graph)	SLIT pre vs post p = 0.001 Placebo Vs. Arm 2 p =0.48 SLIT vs Placebo p =0.93
Niu, 2006[8]	Dust mite	SLIT Placebo	24 weeks	FEV1		85 90	95 90	SLIT pre vs post p=0.048 SLIT vs Placebo NS
Ippoliti, 2003[64]	Dust mite	SLIT Placebo	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
Lue, 2006[7]	Dust mite	SLIT Placebo	6 months	FEV1				Pre/post treatment SLIT: PEFR in the evening improved p=0.0088, but not in am. FEV1 improved also p =0.01. No improvement in control group. However after treatment FEV1 SLIT compared to control there was no significant improvement.

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Lue, 2006[7]	Dust mite	SLIT Placebo	24 weeks	FEV1				pre/post tx SLIT: FVC p=0.042, FEV1 p=0.048, PEF0.001 improved; however, comparing SLIT to placebo there was no significant improvement in PFT
Sambugaro 2003[9]	Dust mite-grass mix-ragweed and Parietaria	SLIT/ 8-d induction SLIT/ 15-d induction SLIT/ 30-d induction	2 years	FEV1				All 3 SLIT arms had improvement FEV1 pre/post tx p<0.05
Marogna, 2004[39]	Dust mite, birch, grass mix, parietaria, mugwort	SLIT Pharmaco-therapy	3 years	Metacholine challenge				pre/post tx SLIT: significant reduction in M CH positive cases; not significant in controls
Marogna, 2007[40]	Birch and Grass	SLIT Birch SLIT Birch+Grass	4 years	Metacholine challenge				Pre/post all SLIT groups had significant improvement in methacholine challenge,but not in controls; FEV1 significant improvement in birch p
Marogna, 2008[41]	Birch and Grass	SLIT Pharma-cotherapy	3 years	Metacholine challenge				SLIT pre/post number of subjects significantly decreased p<0.001, controls pre/post p NS
Alvarez-Cuesta, 2007[63]	cat	SLIT Placebo	1 year	Total symptoms natural challenge test (cat room) 5 assessments in 90 minutes	0-27	578.5 564.9	217.06 529.5	SLIT pre vs post p <0.001 Placebo pre vs post p NS SLIT vs Placebo p < 0.0001

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Marogna 2010[35]	Birch	SLIT Montelukast	5 years	Methacholine challenge PD 20; FEV1; MEF		FEV1 78.5(1.0); PD 20 326.4(50.1); MEF 58.1(2.0) FEV1 76.4 (1.3) PD20 288.6(44.9); MEF 64.3(2.1)	FEV1 96.2(1.2); PD20 919.3(85.7); MEF 85.5(2.2) FEV1 81.2(1.4); PD20 478.7 (76.2); MEF 67.7(1.8)	FEV1: SLIT vs Mont p<0.0001 PD20: SLIT pre vs post p<0.001; Mont pre vs post p=0.019 SLIT vs Mont p=0.001 MEF: SLIT vs Mont p<0.0001
Voltolini 2001 [32]	Alder, birch, hazel	SLIT medications	2 yrs	Nasal provocation,		NR	NR	SLIT vs Meds NS
Voltolini, 2010[34]	Birch	SLIT Placebo	2 years	GINA Asthma severity				SLIT vs placebo post tx: GINA asthma severity decreased (p<0.05)
Marogna, 2009[37]	Grass mix	SLIT Inhaled Corticosteroids	5 years	PD20				post tx SLIT vs controls: significant difference in PD20
Stelmach 2011[38]	Grass mix	SLIT pre-coseasonal SLIT continuous placebo	2 years (2010)	FEV1		98.3(2.8 SEM) 101.9(2.4) 99.7(2.4)	100.2(2.9) 102.8(2.7) 102.3(1.9)	P values not reported
Bush 2011[45]	Dust mite	SLIT High dose; SLIT low dose; placebo	12-18 months	PD20 with antigen challenge		70 ±18 NR NR	101+13 NR NR	SLIT high vs Placebo p=0.04 SLIT low vs Placebo NS
Tari, 1990[46]	Dust mite	SLIT Placebo	12 months	FEV1 Metacholine challenge		SLIT group 280.8 +/- 16.4	SLIT group 502 +/- 26.6	SLIT pre/post p< 0.05
Marogna 2010[49]	Dust mite (PD20 is inclusion criteria)	SLIT 3 yrs; SLIT 4 yrs; SLIT 5 yrs.	15 years	PD20 (methacholine challenge)		163.6 124.0 250.5 significantly different at baseline	1025 1020 1070	SLIT 3y pre vs post: Signficance lost after yr 8, SLIT 4y pre vs post <0.05; SLIT 5y pre vs post p <0.05

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

TABLE E11.- QUALITY OF LIFE- SLIT

Study	ARMS	QOL
O'Hehir 2009[44] O'Hehir 2009[44]	SLIT Placebo	RQLQ significantly improved SLIT pre versus post-treatment score, p <0.01
Okubo, 2008[11]	SLIT Placebo	Japanese Allergic Rhinitis QOL standard questionnaire. The scores are significantly lower in the SLIT group at the end of study, p<0.05
Fujimura 2011[12]	SLIT Placebo	JRQLQ: SLIT vs Placebo p<0.01
deBot 2011[16]	SLIT placebo	PRQLQ - Adol RQLQ
Skoner, 2010[21]	High dose SLIT Medium dose SLIT Placebo	RQLQ RQLQ RQLQ
Di Rienzo, 2006[22]	SLIT Placebo	RQLQ scores were 1.13 +/-1.41 before SLIT and 0.50 +/- 1.52 after SLIT in actively treated patients (P = 0.017), and 0.90 +/- 1.40 before SLIT and 1.83 +/- 1.14 after SLIT in placebo-treated patients. Inter-group comparison, the RQLQ score was comparable before SLIT in the groups, while a significant difference was found in favor of actively treated patients compared with placebo in the cypress pollen season after SLIT (P = 0.02)
Makino, 2010[23]	SLIT Placebo	Japanese Juniper RQLQ; 9/5 +/- 8.3 when compared to placebo p=0.048 15.9 +/- 19.6
Voltolini, 2010[34]	SLIT Placebo	mean number of days with asthma during the second pollen season: 2 mean number of days with asthma during the second pollen season: 7 p<0.05
Moreno-Ancillo, 2007[42]	SLIT Placebo	Overall QOL improved in all areas p=0.006 QOL improved in all areas p=0.260
De Blay, 2007[61]	SLIT Placebo	At the end of the study, overall QoL scores were better for the SLIT group than the placebo group (least-square mean value, 1.35 vs 1.80; P = .07). The QoL score for “nasal discomfort” at the last visit was also better for the SLIT group (least-square mean value, 1.82 vs 2.37; P = .08), although not significantly.

TABLE E12.- SECONDARY OUTCOMES -SLIT

Study	ARMS	Adherence	Disease modification	Prevention of asthma	Development of new sensitivities
Cortellini 2010 [4]	SLIT Alternaria placebo	85-95% adherence determined by volume of extract in returned vials			
Niu, 2006[8]	SLIT Placebo	NR	At baseline 0 and 49 subjects had intermittent and mild/moderate asthma respectively. At 24 weeks the numbers changed to 26 and 23 respectively At baseline 0 and 48 subjects had intermittent and mild/moderate asthma respectively. At 24 weeks the numbers changed to 19 and 29 respectively. (between group comparison, p value = 0.043)	NR	NR
deBot 2011[16]	SLIT placebo	Post score SLIT 0.93, placebo 0.91 Post score SLIT 0.93, placebo 0.90	SLIT vs Placebo NS SLIT vs Placebo NS	NR	NR
Skoner, 2010[21]	SLIT High dose SLIT Medium dose Placebo	91.6 +/- 9.7 93.1 +/- 7.8	NR	NR	NR
Novembre, 2004[26]	SLIT Control	NR	NR	At the end of study 8 developed asthma At the end of study 18 developed asthma	NR
Marogna 2010[35]	SLIT Monteleukast	SLIT adherence >80% in 10 patients, >60% in 5 patients; Monteleukast adherence >80% 14 pts.	NR	NR	NR
Marogna, 2009[37]	SLIT Placebo	more than 80% in 17/23 patients and more than 60% in 4/23 patients more than 80% in all patients	NR	NR	NR
Marogna, 2004[39]	SLIT Control	>80% in 195/271, 60-80% in 49/271 and poor in 27/271 Not reported	NR	NR	16/271 had new skin sensitizations 64/170 (intergroup comparison p<0.001)

Study	ARMS	Adherence	Disease modification	Prevention of asthma	Development of new sensitivities
Marogna, 2008[41]	SLIT Control	NR	NR	lower occurrence of persistent asthma in SLIT (2/130) than in control (19/66). There was also more frequent intermittent and persistent asthma in the control group (30/66) than SLIT (17/130)	4/130 23/66 ; OR= 0.06
Moreno-Ancillo, 2007[42]	SLIT Placebo	NR	VAS p=0.006 VAS p=0.184	NR	NR
Hirsch, 1997[43]	SLIT Placebo	8/15 were compliant 10/15 were compliant	NR	NR	NR
Tabar, 2005[70]	Cluster Conventional	5 didn't complete initial phase 4 didn't complete initial phase	NR	NR	NR
Marogna 2010[49]	SLIT 3 yrs, SLIT 4 yrs, SLIT 5 yrs.	NR	NR	NR	New sensitivities: SLIT 3--21.4%, SLIT 4—12.5%, SLIT 5 11.7%
Pfaar 2008[57]	SLIT Placebo	18.1% discontinued 10.9% discontinued Compliance: The mean percentage of days with 100% dose intake of study medication was 85% in the active group and 94% in the placebo group.	NR	NR	NR
Valovirta 2006[59] Savolainen 2006[60]	SLIT dose 1 SLIT dose 2 Placebo	NR	NR	After a follow up for 5 years asthma developed in: 2/10 children. 6/10 children 6/10 children	NR
Yonekura, 2010[67]	SLIT Placebo	NR	Severity of asthma reduced in 2/8 patients; atopic dermatitis in 1/5 Severity of asthma reduced in 3/7 patients; atopic dermatitis in 0/2	NR	NR

QOL:QUALITY OF LIFE, VAS: VISUAL ANALOG SCALE, RQLQ

TABLE E13.- BIOMARKERS –SLIT

a) IgG

Study	Arms	Total IgG	IgG4
Amar 2009[36]	Timothy Monotherapy		increased by .05; p = 0.005
Amar 2009[36]	Multiallergen therapy		increased by .03; not significant
Amar 2009[36]	Placebo		decreased by 0.01; NS. Significant difference among all 3 arms (p =0 .02)
Bowen, 2004[20]	SLIT		Significantly increased (p < .001) compared to placebo
Bowen, 2004[20]	Placebo		Reported
D'Ambrosio 1996 [17]			No statistically significant change could be detected in specific IgG4 in either group.
De Blay 2007[61]	SLIT		Reported: no change
De Blay 2007[61]	Placebo		Reported: no change
De Blay 2007[61]			Baseline specific IgG4 antibodies at inclusion showed a significantly (P = 0.03) higher baseline level for the SLIT group. This difference was more marked at the end of the study. The IgG4 antibody level increased from 0.42 +/- 0.48 to 0.80 +/- 0.92 mg/L for the SLIT group and remained unchanged (0.27 +/- 0.32 vs 0.26 +/- 0.27 mg/L) for the placebo group (P = 0.001) . The Spearman rank correlation between the anti-Dactylis specific IgG4 level at the end of the study and the cumulative IR dose during the treatment period approached significance for the SLIT group (r = 0.26, P =0.08) but not for the placebo group (r = 0.02, P = 0.87).
Guez 2000[48]	Active SLIT		no change
Guez 2000[48]	Placebo		Reported: no change
Hirsch 1997[43]	SLIT	Reported: NS	
Hirsch 1997[43]	Placebo	Reported: NS	Reported: decreased, p<0.05
Hordijk 1998[13]	SLIT	significantly higher than placebo	no significant change from baseline
Hordijk 1998[13]	Placebo	increased significantly	no significant change from baseline
Horiguchi, 2008[10]	SLIT		increased significantly in the active group but not in the placebo and the a significant difference was observed between the groups (p<0.05)
Horiguchi, 2008[10]	Placebo		no change
La Rosa 1999[18] Leonardi 2009[19]	SLIT		significant increase in levels after 2 yrs (p=0.02)
La Rosa 1999[18] Leonardi 2009[19]	Placebo		no significant change in levels
Lima 2002[25]	SLIT		increased
Lima 2002[25]	Placebo		no change

Study	Arms	Total IgG	IgG4
Lue 2006[7]	SLIT		Statistically significant increase within group and when compared to placebo p=0.026
Lue 2006[7]	Placebo		no major change
Mauro, 2007[72]	SLIT		increase, not significant
Mungan, 1999[73]	SLIT		there was a significant increase in levels at the 12th month following therapy, p<0.05
Nelson, 1993[3]	SLIT	mean values before and after treatment are 2.7+/-0.13 and 2.81+/-0.16 (arbitrary units) respectively (p value=NS) No effect of treatment on IgG levels.	
Cortellini 2010 [4]			No significant difference between groups
Nelson, 1993[3]	Placebo	mean values before and after treatment are 2.57+/-0.13 and 2.58+/-0.11 (arbitrary units) respectively (p value=NS)	
O'Hehir, 2009[44] O'Hehir 2009[44]	SLIT		Mean Der p1 baseline value=596, at 1 year= 800, Mean Der p2 baseline value=274, at 1 year= 528 p values for between group comparisons: IgG4 Der p1= 0.57, IgG4 Der p2= 0.17
O'Hehir, 2009[44] O'Hehir 2009[44]	Placebo		Mean Der p1 baseline value=82, at 1 year= 279, Mean Der p2 baseline value=31, at 1 year= 99
Bush 2011[45]	High dose; Low dose; placebo		IgG4 significantly increase in Arm 1 compared to placebo. No significant change in low dose group
Ott, 2008[27] Sieber 2012[28]	SLIT-rush		At follow-up: 0.02 +/- 0.30
Ott, 2008[27] Sieber 2012[28]	Placebo		At follow-up: -0.03 +/- 0.10 (between groups p value= 0.518)
Pajno 2000[2]	SLIT	Mean at baseline: 33.0, after 2 years: 31.3	Mean at baseline: 2.85, after 2 years: 2.53
Pajno 2000[2]	Placebo	Mean at baseline: 26.0, after 2 years: 31.9, Between group differences NS	Mean at baseline: 2.7, after 2 years: 2.66, Between group differences NS
Panzner 2008[29]	SLIT	Baseline: 27.13+/- 17.46, End of 1 yr: 47.82+/- 13.68 (pvalue: 0.0240)	
Panzner 2008[29]	Placebo	Baseline: 56.97+/- 22.79, End of 1 yr: 67.67+/- 21.49 (pvalue: 0.3038)	
Pajno 2011[55]			Both groups had significant increase in specific IgG4 at end of study compared to baseline
Pfaar 2008[57]	SLIT	Other lab measure reported was IgG1 values. At end of 1.5 years SLIT vs Placebo: p value <0.001	at end of 1.5 years SLIT vs Placebo: p value <0.001
Pradalier 1999[58]	SLIT		Baseline: 5.7+/- 3.8%; end of study: 8.7+/- 10.9% (p<0.0001)
Pradalier 1999[58]	Placebo		Baseline: 6.0+/- 3.3%; end of study: 6.8+/- 4.5% (p=0.002) Between group comparison p<0.03

Study	Arms	Total IgG	IgG4
Purello-D'Ambrosio 1999[1]	SLIT		Baseline: 2.52+/- 0.333; 10 months: 2.57+/- 0.411 (p=0.7798)
Purello-D'Ambrosio 1999[1]	Placebo		Baseline: 2.6637+/- 0.6637 ; 10 months: 2.5850+/- 0.704 (p=0.3519)
Quirino, 1996[75]	SLIT	Reported, no change	significant difference before and after
Skoner, 2010[21]	High dose SLIT	mean change: 2.29 +/- 3.97	mean change: -0.09 +/- 0.77
Skoner, 2010[21]	Medium dose SLIT	mean change: 1.69 +/- 3.98	mean change: 0.64 +/- 1.65
Skoner, 2010[21]	Placebo	mean change: -0.08 +/- 1.81	mean change: -0.09 +/- 0.77
Stelmach, 2009 [5] Penagos 2008[6]	SLIT		0.31 µg/ L
Stelmach, 2009 [5] Penagos 2008[6]	Placebo		0.25 µg/L
Tari 1990[46]	SLIT	5.23 +/- 3.1 significant increase p<0.001.	10.71 +/- 3.81
Tari 1990[46]	Placebo	2.32 +/- 1/42 no change	2.78 +/- 2.02
Troise 1995[68]	SLIT	(%) 32.6+/- 12.7 before 34.6 +/-7.9 after	(%) 20.7 +/- 5.4 before 27.8 +/-8.2 after
Troise 1995[68]	Placebo	(%) 28.2+/- 5.2 before 28.1 +/-10.1 after	(%) 23 +/-7.4 before 28.2 +/-7.1 after
Tseng 2008[15]	SLIT		change from baseline to 24th week 772.9 +/- 1,002.8 p-value: <0.001
Tseng 2008[15]	Placebo		change from baseline to 24th week -92.4 +/- 290.1 change from baseline to 24th week 772.9
Vervloet 2007[53]	SLIT		Baseline: 171.8+/- 74.3, after treatment: 481.6 +/- 623.4
Vervloet 2007[53]	Placebo		Baseline: 198.0+/- 165.3, after treatment: 267.1 +/- 370.4 (p value :0.03)
Vourdas 1998[54]	SLIT		After an initial increase in specific IgG4 during the first pollen season, the values decreased in both groups.

b) IgE

Study	Arms	IgE
Amar 2009[36]	Timothy Monotherapy	Mean IgE baseline**:** 0.93 increased by .07; p = 0.02
Amar 2009[36]	Multiallergen therapy	Mean IgE baseline: 0.93 increased by .10; p = 0.008
Amar 2009[36]	Placebo	Mean IgE baseline: 0.81 decreased by .06; NS. Significant difference among all 3 arms (p = .02)
Bahceciler 2001[47]	SLIT	pre: median 420 (range 42-2751); post: 295 (40-1701) Total IgE levels were reported but no significant difference was found
Bahceciler 2001[47]	Placebo	pre: median 405 (range:197-5967); post: 536 (166-3948)
Bowen, 2004[20]	SLIT	Mean IgE baseline**:** 15.9. Significantly increased (p < .001) compared to placebo
Bowen, 2004[20]	Placebo	Mean IgE baseline: 16.9

Study	Arms	IgE
D'Ambrosio 1996 [17]		No statistically significant change could be detected in specific IgE in either group.
Eifan 2010[71]	SLIT	Df = 51.1; Dpt = 59.4. Significant decrease on IgE D.f at 12 months (p=0.04)
Guez 2000[48]	Active SLIT	Mean IgE baseline **:** 25.3 (derp) 18.8 (derf) . Decreased slightly at the end
Guez 2000[48]	Placebo	Mean IgE baseline: 37 (derp) 31 (derf) . Decreased slightly at the end
Hirsch 1997[43]	SLIT	Mean IgE baseline39.1 kU/l Increased more than placebo, P<0.01
Hirsch 1997[43]	Placebo	Mean IgE baseline:33.3 kU/l Increased, p<0.01
Hordijk 1998[13]	SLIT	no significant change from baseline
Hordijk 1998[13]	Placebo	no significant change from baseline
Horiguchi, 2008[10]	SLIT	Mean IgE baseline: 4.18 (cedar pollen RAST) no change at the end
Horiguchi, 2008[10]	Placebo	Mean IgE baseline**:** 4.14 (cedar pollen RAST) no significant change from baseline
La Rosa 1999[18] Leonardi 2009[19]	SLIT	Reported no significant difference between the groups
La Rosa 1999[18] Leonardi 2009[19]	Placebo	no significant change from baseline
Lima 2002[25]	SLIT	Mean IgE baseline**:** 250 KU/L +/-257. No significant change from baseline
Lima 2002[25]	Placebo	Mean IgE baseline **:** 189 KU/L +/-251. No significant change from baseline
Lue 2006[7]	SLIT	Mean IgE baseline **:** 500 IU/L. Increased within group, not statistically significant when compared with placebo
Lue 2006[7]	Placebo	Mean IgE baseline**:** 400 IU/L. No significant change from baseline
Mauro, 2007[72]	SLIT	Mean IgE baseline**:** 52.8 kU/L Reported increase from baseline
Mungan, 1999[73]	SLIT	Mean IgE baseline**:** 311.89 (kU/L) Reported No changes observed in IgE levels in the 6th and 12th months of therapy compared to baseline
Mungan, 1999[73]	Placebo	Mean IgE baseline **:** 288.40 (kU/L) No changes observed in IgE levels in the 6th and 12th months of therapy compared to baseline
Nelson, 1993[3]	SLIT	Mean IgE baseline **:** 0.86 (PRU) +/-0.36 mean values before and after treatment are 0.86+/-0.36 and 1.00+/-0.35 PRU respectively (p value=NS)
Cortellini 2010 [4]		Specific IgE significant increase in slit vs placebo.
Nelson, 1993[3]	Placebo	mean values before and after study are -0.12+/-0.27 and 0.05+/-0.32 PRU respectively (p value=NS) no effect of treatment IgE levels.
Niu 2006[8]	SLIT	Mean IgE baseline**:** 829.8. The change in total IgE from baseline to 24 weeks is 129.7 +/- 460.6, Specific IgE was reported, no significant change.
Niu 2006[8]	Placebo	Mean IgE baseline**:** 780.6 The change in total IgE from baseline to 24 weeks is - 85.1 +/- 59.8 (group difference, p value= 0.063)
O'Hehir, 2009[44] O'Hehir 2009[44]	SLIT	Mean Der p1 baseline value=7, at 1 year= 10, Mean Der p2 baseline value=26, at 1 year= 31 p values for between group comparisons: IgE Der p 1= 0.40, IgE Der p 2= 0.25
O'Hehir, 2009[44] O'Hehir 2009[44]	Placebo	Mean Der p1 baseline value=32, at 1 year= 28, Mean Der p2 baseline value=8, at 1 year= 6

Study	Arms	IgE
Bush 2011[45]	High dose; Low dose; placebo	Specific IgE no significant change over study
Ott, 2008[27] Sieber 2012[28]	SLIT-rush	Mean IgE baseline **:** 13.35 At follow-up: 5.74 +/- 16.88
Ott, 2008[27] Sieber 2012[28]	Placebo	Mean IgE baseline**:** 7.78 At follow-up: 2.02 +/- 9.78 (between groups p value= 0.2578)
Sieber 2012[28]	None reported	Baseline: SLIT specific IgE 27; placebo 29 No significant difference in baseline values SLIT: total IgE 198; placebo 258
Pajno 2000[2]	SLIT	Mean IgE baseline **:** 45.4 Mean at baseline: 45.4, after 2 Baseline: 52.2, after 2 years: 65.3, Between group differences NS years: 52.6
Pajno 2000[2]	Placebo	Mean IgE baseline **:** 52.2 Mean at baseline: 52.2, after 2 years: 65.3, Between group differences NS
Panzner 2008[29]	SLIT	Mean IgE baseline: 20 Baseline: 57.04+/- 19.8, End of 1 yr: 57.69+/- 17.63 (pvalue: 0.3683). Between group comparisons: p value Sublingual active vs placebo: 0.1994
Panzner 2008[29]	Placebo	Mean IgE baseline: 15 Baseline: 47.21+/- 14.79, End of 1 yr: 53.48+/- 20.81 (pvalue: 0.1373)
Pajno 2011[55]		Baseline specific IgE: Arm 1- 11.2, Arm 2- 9.9
Pfaar 2008[57]	SLIT	there was no consistent trend for change in either group
Pradalier 1999[58]	SLIT	Mean IgE baseline: 91.3 Baseline: 91.3+/- 239.9; end of study: 244.5+/- 459.1 (p<0.0001)
Pradalier 1999[58]	Placebo	Mean IgE baseline **:** 78.8 Baseline: 78.8+/- 105.9; end of study: 144.0+/- 231.0 (p<0.0001) between group comparison p<0.04
Purello-D'Ambrosio 1999[1]	SLIT	Baseline: 14.058+/- 14.136; 10 months: 19.304+/- 24.763 (p value=0.0277)
Purello-D'Ambrosio 1999[1]	Placebo	Baseline: 17.42+/- 13.12; 10 months: 22.19+/- 20.295 (p=0.034)
Quirino, 1996[75]	SLIT	significant difference before and after
Scadding, 1986 [76]	SLIT	Reports pre and post values for each patient
Skoner, 2010[21]	High dose SLIT	mean change: 19.75 +/- 56377
Skoner, 2010[21]	Medium dose SLIT	mean change: 25.93 +/- 52.83
Skoner, 2010[21]	Placebo	mean change: 2.55 +/- 4.14
Stelmach, 2009 [5] Penagos 2008[6]	SLIT	Mean IgE baseline 549.3 (kU/L) Post 496.4 kU/L
Stelmach, 2009 [5] Penagos 2008[6]	Placebo	Mean IgE baseline **:** 424.6 (kU/L) Post: 503.4 kU/L
Tari 1990[46]	SLIT	Reported no change

Study	Arms	IgE
Tari 1990[46]	Placebo	Reported significant rise
Troise 1995[68]	SLIT	Reported (total kU/l) 209+/- 238 before 232 +/-236 after
Troise 1995[68]	Placebo	Reported (total kU/l) 182+/- 150 before 190 +/-126 after
Tseng 2008[15]	SLIT	Mean IgE baseline: Der p: 129, Der f: 170 change from baseline to 24th week s 49.0 +/- 73.9 p value: 0.002
Tseng 2008[15]	Placebo	Mean IgE baseline: Der p: 98, Der f: 119 change from baseline to 24th week is 21.0 +/- 46.7 p-value: 0.018
Vervloet 2007[53]	SLIT	Mean IgE baseline **:** 18.9 specific (not total) IgE to Juniperus Baseline specific IgE: 9.1+/- 11.1, after treatment: 38.8 +/- 35.1
Vervloet 2007[53]	Placebo	Mean IgE baseline: 23.3 Baseline: 11.3+/- 14.4, after treatment: 20.4 +/- 23.4 (p value :0.04)
Vourdas 1998[54]	SLIT	No significant changes in specific IgE was detected.

c) Other Markers

Study	Arms	COMMENTS
Horiguchi, 2008[10]	SLIT	The Th1/Th2 levels, IL-4 and IL-5 are reported
Ippoliti, 2003[64]	SLIT	The other lad measures reported are CD40+ Bcells, serum ECP, IL-13 and ACTH levels.
Lima 2002[25]	SLIT	IL-12 mRNA levels reported in sublingual biopsies
Marogna 2005[33]	SLIT	eosinophil counts 61% of patients had no eos in nasal smear in SLIT vs 14% in placebo p <0.01
Marogna, 2007[40]	SLIT	Nasal eosinophils: At 3 years Nasal eos change in control group NS. In Birch alone p<0.05, In grass alone p<0.01, in birch-grass group p<0.05
Passalacqua 1999[52]	All study	Neutrophils, eosinophils and ICAM expression on nasal epithelium (early inflammation is reduced after SLIT, p= 0.05 for neutrophils and ICAM)
Valovirta, 2006[59] Savolainen 2006[60]	All study	Reported in Savolainen 2006: originally 5016. IL-10 values reported at 2 years. IL-5 values also reported. This is a subset of the original study, with 10 patients from each arm. Allergen and PPD induced FOXP3 mRNA, IL-17, IL-23 and IL-27 expression has been evaluated.

TABLE E14. SAFETY -SLIT

a)SLIT LOCAL REACTIONS

Study	SLIT Allergen	Number of Patients in Arm	Number of events and description	% of patients	Severity
O'Hehir, 2009[44]	Dust mite	15	8 patients experienced mild immediate mouth and/or throat itchiness resolving spontaneously or with antihistamines, usually within 5 minutes	60%	Mild
O'Hehir 2009[44]	Placebo	15	1 patient experienced mild immediate mouth and/or throat itchiness resolving spontaneously or with antihistamines, usually within 5 minutes.	7%	Mild

Study	SLIT Allergen	Number of Patients in Arm	Number of events and description	% of patients	Severity
Pajno, 2000[2]	Dust mite	12	2 patients presented local delayed reactions: one case of swelling of the mouth, lips, and face (at 2 h) and one case of itching of the mouth (at 3 h). Resolved spontaneously without drugs	16%	Mild
Tahamiler, 2007[14]	Dust mite (AE reported in total)	181	94 patients complained of oral pruritus.	52%	Mild
Marogna, 2004[39]	Dust mite, Birch, Weed mix, Grass mix	319	3 dropouts because of oral itching	0.9%	Unspecified
Marogna, 2008[41]	Dust mite, Birch, Parietaria, Grass mix	144	1 dropouts because of oral itching	0.6%	Unspecified
Bush 2011[45]	High dose SLIT Low dose SLIT Placebo (Dust mite)	19 17 17	4 patients presented local events in the high-dose SLIT group, 3 patients presented local events in the low-dose SLIT group 2 patients presented local events in placebo group Mouth and throat irritation were the most commonly reported local AEs. Most of these events occurred during the maintenance phase. Only 2 events occurred during the escalation phase (1 in the high-dose group, 1 in the low-dose group).	21% 18% 12%	Mild Mild Mild
Marogna 2010[49]	SLIT 3yrs (Dust mite) SLIT 4 yrs (Dust mite) SLIT 5 yrs (Dust mite)	19 21 17	5 patients (2 in the SLIT3 group, 1 in the SLIT4 group, and 1 in the SLIT5 group) had transient oral itching during the build-up phase.	9%	Mild
deBot 2011[16]	Dust mite placebo	125 126	14 patients reported local adverse events 18 patients reported local adverse events Local events : oral pharyngeal irritation/swelling	11.2% 14.3%	Unspecified Unspecified
Hirsch, 1997[43]	Dust mite Placebo	15 15	5 patients reported local events. 1 patient required dose reduction. 1 patient reported local events. Local events defined as swelling, reddening, and tingling of the tongue, buccal mucosa and/or gingiva within less than 30 minutes of application.	33% 6%	Mild Mild
Rodriguez, 2006[65]	Dust mite + Grass mix-updosing Dust mite + Grass mix-no updosing	69 66	16 patients (28 events) had oral itching- 1 patient (2 events) had sublingual edema. 1 patient withdrew due to sublingual edema. 21 patients (39 events) had oral itching- 4 patient (7 events) had sublingual edema. 1 patient withdrew due to tongue and mouth edema.	23% 32%	Unspecified Unspecified
Guez, 2000[48]	Dust mite	36	2 patients reported local adverse reactions (mouth itching and burning	5.5%	Mild
Pfaar, 2008[57]	Grass mix Placebo	94 91	69 patients in the active group presented local events: Cases of hypersensitivity (predominantly oral allergy syndrome) :61.7% Oral paresthesia:13.8% - Throat irritation :10.6% 35 patients in the placebo group presented local events: Cases of hypersensitivity (predominantly oral allergy syndrome):19.8% Oral paresthesia: 5.5% - Throat irritation: 0%	73.4% 38.5%	Mild Mild

Study	SLIT Allergen	Number of Patients in Arm	Number of events and description	% of patients	Severity
Pradalier, 1999[58]	Grass mix	62	9 patients (eight adults and one child, 12 years old) presented local events: Minor buccopharyngeal effects; 4 occurrences of labial or buccal tickling after drops intake, and 5 occurrences of itching and edema in the oral cavity, they were mild and brief (maximum 90 min).	14.5%	Mild
De Blay, 2007[61]	Grass Mix Placebo	61 57	59 patients presented local AEs (27 had oral irritation, 22 had throat irritation and 10 had oral or lip edema) 11 patients presented local AEs (1 had oral irritation, 7 had throat irritation and 3 had mouth ulcers)	97% 19%	Unspecified Unspecified
Stelmach 2011[38]	Grass mix (SLIT arms reported together) placebo	40 20	18 patients reported local reactions such as sublingual itching 3 patients reported local reactions such as sublingual itching	45% 15%	Unspecified Unspecified
Novembre, 2004[26]	Grass mix	54	1 patient had itching in the throat that resolved without requiring treatment discontinuation.	0.2%	Mild
Hordijk, 1998[13]	Grass mix Placebo	27 30	3 patients presented local AEs 1 patient presented local AEs. Local reactions consisted of itching of the palate and tongue and did not require special treatment or a reduction of the dose.	11% 3%	Mild Mild
Panzner, 2008[29]	Grass mix Placebo	20 15	3 patients (11 events) had local events 1 patients (1 event) had local events Local adverse effects: undesirable taste, difficulty in swallowing, tongue or lips swelling, burning of the lips or mouth, itching of the tongue, throat or mouth.	15% 7%	Unspecified Unspecified
Sabbah, 1994[31]	Grass Mix Placebo	29 29	4 patients had buccopharyngeal pruritis 1 patient had buccopharyngeal pruritis	14% 3%	Mild Mild
Sieber 2012[28] Ott 2008[27]	 Grass Placebo	 142 67	In total, 65.7% of all patients (140/213) experienced a treatment-emergent AE; SLIT: 6 patients presented local reaction Placebo: 2 patients presented local events Local reactions defined as local itching and burning in the oral cavity and tongue.	 4% 3%	 Unspecified Unspecified
Amar, 2009[36]	Timothy single Timothy multiple Placebo	19 17 17	16 subjects experienced adverse events 11 subjects experienced adverse events. 1 subject dropped due to persistent lip and mouth swelling 1 subject experienced adverse events. Adverse events included itching, burning, irritation, numbness, tingling sublingually or in the mouth, swelling of the sublingual area or mouth, sore throat, cold sores.	84% 65% 6%	Mild Mild Mild
Horiguchi, 2008[10]	Japanese Cedar Placebo	43 24	11 patients subjects exhibited mild oral pruritus or oral pain 2 patients subjects exhibited mild oral pruritus or oral pain (Common Terminology Criteria for Adverse Event grade 1). All adverse effects were transient and resolved spontaneously.	26% 8%	Mild Mild
Okubo, 2008[11]	Japanese Cedar	37	6 patients presented mild mouth itching.	16%	Mild

Study	SLIT Allergen	Number of Patients in Arm	Number of events and description	% of patients	Severity
Di Rienzo, 2006[22]	Mountain Cedar Placebo	19 15	7 patients 3 patients Local adverse reactions, all slight-moderate , not requiring interruption of treatment. Reaction not defined.	36.8% 20%	Mild
Marogna, 2005[33]	Birch	39	Only 4 patients reported oral itching in the induction phase. This side effect was mild and required no treatment or dosage adjustment.	14%	Mild
Horak 1998[24]	Birch	21 20	2 patients reported itching tongue and mouth 2 patients reported itching tongue and mouth	9% 10%	Mild Mild
Vourdas, 1998[54]	Olive Placebo	33 29	8 patients presented local symptoms: 8 patients had buccal itching or oropharyngeal pruritus, 1 patient had labial swelling 2 patients presented buccal itching, labial swelling.	45% 7%	Mild Mild
Vervloet, 2007[53]	Bald Cypress Placebo	38 38	7 patients presented local events during rush phase- 3 patients during maintenance phase. 1 patient required dose reduction 5 presented local events during rush phase Local events: mouth itching, itching of ear, nose itching, nasal obstruction, tongue itching, face hot flush.	18% 13%	Unspecified Unspecified
Valovirta, 2006[59] Savolainen 2006[60]	 Tree mix-high Tree mix-low Placebo	 32 33 32	Oral local reactions 16 patients 12 patients 8 patients	 50% 36% 25%	 Unspecified Unspecified Unspecified
Marogna, 2007[40]	Birch Grass mix Birch + Grass mix	11 12 13	A mild oral itching was reported by 3 patients (1 in each SLIT group). No pharmacologic intervention or dose adjusting was required for these events.	9% 8.3% 7.7%	Mild Mild Mild
Bowen, 2004[20]	 Ragweed Placebo	 43 40	local intolerance 9 patients: tongue itch and swelling 13 patients; throat itch, swelling, or tightness	 21% 32.5%	Unspecified
Nelson 1993[3]	Cat Placebo	20 21	8 patients had pharyngeal pruritus 4 patients complained of pharyngeal pruritus	40% 19%	Mild Mild
Pozzan 2010[62]	Alternaria	34	6 patients reported side-effects; in general mild and transient (mouth itching, gastrointestinal discomfort). One of these six patients discontinued the SLIT treatment after 8 months of treatment. No serious adverse events were observed in the two groups.	17%	Mild

Study	SLIT Allergen	Number of Patients in Arm	Number of events and description	% of patients	Severity
Moreno-Ancillo, 2007[42]			Total: 106 adverse events in 34 patients (66.7%) in the active immunotherapy group and 24 reactions in 12 patients (24.5%) in the placebo group		
	Grass mix and Olive	51	33 patients-92 events: 65% of the patients (0.76% of the doses) had local AEs	65%	Mild
	Placebo	49	8 patients- 14 events: 16% of the patients (0.11% of doses) had local AEs,	16%	Mild
			The most frequent local reactions were aphthae, itching and/or irritation of the mouth and/or tongue, ear pruritus, and throat itching.		
			Most reactions appeared immediately, were of short duration, and resolved spontaneously without sequelae		
La Rosa 1999[18]	Parietaria	20	5 patients with local symptoms: 3 had oral itching, 2 had labial swelling	25%	Unspecified
Leonardi 2009[19]	Placebo	21	4 patients with local symptoms: 2 had oral itching, 2 had labial swelling	19%	Unspecified
Roder 2007[30]	Grass mix	108	42 patients with oral pharyngeal irritation/swelling	39%	Unspecified
	Placebo	96	16 patients with oral pharyngeal irritation/swelling	17%	Unspecified
Pajno 2004[50]	Parietaria	15	1 patient with itching in mouth and throat – maintenance dose decreased	7%	Mild
Lima, 2002[25]	Timothy grass	28	380 events were very mild local reactions, consisting of itching and swelling in the floor of the mouth following sublingual drops, almost always during the up-dosing phase. Not troublesome for the patient and none required treatment.	80%	Mild

b)**SLIT SYSTEMIC REACTIONS: UPPER RESPIRATORY EVENTS: Rhinitis/Nasal Reactions**

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Tari 1990[46]	Dust mite	32	8 patients presented severe nasal symptoms *(subjects exceeded maximum dose)	25%	Severe*
Tahamiler 2007[14]	Dust mite (AE reported in total)	181	67 patients reported rhinitis.	37%	Mild
Rodriguez, 2006[65]	Dust mite + Grass mix-updosing	69	2 patients (2 events) had rhinitis. 1 patient withdrew due to asthma, rhinitis and pruritus	3%	Unspecified
	Dust mite + Grass mix-no updosing	66	4 patients (5 events) had rhinitis	6%	Unspecified
deBot 2011[16]	Dust mite	125	115 patients reported upper respiratory adverse events	92%	Unspecified
	placebo	126	118 patients reported upper respiratory adverse events	93%	Unspecified
			Upper respiratory events : Nasal complaints/rhinitis		
Sambugaro, 2003[9]	Dust mite, Grass mix, Tree mix	18	1 patient belonging to the 15-day induction group had nose itching and sneezing. He did not require treatment or discontinuation of SLIT.	5.5%	mild
Panzner, 2008[29]	Grass mix	20	4 patients (19 events) presented rhinitis	20%	Unspecified

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Pradalier, 1999[58]	Grass mix	62	5 patients with upper respiratory effects (1 with tonsillitis/pharyngitis, 4 with rhinitis), Symptoms were minor and of short duration (from a few minutes to 1h) except for 1 patient who was withdrawn due to the rhinitis symptoms.	8%	Unspecified
	Placebo	61	1 patient had tonsillitis/pharyngitis	1.6%	Unspecified
Sieber 2012[28]			In total, 65.7% of all patients (140/213) experienced a treatment-emergent AE;		Unspecified
	Grass	142	SLIT: 31 (22%) patients had nasopharyngitis, 4 (3%) had sinusitis	25%	
Ott 2008[27]	Placebo	67	Placebo: 12 (18%) patients had nasopharyngitis, 3 (4.5%) had sinusitis	22%	
Hordijk, 1998[13]	Grass mix	27	3 patients presented upper respiratory AEs	11%	Mild
	Placebo	30	5 patients presented upper respiratory AEs Upper respiratory: Ear, nose and throat complains. These reactions did not require special treatment or a reduction of the dose.	17%	Mild
Sabbah, 1994[31]	Grass Mix	29	5 patients had rhinitis	17%	Mild
	Placebo	29	4 patient had rhinitis	14%	Mild
Vervloet, 2007[53]	Bald Cypress	38	1 events of rhinitis	2.6%	Unspecified
	Placebo	38	3 event of rhinitis	8%	Unspecified
Horak 1998[24]	Birch	21	3 patients reported runny nose and sneezing	14%	Mild
	Placebo				
Valovirta, 2006[59]	Tree mix-high	32	- -	__	
	Tree mix-low	33	1 patient had hinitis	3%	Unspecified
Savolainen 2006[60]	Placebo	32	1 patient had hinitis	3%	Unspecified
Bush 2011[45]	Placebo	17	1 patient in the placebo dropped due to unrelieved rhinitis symptoms during maintenance treatment.	6%	Moderate
Guez 2000[48]	Placebo	36	1 patient reported an episode of rhinosinusitis.	3%	Mild
La Rosa 1999[18]	Parietaria	20	1 patient: Rhinitis	5%	Unspecified
Leonardi 2009[19]	Placebo	21	1 patient: Rhinitis	5%	Unspecified
Roder 2007[30]	Grass mix	108	89 patients with rhinitis	82%	Unspecified
	Placebo	96	76 patients with rhinitis	79%	Unspecified

c) **SLIT SYSTEMIC REACTIONS: LOWER RESPIRATORY REACTIONS**

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
O'Hehir, 2009[44]	Dust mite	15	1 patient described chest tightness at 10 minutes, resolving with inhaled b2-agonist.	7%	Mild
O'Hehir 2009[44]	Placebo	15	1 patient complained of transient chest tightness on one occasion.	7%	Mild
Tari, 1990[46]	Dust mite	32	8 patients had mild asthma	25%	Mild
			3 patients presented severe asthma (*patients exceeded max dose)	9%	Severe*

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
deBot 2011[16]	Dust mite placebo	125 126	84 patients reported lower respiratory adverse events 87 patients reported lower respiratory adverse events Lower respiratory events : Shortness of breath/cough	67% 69%	Unspecified Unspecified
Bush 2011[45]	High dose SLIT (Dust mite)	19	1 subject in the high-dose group experienced increased asthma	5%	Moderate
Pradalier, 1999[58]	Grass mix Placebo	62 61	2 patients presented lower respiratory reactions (bronchospasm/dyspnea/asthma) 5 patients presented lower respiratory reactions (1 had bronchitis, 4 had bronchospasm/dyspnea/asthma)	3% 8%	Unspecified Unspecified
Hordijk, 1998[13]	Grass mix Placebo	27 30	1 patients presented respiratory AEs 3 patients presented respiratory AEs These reactions did not require special treatment or a reduction of the dose.	4% 10%	Mild Mild
Sieber 2012[28] Ott 2008[27]	Grass Placebo	142 67	In total, 65.7% of all patients (140/213) experienced a treatment-emergent AE; SLIT: 6 (4%) patients had asthma, 7 (5%) had bronchitis, 6 (4%) patients had influenza Placebo: 3 (4.5%) patients had asthma, 1 (1.5%) had bronchitis, 2 (3%) patients had influenza	13% 9%	Unspecified Unspecified
Panzner, 2008[29]	Grass mix	20	6 patients (33 events) presented lower respiratory events (painful or difficult breathing, breathlessness, cough)	30%	Unspecified
Marogna, 2008[41]	Birch and Grass mix	144	1 dropouts due to asthma	0.6	Unspecified
Vervloet, 2007[53]	Bald Cypress	38	1 event of asthma	2%	Unspecified
Nelson, 1993[3]	Cat Placebo	20 21	2 patients had respiratory events (1 asthma, 1 cough) 6 patients had respiratory events (5 asthma, 1 cough)	10% 28%	Unspecified Unspecified
Guez, 2000[48]	Placebo	36	1 patient reported an episode of mild asthma.	3%	Mild
Marogna, 2004[39]	Dust mite, Birch, Weed mix, Grass mix	319	1 dropout due to asthma	0.3%	Unspecified
La Rosa 1999[18] Leonardi 2009[19]	Parietaria Placebo	20 21	0 patients 2 patients: 1 mild asthma attack, 1 severe asthma attack	0% 10%	 Mild; severe
Roder 2007[30]	Grass mix Placebo	108 96	29 patients with shortness of breath/cough 28 patients with shortness of breath/cough	27% 29%	Unspecified Unspecified

d) **SLIT SYSTEMIC REACTIONS: CUTANEOUS: (rash/urticaria/angioedema)**

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Tari, 1990[46]	Dust mite	30	3 patients presented urticaria.	10%	Unspecified

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Marogna 2010[49]	SLIT3yrs (Dust mite) SLIT4 yrs (Dust mite) SLIT5 yrs (Dust mite)	19 21 17	Two patients (1 in the SLIT3 group and 1 in the SLIT5 group) reported 1 episode of generalized itching on maintenance. All events occurred 30 minutes after dosing and spontaneously disappeared without therapy.	5% _ 6%	Mild Mild Mild
deBot 2011[16]	Dust mite placebo	125 126	71 patients reported cutaneous adverse events 82 patients reported cutaneous adverse events Cutaneous events : Eczema, itch, rash	57% 65%	Unspecified Unspecified
Novembre, 2004[26]	Grass mix Placebo	54 59	1 patient with cutaneous rash, spontaneously resolved without intervention. 1 patient had cutaneous rash	2% 2%	Mild Mild
Pradalier, 1999[58]	Grass mix Placebo	62 61	6 patients with cutaneous symptoms (dermographism, itching and urticaria) 4 patients with cutaneous symptoms (dermographism, and itching) Cutaneous signs were minor and lasted at most 1 h. 1 patient was withdrawn after generalized urticaria which lasted 48 h	10% 6%	unspecified unspecified
Sieber 2012[28] Ott 2008[27]	Grass Placebo	142 67	In total, 65.7% of all patients (140/213) experienced a treatment-emergent AE; SLIT: 6 (4%) patients had acne, 5 (3.5%) had eczema Placebo: 4 (1.5%) patients had acne, 4 (6%) had eczema	8% 12%	Unspecified Unspecified
Marogna, 2008[41]	Birch and Grass mix	130	1 patient reported 1 episode of generalized itching (without skin lesions) within 30 minutes of taking the dose. This adverse event appeared during the maintenance phase, self-resolved without therapy	0.7%	Mild
Moreno-Ancillo, 2007[42]	Grass mix and Olive	51	1 patients presented urticaria in which medical treatment was not necessary.	10%	Mild
Vervloet, 2007[53]	Bald Cypress Placebo	38 38	1 event of urticaria 1 event of urticaria and 1 event of eczema	3% 3%	Unspecified Unspecified
Horiguchi, 2008[10]	Japanese Cedar	42	2 patients in the active group complained of mild urticaria of the face or breast. All adverse effects were transient and resolved spontaneously. No intervention was necessary.	5%	Mild
Sabbah, 1994[31]	Placebo	29	2 patient had skin symptoms	7%	Mild
Marogna, 2004[39]	Dust mite, Birch, Weed mix, Grass mix	319	4 patients reported one episode of generalized itching within 30 minutes after taking the dose. These four adverse events appeared during the maintenance phase and self-resolved without therapy in <2h.	1.5%	Mild
Roder 2007[30]	Grass mix Placebo	108 96	42 patients with eczema/itch/rash 34 patients with eczema/itch/rash	39% 35%	Unspecified Unspecified

e) **SLIT SYSTEMIC REACTIONS: GASTROINTESTINAL (nausea/pain/diarrhea)**

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Tahamiler, 2007[14]	Dust mite (AE reported in total)	181	25 patients presented gastrointestinal tract upset	14%	Mild

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Tari, 1990[46]	Dust mite	32	4 patients with GI symptoms: abdominal swelling and/or pain, and/or diarrhea	12%	Unspecified
Bush 2011[45]	High dose SLIT Low dose SLIT (Dust mite)	19 17	1 patient withdrew due to abdominal cramps and diarrhea during escalation 1 patient withdrew due to nausea and diarrhea during the dose escalation	5% 6%	Moderate Moderate
deBot 2011[16]	Dust mite placebo	125 126	85 patients reported General gastrointestinal complaints 76 patients reported General gastrointestinal complaints	68% 60%	Unspecified Unspecified
De Blay, 2007[61]	Grass mix Placebo	61 57	12 patients presented GI symptoms (7 had abdominal pain and 5 had diarrhea) 4 patients presented GI symptoms (2 had abdominal pain and 2 had diarrhea)	20%	Unspecified Unspecified
Novembre, 2004[26]	Grass mix	54	1 patient experienced mild gastrointestinal complaints that spontaneously resolved without requiring treatment	2%	Mild
Pradalier, 1999[58]	Grass mix Placebo	62 61	2 patients whit GI symptoms (diarrhea) 2 patients whit GI symptoms (diarrhea)	3% 3%	Unspecified Unspecified
Hordijk, 1998[13]	Grass mix Placebo	27 30	1 patients presented GI AEs, did not require treatment or dose reduction. 1 patients presented GI AEs, did not require treatment or dose reduction	4% 3%	Mild Mild
Sabbah, 1994[31]	Grass Mix Placebo	29 29	1 patients had digestive signs 1 patient had digestive signs	3% 3%	Mild Mild
Sieber 2012[28] Ott 2008[27]	Grass Placebo	142 67	In total, 65.7% of all patients (140/213) experienced a treatment-emergent AE; SLIT: 7(5%) patients gastritis, 5(3.5%) patients diarrhea, 3(2%) other GI symptoms Placebo: 2(3%) patients gastritis, 2 (3%) patients diarrhea, 2 (3%) other GI symptoms	10.5% 9%	Unspecified Unspecified
Vervloet, 2007[53]	Bald Cypress Placebo	38 38	2 events of gastric pain, 2 events of diarrhea, with 1 dropout due to gastric pain and vomiting 1 event of diarrhea	5% 2.5%	Unspecified Unspecified
Valovirta,2006[59] Savolainen 2006[60]	Tree mix-high Tree mix-low Placebo	32 33 32	1 patient had abdominal pain 2 patient had abdominal pain --	3% 6% --	Unspecified Unspecified
La Rosa 1999[18] Leonardi 2009[19]	Parietaria Placebo	20 21	19 patients (12 in the active group and 7 in the placebo group) had gastrointestinal complaints. These complaints led to withdrawal from the trial in 4 cases in the active group and in 1 case in the placebo group.	60% 33%	Unspecified Unspecified
Bowen, 2004[20]	Ragweed	43	9 patients had nausea,	21%	unspecified
Marogna, 2004[39]	Dust mite, Birch, Weed mix, Grass mix	319	1 dropout due to abdominal pain.	0.3%	Unspecified
Marogna, 2008[41]	Birch, Grass mix	144	1 dropout due to abdominal pain.	0.7%	Unspecified
Stelmach	Dust mite (SLIT arms	40	Stomach aches in the first year of immunotherapy, 3.5% vs. %0.5% and 6% vs.	NC	Unspecified

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
2011[38]	reported together) placebo	 20	5.6% in the second year of immunotherapy.		 Unspecified
Roder 2007[30]	Grass mix Placebo	108 96	80 patients with gastrointestinal complaints 70 patients with gastrointestinal complaints	74% 73%	Unspecified Unspecified
deBot 2011[21]	Dust mite Placebo	125 126	85 patients with gastrointestinal complaints 76 patients with gastrointestinal complaints	68% 60.3%	Unspecified Unspecified

f) **SLIT SYSTEMIC REACTIONS: CARDIOVASCULAR**

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Hordijk, 1998[13]	Grass mix Placebo	27 30	1 patient presented cardiovascular AEs 1 patient presented cardiovascular AEs These reactions did not require special treatment or a reduction of the dose.	4% 3%	Mild Mild
Vervloet, 2007[53]	BaldCypress	38	1 event of chest pain chest pain	3%	Mild

g) **SLIT SYSTEMIC REACTIONS: OCULAR REACTIONS**

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
deBot 2011[16]	Dust mite placebo	125 126	69 patients reported ocular adverse events: Conjunctivitis 82 patients reported ocular adverse events: Conjunctivitis	55% 65%	Unspecified Unspecified
Panzner, 2008[29]	Grass mix	20	3 patients (7 events) presented conjunctivitis	15%	unspecified
Pfaar, 2008[57]	Grass mix Placebo	94 91	69 patients in the active group presented local events: Conjunctivitis (6.4%) and eye pruritus (6.4%) 35 patients in the placebo group presented local events: Conjunctivitis (3.3%) and eye pruritus (2.2%).	73.4% 38.5%	Unspecified Unspecified
Vourdas, 1998[54]	Olive	32	1 patient presented conjunctivitis symptoms	3%	Mild
Horak 1998[24]	Birch Placebo	21 20	2 patients reported ocular itching 3 patients reported ocular itching	9% 15%	Mild Mild
Rodriguez, 2006[65]	Dust mite + Grass mix-updosing Dust mite + Grass mix-no updosing	69 66	5 patients (5 events) had ocular itching 1 patients (2 events) had ocular itching	7% 1.5%	Unspecified Unspecified
Vervloet 2007[53]	Placebo	38	1 event of conjunctivitis	3%	Unspecified
La Rosa 1999[18] Leonardi 2009[19]	Parietaria Placebo	20 21	1 patient with conjunctivitis 1 patient with conjunctivitis	5% 5%	Unspecified Unspecified
Roder 2007[30]	Grass mix Placebo	108 96	53 patients with conjunctivitis 54 patients with conjunctivitis	49% 56%	Unspecified Unspecified

Tari 1990[31]	Dust mite	30	6 patients with severe eye symptoms	20%	Severe
deBot 2011[21]	Dust mite Placebo	125 126	69 patients with conjunctivitis 82 patients with conjunctivitis	55% 65%	Unspecified Unspecified

h) **SLIT SYSTEMIC REACTIONS: GENERAL SYMPTOMS**

Study	**SLIT Allergen**	**Number of Patients in Arm**	**Description**	**% of patients**	**Severity**
Pajno, 2000[2]	Dust mite Placebo	12 12	4 patients : reported tiredness 1 patient : reported tiredness These side-effects resolved spontaneously without drugs	30% 8%	Unspecified Unspecified
Hirsch, 1997[43]	Dust mite	15	1 patient dropped out after 8 weeks of therapy (14 years old), complaining of local swelling under the tongue and a subjective feeling of weakness after having reached the maintenance dose.	7%	Unspecified
Hordijk, 1998[13]	Grass mix Placebo	27 30	4 patients presented other AEs (2 mental complaints-2 increase of hay fever complaints) 4 patient presented other AEs (1 nervous system- 1 muscle weakness- 2 clotting disorders)	15% 13%	Mild Mild
Sieber 2012[28] Ott, 008[27]	 Grass Placebo	 142 67	In total, 65.7% of all patients (140/213) experienced a treatment-emergent AE; SLIT: 8 (6%) patients had headache, 4 (3%) patients had back pain Placebo: 2 (3%) patients had headache, 2 (3%) patients had back pain	 8% 6%	 Unspecified Unspecified
De Blay, 2007[61]	Grass mix Placebo	61 57	5 patients presented headache 5 patients presented headache	8%	Unspecified Unspecified
Panzner, 2008[29]	Grass mix	20	2 patients (2 events) presented general symptoms; 1 headache, 1 fatigue	10%	Unspecified
Moreno-Ancillo, 2007[42]	 Grass mix and Olive Placebo	 51 49	106 adverse events in 34 patients (66.7%) in the active immunotherapy group and 24 reactions in 12 patients (24.5%) in the placebo group 6 patients-14 events: conjunctivitis, rhinitis, and mild asthma. 6 patients-10 events: conjunctivitis, rhinitis, and mild asthma. All systemic reactions were mild; only 7 required medical treatment. Most reactions appeared immediately, were of short duration, and resolved spontaneously without sequelae.	 12 % 12 %	 Mild Mild
Rodriguez, 2006[65]	Dust mite + Grass mix-updosing	69	1 patient withdrew due to headache	1%	Unspecified
Valovirta, 2006 Finland[59] Savolainen 2006[60]	Tree mix-high	32	1 patient had flushing	3%	Unspecified
Bush 2011[45]	Placebo	17	1 patient withdrew in the placebo group for increased headache intensity and reduced hearing during the dose escalation	6%	moderate

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Stelmach 2011[38]	Dust mite (arm 1 + 2 reported together) placebo	40 20	Headaches in first year of immunotherapy, 4.1% vs 4% and 0 vs %.2% in the second year of immunotherapy	NC	Unspecified Unspecified
Lima, 2002[25]	Timothy grass Placebo	28 28	In total, 28 patients (475 events) in the immunotherapy group and 28 patients (90 events) in the in the placebo group presented AEs. (93 of 475: 19.6%) were moderate general reactions (64 of 90: 71%) were moderate general reactions Reactions included infection, malaise and rhinitis, and were unrelated temporally to the taking of the treatment.	NC	Moderate Moderate
Roder 2007[30]	Grass mix Placebo	108 96	10 patients with allergy (not specified) 9 patients with allergy (not specified)	9% 9%	Unspecified Unspecified
Pajno 2004[50]	Parietaria Placebo	15 15	3 patients with tiredness after drop ingestion- 1 dropout due to abdominal pain, shortness of breath, and wheezing 20 mins after drops ingestion 2 patients with tiredness after drop ingestion	27% 13%	Mild Mild
deBot 2011[21]	Dust mite Placebo	125 126	75 patients with allergy (not specified) 84 patients with allergy (not specified)	60% 67%	Unspecified Unspecified
Tseng 2008[22]	Dust mite Placebo	30 33	19 patients with side effects including tongue numbness, as most common AE, and epistaxis, mouth ulceration, asthma attacks 7 patients with side effects including tongue numbness, as most common AE, and epistaxis, mouth ulceration, asthma attacks	63% 21%	Mild Mild
Niu 2006	Dust mite	56	5 patients with 10 incidences of mild-moderate local reactions (tongue disorder, vomiting, abdominal pain, circumoral paresthesia)	9%	Mild-moderate

NC not calculated

l) **SLIT ANAPHYLACTIC REACTIONS**

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
No study reported any anaphylactic reaction					

TABLE E15: SUMMARY TABLE OF SUBLINGUAL IMMUNOTHERAPY- STUDY CHARACTERISTICS, CLINICAL OUTCOMES, AND RISK OF BIAS-**SLIT**

STUDY CHARACTERISTICS							CLINICAL OUTCOMES								QUALITY
Study	**Allergen**	**No. Subject**	**Mono-Sensitizd Subjects**	**Children Only**	**Treatm Duration**	**µg per month**	**Asthma**	**Asthma+ Rhinitis/ RC**	**Rhinitis RC**	**Ocular**	**Medi-cation**	**Medi-cation+ Symptoms**	**QOL**	**PFT**	**Risk of Bias**
Pajno, 2000[2]	Dust mites: D.pter	24	X	X	2 years	9.6 Der p1, 4.8 Der f	S	NR	NR	NR	S	NR	NR	NR	Low
Hirsch, 1997[43]	Dust mites: D.pter	30		X	1 year	47.5 Der p1	S	NR	NS	NR	NS	NR	NR	NR	Medium
O'Hehir, 2009[44]	Dust mites: D.pter	30	X		1 year	1425 Der p1, 283 Dep p2	NR	NR	S	NR	NR	NR	S	NR	High
Ippoliti, 2003[64]	Dust mites: D.pter	86	X	X	6 months	9.6 Der p1, 4.8 Der p2	S	NR	S	NR	NR	NR	NR	S	Medium
Tari, 1990[46]	Dust mites: D. pter/D.far	58		X	18 months	NR	S	NR	S	NS	NR	NR	NR	S	Low
Lue, 2006[7]	Dust mites: D.pter/D.far	20	X	X	6 months	500 Der f, 283.3 Der p	S	NR	NR	NR	S	NR	NR	S	Medium
Sambugaro, 2003[8]	Dust mites: D.pter/D.far	30		X	24 weeks	500 Der f, 283.3 Der p	S	NR	NR	NR	NS	NR	NR	S	High
Tahamiler * 2007[14]	Dust mites: D.pter/D.far	NR			2-3 years	NR	NR	NR	S	NR	NR	NR	NR	NR	High
Tseng, 2008[15]	Dust mites: D.pter/D.far	63	X	X	3 weeks induction, 21 weeks mainten-ance	260 Derp, 451.7 Der f	NR	NR	NS	NR	NR	NR	NR	NR	Medium

STUDY CHARACTERISTICS							CLINICAL OUTCOMES								QUALITY
Study	**Allergen**	**No. Subject**	**Mono-Sensitizd Subjects**	**Children Only**	**Treatm Duration**	**µg per month**	**Asthma**	**Asthma+ Rhinitis/ RC**	**Rhinitis RC**	**Ocular**	**Medi-cation**	**Medi-cation+ Symptoms**	**QOL**	**PFT**	**Risk of Bias**
Bahceciler 2001[47]	Dust mites: D.pter/D.far	15	X	X	6 months	93.3 Der p1 81.67Der f1	S	NR	NS	NR	S	NR	NR	NR	Medium
Guez 2000[48]	Dust mites: D.pter/D.far	72			24 months	91.6 Der p1 70.83Der f1	NR	NR	S	NR	NS	S	NR	NR	Medium
Bush 2011[45]	Dust mites: D. far	31			12-18 months	2100 Der f1	NR	NS	NR	NR	NS	NR	NR	S	Medium
Marogna 2010[49]	Dust mites: D. pter	57				NR	NR	NR	NR	NR	P values NR	P values NR	NR	S at 5 years	Medium
deBot 2011[16]	Dust mites: D. pter	257		X		16.24 Der p1	S	NR	NS	NS	NS	NR	NS	NR	High
Nelson 1993[3]	Animal: cat	44			105 days	12.9-257.1 Fel d1	NR	NR	S	NR	NR	NR	NR	NR	Medium
Alvarez-Cuesta, 2007[63]	Animals: cats NOTE: outcomes reported only during challenges,	50			12 months	15.3 Fel d1	NR	NR	NR	NR	NR	NR	NR	NR	High
Pozzan 2010[62]	Molds: Alternaria	52			3 years	3.6 Alt a1	NR	S	NR	NR	S	NR	NR	NR	Medium

STUDY CHARACTERISTICS							CLINICAL OUTCOMES								QUALITY
Study	**Allergen**	**No. Subject**	**Mono-Sensitizd Subjects**	**Children Only**	**Treatm Duration**	**µg per month**	**Asthma**	**Asthma+ Rhinitis/ RC**	**Rhinitis RC**	**Ocular**	**Medi-cation**	**Medi-cation+ Symptoms**	**QOL**	**PFT**	**Risk of Bias**
D'Ambrosio 1999 [1]	Weeds: Parietaria	30	X		9 months	1.52Par j1	NR	S	S	S	S	S	NR	NR	Medium
D'Ambrosio, 1996 [17]*	Weeds: Parietaria	40	X		8 months (mid Jan to end Sep)	1.44 Par j1	NR	S	NR	NR	NR	S	NR	NR	High
la Rosa 1999 [18]	Weeds: Parietaria	41	X	X	2 years	2.2 Par j1	NR	NR	S	NR	NS	NR	NR	NR	Low
Pajno 2004 [50]	Weeds: Parietaria	30		X	13 months	1.56 Par j1	NS	NR	NS	NR	NS	NR	NR	NR	Medium
Passalacqua, 1999 [52]	Weeds: Parietaria	30			8 months	1.0 Par j1	NR	NR	NR	NR	S	S	NR	NR	Low
Bowen 2004[20]	Weeds: Ragweed	83	X		3 months (estimated duration)	3480Amb a1	NR	NR	S	NS	NS	NR	NR	NR	Medium
Skoner, 2010[21]	Weeds: Ragweed	115			17 +/- 3 weeks	High 1440 Amb a1, Low: 144	NR	NR	NR	NR	S	S	NR	NR	Low
Hordijk, 1998[13]	Grass Mix	69			10 months	NR	NR	NR	S	NR	NR	NR	NR	NR	Medium
Novembre * 2004[26]	Grass: Grass mix	113		X	3 years	4.8 Der p1, 2.4 Der	NR	NR	NS	NR	S	S	NR	NR	High

STUDY CHARACTERISTICS							CLINICAL OUTCOMES								QUALITY
Study	**Allergen**	**No. Subject**	**Mono-Sensitizd Subjects**	**Children Only**	**Treatm Duration**	**µg per month**	**Asthma**	**Asthma+ Rhinitis/ RC**	**Rhinitis RC**	**Ocular**	**Medi-cation**	**Medi-cation+ Symptoms**	**QOL**	**PFT**	**Risk of Bias**
						p2, 12.0 Group V grass 27 Bet v1, 0.7 Par j1									
Ott 2008[27]	Grass: Grass mix	213			3 seasons	500 Group V grass	NR	NR	S	NR	NS	NS	NR	NR	Medium
Panzer 2008[29]	Grass: Grass mix	35			1 year	NR	NS	S	S	S	S	NR	NR	NR	Low
Roder* 2007[30]	Grass: Grass mix	204		X	2 years	1260 Lol p5	NR	NR	NS	NR	NS	NR	NS	NS	Low
Sabbah 1994[31]	Grass: Grass mix	58			120 days	NR	NR	NR	NS	S	S	NR	NR	NR	Medium
Pradalier 1999[58]	Grass: Grass mix	126			4 months	233.75 Phl p5	NR	NR	NS	NR	NS	NR	NR	NR	Medium
Marogna* 2009[37]	Grass: Grass mix	51	X		5 years	70 Phl p1	S	NR	S	NR	S	NR	NR	S	Medium
Feliziani 1995[56]	Grass: Grass Mix	34			until end of pollen season	NR	NR	NR	S	NR	S	NR	NR	NR	Medium
Pfaar 2007[57]	Grass: Grass mix	185	X		1.5 years	1200 Group V grass	NR	NR	NR	NR	NR	S	NR	NR	Medium

STUDY CHARACTERISTICS							CLINICAL OUTCOMES								QUALITY
Study	**Allergen**	**No. Subject**	**Mono-Sensitizd Subjects**	**Children Only**	**Treatm Duration**	**µg per month**	**Asthma**	**Asthma+ Rhinitis/ RC**	**Rhinitis RC**	**Ocular**	**Medi-cation**	**Medi-cation+ Symptoms**	**QOL**	**PFT**	**Risk of Bias**
Stelmach 2011[38]	Grass: Grass Mix	60	X	X	12 months	300 Group V grass	NR	NR	NR	NR	NR	NR	NR	P values NR	Medium
De Blay 2007[61]	Grass Mix: Orchard, Timothy Perennial ryegrass	118			10 months	275 Group III grass	NR	NR	NS	NR	NR	NR	NR	NR	Medium
Lima 2002[25]	Grass: Timothy	56			18 months	900 Phl p5	NS	S	NS	NS	NS	NR	NR	NR	Low
Pajno 2011[55]	Grass: Timothy	80		X	4 months/ yr for 2 years	NR	NS	NR	NR	NR	NS	NS	NR	NR	Medium
Horiguchi 2008[10]	Trees: Japanese cedar	67			7 months	6.0 Cry j1	NR	NR	S	NR	NR	NR	NR	NR	Medium
Okubo 2008[11]	Trees: Japanese cedar	61			6 months	NR	NR	NR	NS	NR	NS	NS	S	NR	Medium
Makino 2010[23]	Trees: Japanese cedar	25			5 months	60 Cry j1, 8-20 Cry j2	NR	NR	NR	NR	NS	NS	S	NR	Medium
Fujimura 2011 [12]	Trees: Japanese cedar	103			20 months	6-16.8 Cry j1	NR	NR	NR	NR	NR	S (peak season)	S	NR	Low
Marogna 2005[33]	Trees: White birch	79	X		3.5 years	8.5 Bet v1	NR	S	NR	NR	S	NR	NR	NR	Medium
Voltolini 2009 [34]	Trees: Birch	24			2 courses of 4 months (pre/ co-	1.725 BetV1	S	NR	S	NR	NR	NR	NR	NR	Medium

STUDY CHARACTERISTICS							CLINICAL OUTCOMES								QUALITY
Study	**Allergen**	**No. Subject**	**Mono-Sensitizd Subjects**	**Children Only**	**Treatm Duration**	**µg per month**	**Asthma**	**Asthma+ Rhinitis/ RC**	**Rhinitis RC**	**Ocular**	**Medi-cation**	**Medi-cation+ Symptoms**	**QOL**	**PFT**	**Risk of Bias**
					seasonally)										
Marogna 2010[35]	Trees: Birch	33			5 year	8.3 Bet v1	S	NR	S	NR	S	NR	NR	S	High
Di Rienzo, 2006[22]	Trees: Mountain cedar	34			4 to 5 months (Presea son Decemb er - April)	NR	NR	NR	NR	NR	NR	NS	S	NR	High
Vervloet2007[53]	Trees: Bald-cypress	76	X		120 days	6840 Jun a1	NR	NS	NS	NS	S	NR	NR	NR	High
Vourdas1998[54]	Trees: Olive	70		X	seasonal (5 to 6 months each year) for 2 years	736.3 Ole e1	NR	NR	NS	NR	NS	NR	NR	NR	Medium
Valovirta, 2006[59]	Trees: Tree mix	98		X	5 weeks build-up 18 months mainte-nance	High: 120 Bet v1/Aln g1/Cor a1 Low: 14.4 Bet v1/Aln g1/Cor a1	High: S Low:NS	High: S Low: S	High: S Low: S	NR	High: S Low: NS	NR	NR	NR	Medium
Marogna* 2007[40]	Trees: White birch Grass: Grass mix	48			4 years	100 Bet v1	NR	S	NR	NR	S	S	NR	S	Medium

STUDY CHARACTERISTICS							CLINICAL OUTCOMES								QUALITY
Study	**Allergen**	**No. Subject**	**Mono-Sensitizd Subjects**	**Children Only**	**Treatm Duration**	**µg per month**	**Asthma**	**Asthma+ Rhinitis/ RC**	**Rhinitis RC**	**Ocular**	**Medi-cation**	**Medi-cation+ Symptoms**	**QOL**	**PFT**	**Risk of Bias**
Moreno-Ancillo, 2007 [42]	Grass: Grass mix Trees: Olive	105	X		10 months	60 Grp V grass, 90 Ole e1	S	NR	S	S	NS	NS	S	S	Low
Sambugaro* 2003 [9]	Dust mites : D.pter/D.far Grass: Grass mix Weeds: Ragweed Parietaria	24			2 years	4.8 Der p1, 2.4 Der p2, 12.0 GrpV grass, 27 Bet v1, 0.7 Par j1	NR	NR	NR	NR	NR	S	NR	S	Medium
Amar, 2009 [36]	Grass: Timothy Trees: Ash,Maple, Red/green American elm Cottonwood Weeds: Kochia, ragweed, Sagebrush Russian thistle	58			15 months	570 Phl p5	NR	NR	NS	NR	NS	NR	NR	NR	Low
Marogna* 2004 [39]	Trees: White birch Dust mites: D.pter	511			3 years	3.25 Der f1/f2, 5.83 Phl p1, 5.83 Par j1,	NR	NR	NR	NR	NR	NR	NR	S	Medium

STUDY CHARACTERISTICS							CLINICAL OUTCOMES								QUALITY
Study	**Allergen**	**No. Subject**	**Mono-Sensitizd Subjects**	**Children Only**	**Treatm Duration**	**µg per month**	**Asthma**	**Asthma+ Rhinitis/ RC**	**Rhinitis RC**	**Ocular**	**Medi-cation**	**Medi-cation+ Symptoms**	**QOL**	**PFT**	**Risk of Bias**
	Weeds: Mugwort/ Parietaria Grass: Grass mix					8,33 Bet v1									
Marogna* 2008[41]	Dust mite Trees: White birch Grass: Grass mix Weed: Parietaria	216		X	3 years	40 De p1, 40 Der p2, 3.33 Phl p1, 3.33 Par j1, 8,33 Bet v1	NR	NR	NR	NR	NR	S	NR	S	High
Rodriguez *, 2006[65]	Dust mite Grass mix Note: this study reported adverse events only	135			3 months	60 Grp V grass 24 Der p1/2	NR	NR	NR	NR	NR	NR	NR	NR	Medium

RC; Rhinoconjunctivitis, D.Pter: Dermatophagoides pteronyssinus, D.Far; Dermatophagoides farinae
*Denotes studies in which comparator is other than a placebo group. These studies use pharmacotherapy/conventional therapy as a comparator: 4961, 1333, 4040, 4784, 3400, 3402, 3403, 3405. Study 5470 compared 3 years of sublingual immunotherapy to 2 years of sublingual immunotherapy. Study 4790 compared two groups of sublingual immunotherapy with identical maintenance dose, one group with updosing and the other without updosing.
Studies shaded in gray did not report any significant findings in any of the outcome categories on this table.
S= significant improvement in sublingual group when compared to controls and/or comparison of pre-treatment to post-treatment scores.
NS= no significant improvement
NR=not reported

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Appendix F. Evidence Tables for Sublingual Immunotherapy Versus Subcutaneous Immunotherapy

TABLE F1.- STUDY CHARACTERISTICS SCIT vs SLIT

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Mauroa 2007[1] Italy	Rhinitis	Seasonal	Multiple	Tree pollen (Birch, Alder, Hazel)	Age: 18-60 years old No previous immunotherapy Positive specific IgE test Minimum duration of disease: 2 years Monosensitized individuals only	Not stated
Piazza 1993[2] Italy	Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Positive skin test	Not stated
Tahamiler 2006[3] Turkey	Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 2 years No pregnant women	Not stated
Khinchi 2004[4] Denmark	Rhinoconjunctivitis	Seasonal	Single	Trees: White Birch	No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 2 years No perennial allergy	Industry
Eifan 2010[5] Turkey	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Non-profit
Mungan 1999 [6] Turkey	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 3 years	Not stated
Yukselen 2011[7] Turkey	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: children No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 1 year	Industry
Keles 2011[8]	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides	Age: 5-12 years Minimum duration of disease: 2 years	Industry

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Turkey				pteronyssinus and farinae	Positive skin test	

TABLE F2.- PATIENT CHARACTERISTICS- SCIT vs SLIT

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Mauroa 2007[1]	47	SLIT SCIT	39 (Range 18-57) 40 (Range 20-59)	60/40 45/55	20/5 20/1	NR NR
Piazza 1993[2]	31* Study had 3rd arm not recorded since it was Intranasal IT	SLIT SCIT	13 (Range 8-24) 23 (Range 13-38)	NR NR	14/0 17/0	NR NR
Tahamiler 2006[3]	230* Dropouts (37) reported as total. Results reported for those completing study	SLIT SCIT	26 +/- 6 (Range 12-51) 25+/- 5 (Range 13-49)	49/51 48/52	97/NR 96/NR	NR NR
Khinchi 2004[4]	71	SLIT SCIT Placebo	30 (Range 20-58)	61/39 52/48 63/37	23/9 24/5 24/9	NR NR NR
Eifan 2010[5]	48	SLIT 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
Mungan 1999[6]	36	SLIT 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
Yukselen 2011[7]	32	SCIT + placebo drops SLIT + 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
Keles 2011[8]	60	SCIT SLIT 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

TABLE F3.- INTERVENTION CHARACTERISTICS- SCIT vs SLIT

Study	Arms	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Mauroa 2007[1]	SLIT- Tree pollen (birch, alder, hazel) SCIT- Tree pollen (birch, alder, hazel)	conventional therapy	100 IR 8 IR	4653.1 IR 50.65 IR	Daily Every 3 weeks	NR NR	NR
Piazza 1993[2]	SLIT- Dust mite D. Per SCIT- Dust mite D. Per (Alum precipitated)	ONLY rescue medication	250 STU from 70-80,000 SQ U	NR NR	3 times a week Monthly	1 Der p 1 (maintenance) 4.2-4.8 Der p 1 (maintenance)	2 years
Tahamiler 2006[3]	SLIT- Dust mite D. Per-D. Far SCIT- Dust mite D. Per-D. Far	ONLY rescue medication	1-5 drops of 1,000 STU /ml 100,000 SQ-U/ml	NR NR	3 times per week Once every 6-8 weeks	NR NR	3 years
Khinchi 2004[4]	SLIT- Birch+ Placebo injections SCIT- Birch+ Placebo drops Placebo injections + Placebo drops	conventional therapy	49.2 µg Bet v 1 3.28 µg Bet v 1	11182 µg 51 µg	Every other day Monthly	11182 Bet v 1 (cumulative) 51 Bet v 1 (cumulative)	2 years
Eifan 2010[5]	SLIT Dust mite (D. Per-D. Far) SCIT Dust mite(D. Per-D. Far) 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
Mungan 1999[6]	SLIT Dust mite (D. Per-D. Far) SCIT Dust mite (D. Per-D. Far) 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

Study	Arms	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Yukselen 2011[7]	SCIT (plus placebo sublingual drops) SLIT (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 D.pt and 21885 TU of D.f) 173733 TU (86866.5 TU of D.pt and 86,866.5 TU of D.F)	Every 4th week Three times a week	NR NR	1 year
Keles 2011[8]	SCIT SLIT 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

TABLE F4.- QUALITY ASSESSMENT- SCIT vs SLIT

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Mauroa 2007[1]	Low	Low	High	Low	Low	No	Medium
Piazza 1993[2]	Low	High	High	Low	Low	No	Medium
Tahamiler 2006[3]	Low	High	High	High	High	Yes or unclear	High
Khinchi 2004[4]	Low	Low	Low	Low	Low	Yes or unclear	Low
Eifan 2010[5]	Low	Low	High	High	Low	Yes or unclear	Medium
Mungan 1999[6]	Low	High	High	Low	Low	Yes or unclear	Medium
Yukselen 2011[7]	Low	High	High	Low	Low	No	Medium

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Keles 2011[8]	Low	High	High	Low	Low	No	Medium

TABLE F5.- ASTHMA AND ASTHMA COMBINED SCORES- SCIT vs SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan 2010[5]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Total asthma symptom score	0-12	1.4±1.5 0.9±0.7 0.95±0.62	0.2±0.4 0.4±0.6 2.5±1.6	SCIT vs Pharmacotherapy p=0.04 SLIT vs Pharmacotherapy p=0.02
Mungan 1999[6]	Dust mites	SLIT SCIT Placebo	1 year	Asthma symptom score	NR	0.63 1.20 0.71	0.41 0.59 0.88	SLITpre vs post p=NS SCIT pre vs post p<0.01 Placebo, pre vs post p=NS
Yukselen 2011[7]	Dust mites	SCIT SLIT Placebo	1 year	Asthma symptom score	0-12	2.4 3.7 2.7	1.0 (100% improvement) 2.7 (3.3% improvement) 2.6	SCIT pre vs post p=0.005 SLIT, pre vs post p= 0.012 SCIT vs SLIT p=0.01
Keles 2011[8]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Asthma symptom score	NR	0.25 0.12 0.12 0.13	0 0 0 0.23	SCIT vs Pharmacotherapy p=significant SCIT+SLIT vs Pharmacotherapy, p=SIgnificant

TABLE F6.- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES SCIT vs SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan 2010[5]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Total rhinitis symptom score	0-12	1.3±0.9 1.8±0.9 1.56±1.05	1.5±1.0 1.2±0.9 2.9±0.7	SCIT vs Pharmacotherapy p=0.01 SLIT vs Pharmacotherapy p=0.03
Mungan 1999[6]	Dust mites	SLIT SCIT Placebo	1 year	Rhinitis symptom score	NR	0.87 0.84 0.82	0.50 0.45 0.67	SLIT pre vs post p<0.01 SCIT pre vs post p<0.05 Placebo, pre vs post p=NS
Tahamiler 2006[3]	Dust mite	SLIT SCIT	6 years	Rhinitis and conjunctivitis symptom score	0-15	2.4±0.2 2.5±0.4	0.9±0.8 0.5±0.1	SCIT pre vs post p=significant SLIT pre vs post p=significant SCIT vs SLIT p=0.008 (SCIT showed greater reduction)
Khinchi 2004[4]	Birch	SLIT SCIT Placebo	2 years	Improvement in Combined rhinitis conjunctivitis score	NR	NR NR NR	0.36 points 0.75 points -0.2 points	SLIT vs Placebo, p<0.002 SCIT vs Placebo, p<0.002 SLIT vs SCIT, p=NS
Yukselen 2011[7]	Dust mites	SCIT SLIT Placebo	1 year	Rhinitis symptom score	0-12	4.6 4.3 4.0	3.0 (31% improvement) 3.8 (6.6% improvement) 4.1	SCIT pre vs post p=0.005 SLIT pre vs post p= 0.008 SCIT vs placebo p=0.03 SLIT vs placebo p= NS SCIT vs SLIT p= 0.28
Keles 2011[8]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Rhinitis symptom score	NR	0.21 0.36 0.49 0.22	0.06 0.27 0.04 0.41	SCIT+SLIT vs Pharmacotherapy p=SIgnificant

NS: Not significant

TABLE F7.- OTHER CLINICAL SCORES, SCIT vs SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan 2010[5]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Total symptom score	0-24	2.8±2.2 2.8±1.3 2.5±1.3	1.4±1.5 1.6±1.5 5.4±1.7	SCIT vs Pharmacotherapy p=0.01 SLIT vs Pharmacotherapy p=0.01
Yukselen 2011[7]	Dust mites (D.pt and D.f)	SCIT SLIT Placebo	1 year	Total symptom score	0-24	NR	NR	SCIT pre vs post p=0.005 SLIR, pre vs post p=0.005 SCIT vs Placebo p=0.009
Keles 2011[8]	Dust mites (D.pt and D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Total symptom score	NR	0.38 0.17 0.38 0.28	0.05 0.18 0.04 0.36	SCIT vs Pharmacotherapy p=significant SCIT+SLIT vs Pharmacotherapy p=sIgnificant
Eifan 2010[5]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Visual analog score	0-10	4.9±1.5 5.5±1.7 4.9±1.9	2.7±2.1 1.5±1.8 4.6±1.5	SCIT vs Pharmacotherapy p=0.001 SLIT vsPharmacotherapy p=0.02 SCIT, pre vs post p= 0.002 SLIT pre vs post p=0.01
Yukselen 2011[7]	Dust mites (D.pt + D.f)	SCIT SLIT Placebo	1 year	Visual Analog Score	NR	NR	NR	SCIT (rhinitis score) pre vs post p=0.005 SCIT (asthma score) pre vs post p=0.007 SLIT (both scores) pre vs post p=0.02 SCIT vs Placebo p= 0.05 (rhinitis), 0.02(asthma) SLIT vs Placebo p=NS

NS: Not significant

TABLE F8.- MEDICATION SCORES SCIT vs SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan 2010[5]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Total medication score	1-3	2.8±1.2 2.4±1.4 2.5±1.5	1.2±0.9 1.7±1.4 2.8±1.1	SCIT versus Pharmacotherapy, p=0.26 SLIT versus Pharmacotherapy, p=0.03

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Mungan 1999[6]	Dust mites	SLIT SCIT Placebo	1 year	Medication score	0-12	4.93 6.8 6.09	1.97 3.9 5.24	SLIT, pre versus post, p=0.01 SCIT, pre versus post, p=0.01 Placebo, pre versus post, p=NS
Khinchi 2004[4]	Birch	SLIT SCIT Placebo	2 years	Improvement in the Medication score		NR NR NR	0.29 points 0 points 1.35 points	SLIT versus Placebo p<0.002 SCIT versus Placebo p<0.002 SCIT versus SLIT p=NS
Yukselen 2011[7]	Dust mites (D.pt and D.f)	SCIT SLIT Placebo	1 year	Rhinitis medication score	NR	2.3 2.3 1.9	1.0 1.7 1.9	SCIT vs Placebo p= 0.05 SCIT, pre vs post p=0.005 SLIT, pre vs post p= 0.03 SCIT vs SLIT p=0.18
Yukselen 2011[7]	Dust mites (D.pt and D.f)	SCIT SLIT Placebo	1 year	Asthma medication score	NR	1.38 1.1 1.24	1.0 1.1 1.4	SCIT vs Placebo p= 0.05 SCIT, pre vs post p=0.02 SLIT, pre vs post p= 0.18 SCIT vs SLIT p=0.31
Keles 2011[8]	Dust mites (D.pt + D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Asthma medication score	NR	1.02 1.06 1.1 1.13	0.065 0.91 0.085 0.8	SCIT vs Pharmacotherapy p=significant SLIT vs Pharmacotherapy p=significant SCIT+SLIT vs Pharmacotherapy p=sIgnificant
Keles 2011[8]	Dust mites (D.pt + D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Rhinitis medication score	NR	0.33 0.18 0.49 0.14	0 0.067 0 0.096	SCIT vs Pharmacotherapy p=significant SCIT+SLIT vs Pharmacotherapy p=significant
Keles 2011[8]	Dust mites (D.pt +D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Total medication score	NR	0.52 0.69 0.92 0.8	0.06 0.23 0.16 0.73	SCIT vs Pharmacotherapy p=significant SCIT+SLIT vs Pharmacotherapy p=significant

TABLE F9. COMBINED SYMPTOM MEDICATION SCORES, SCIT vs SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Piazza 1993[2]	Dust mite	SLIT SCIT	2 years	Symptom medication score (Rhinitis)	NR	145 162	120 80	SCIT, pre versus post, p<0.001 SLIT, pre versus post, p<0.01 at 3 months but at 2 years p=NS (Values approximated from graphs)
Mauroa 2007[1]	Tree pollen	SLIT SCIT	Pollen season	Symptom medication score (Rhinitis and conjunctivitis)	0-3 (for each)	NR NR	3.63 ±1.08 4.77 ±1.41	SLIT versus SCIT, p=NS

TABLE F10.- ALLERGY CHALLENGES AND FUNCTIONAL OUTCOMES: PFT SCIT vs SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Tahamiler 2006[3]	Dust mite	SLIT SCIT	6 years	Nasal provocation challenge Modified Gerth van Wijk and Dieges method	0-9	5.5±1.4 5.6±1.5	2.8±2.0 1.4±1.2	SLIT pre vs post, p<0.05 SCIT pre vs post, p<0.05
Eifan 2010[5]	Dust mite	SLIT SCIT Pharmacotherapy	1 year	Titrated allergen specific nasal provocation test		NR NR NR	NR NR NR	Significant increase in nasal provocative dose in SLIT (p=0.01) and SCIT (p=0.005) when compared to pharmacotherapy group at the end of 12 months. No significant differences between SLIT and SCIT were observed.
Mungan 1999[6]	Dust mites	SLIT SCIT Placebo	1 year	Methacholine bronchial provocation test		NR NR NR	NR NR NR	SLIT pre vs post p=NS SCIT pre vs post p=NS Placebo pre vs post p=NS
Yukselen 2011[7]	Dust mites	SCIT SLIT Placebo	1 year	HDM-Specific Nasal provocation	NR	NR	NR	SCIT pre vs post, p=0.05 SLIT pre vs post, p=0.01 SCIT vs SLIT p= 0.31

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Yukselen 2011[7]	Dust mites	SCIT SLIT Placebo	1 year	HDM-Specific Bronchial provocation	NR	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 SLIT p= 0.91
Keles 2011[8]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Allergen specific nasal provocation dose	NR	4.9 5 5 7	3 4 4.4 7.5	SCIT vs Pharmacotherapy p=0.005 SLIT vs Pharmacotherapy p=0.044 SCIT+SLIT vs Pharmacotherapy p=0.035
Keles 2011[8]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Methacholine PC20	NR	NR	NR	No significant change was detected in any of the groups

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

TABLE F11.- BIOMARKERS – IgE- SCIT vs SLIT

Study	Allergen	Arms	Time of measure	Biomarker	Value Pre	Value post	Units	Comparative values
Mauroa 2007 [1]	Tree pollen	SLIT SCIT	End of pollen season	IgE Bet v1 specific	44.6±21.7 52.8±23.1	58.4±26.5 53.1±23.4	kU/L	SLIT pre versus post p= NS SCIT pre versus post p= NS
Piazza 1993 [2]	Dust mite	SLIT SCIT	2 years	IgE Dp specific	NR NR	NR NR		Early conspicuous increase (p<0.005) around 3 months but returned to basal values at 2 years no statistically significant change
Eifan 2010 [5]	Dust mite	SLIT SCIT Pharmacotherapy	1 year	IgE D.f/ D.pt specific	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	IU/ml	D.f 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.pt specific: SCIT versus Pharmacotherapy p=0.03

Study	Allergen	Arms	Time of measure	Biomarker	Value Pre	Value post	Units	Comparative values
Mungan 1999[6]	Dust mite	SLIT SCIT Placebo	1 year	IgE D.f/ D.pt specific	505.05 311.89 288.40	NR NR NR	kU/ml	No significant changes in all three arms at 12 months compared to baseline
Yukselen 2011[7]	Dust mites	SCIT SLIT Placebo	1 year	HDM specific IgE	80 68 80	42 48 75	IU/ml	SCIT pre vs post p=0.01 SLIT pre vs post p=0.02 Placebo pre vs post p=0.65
Keles 2011[8]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Derp1 specific IgE	62+/-52 67+/- 33 83+/-27 73+/- 37	61+/- 53 44+/-32 85+/-34 75+/-41	IU/ml	No significant differences pre vs post in all groups. No significant differences between IT groups and pharmacotherapy
Yukselen 2011[7]	Dust mites (D.pt + D.f)	SCIT SLIT Placebo	1 year	D.pt and D.f specific IgG4	NR	NR		SCIT pre vs post D.pt sIgG4 p=0.007 SCIT pre vs post D.f sIgG4 p=0.005 SCIT vs SLIT p=0.003
Keles 2011[8]	Dust mites (D.pt and D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Derp1 specific IgG4	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	Ua/ML	SCIT vs Pharmacotherapy p<0.05 SCIT+SLIT vs Pharmacotherapy p<0.05

TABLE F12. SAFETY SCIT vs SLIT

TABLE F12a. LOCAL REACTIONS- SLIT

SLIT Local Reactions Reported as a Percent of Patients- Oral cavity or Oropharynx Itching

Study	SLIT Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Khinchi 2004[4]	Birch	23	13	56.5	mild
Mungan 1999[6]	Dust mite	15	1	6.7	mild
Tahamiler 2006[3]	Dust mite	97	47	48.5	mild
Yukselen 2011[7]	Dust mite	10	3	30	NR

SLIT Local Reactions Reported as Number of Events - Oral cavity or Oropharynx Itching

Study	SLIT Allergen	Number of patients in arm	Number of events	Number of events per patient	Severity
Mauroa 2007[1]	Tree pollen	20	4	0.2	mild

TABLE F12b. LOCAL REACTIONS - SCIT

SCIT Local Reactions Reported as a Percent of Patients - Injection site reaction

Study	SCIT Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Mungan 1999[6]	Dust mite	10	2	20	NR
Yukselen 2011[7]	Dust mite	10	2	20	NR

SCIT Local Reactions Reported as Number of Events - Injection site reaction

Study	SCIT Allergen	Number of patients in arm	Number of events	Number of events per patient	Severity
Mauroa ,2007[1]	Tree pollen	20	3	0.15	moderate
Piazza 1993[2]	Dust mite	17	3	0.18	moderate
Tahamiler 2006[3]	Dust mite	96	10	0.1	mild
Eifan 2010[5]	Dust mite	16	1	0.06	mild

TABLE F12c. SYSTEMIC REACTIONS - SLIT

SLIT Systemic Reactions Reported as a Percent of Patients- Gastrointestinal (nausea/pain/diarrhea)

Study	Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Khinchi ,2004[4]	Birch	23	1	4.4	mild
Mungan 1999[6]	Dust mite	15	1	6.7	mild
Piazza 1993[2]	Dust mite	14	2	14.3	moderate
Tahamiler , 2006[3]	Dust mite	97	12	12.4	mild

SLIT Systemic Reactions Reported as a Percent of Patients- Respiratory (rhinitis/asthma)

Study	Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Tahamiler 2006[3]	Dust mite	97	30	30.9	mild

SLIT Systemic Reactions Reported as a Percent of Patients- Unspecified

Study	Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Khinchi 2004[4]	Birch	23	21	91.3	15 mild, 6 moderate

TABLE F12d. SYSTEMIC REACTIONS- SCIT

SCIT Systemic Reactions Reported as a Percent of Patients - Gastrointestinal (nausea/pain/diarrhea)

Study	Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Khinchi 2004[4]	Birch	24	1	4.2	mild

SCIT Systemic Reactions Reported as a Percent of Patients - Respiratory (rhinitis/asthma)

Study	SLIT Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Tahamiler 2006[3]	Dust mite	97	30	30.9	mild

SCIT Systemic Reactions Reported as a Percent of Patients -Unspecified

Study	SLIT Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Khinchi 2004[4]	Birch	23	21	91.3	15 mild, 6 moderate

SCIT Systemic Reactions Reported as Number of Events - Respiratory (rhinitis/asthma)

Study	SLIT Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Eifan 2010[5]	Dust mite	16	1	6.2	severe
Mungan 1999[6]	Dust mite	10	1	10	mild
Keles 2011[8]	Dust mite	11	2	18.2	moderate
Study	**SCIT Allergen**	**Number of patients in arm**	**Number of events**	**Number of events per patient**	**Severity**

Mauroa 2007[1]	Tree pollen	20	2	0.1	1 mild, 1 moderate

SCIT Systemic Reactions Reported as Number of Events - Cutaneous (rash/urticaria/angioedema)

Study	SLIT Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Mauroa 2007[1]	Tree pollen	20	1	0.05	mild

SCIT Systemic Reactions Reported as Number of Events - Anaphylaxis

Study	SLIT Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Eifan 2010[5]	Dust mite	16	1	6.2	Severe- Flushing, wheezing and dyspnea requiring adrenaline

REFERENCES SCIT VS. SLIT APPENDIX

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Appendix G. Evidence Tables for Pediatric Studies

1. SUBCUTANEOUS IMMUNOTHERAPY

TABLE G1. - STUDY CHARACTERISTICS SCIT- PEDIATRICS

a) Table G1a. Study characteristics – SCIT- Pediatrics- Asthma

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Hill 1982 Australia [1]	Asthma	Seasonal	Single	Grass: rye	Age: Children Positive skin test Minimum duration of disease: 3 years	Non-profit Industry
Altintas 1999 Turkey [2]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive skin test	Not stated
Pifferi 2002 Italy [3]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Monosensitized individuals only	Not stated
Van Bever 1990 Belgium [4]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Positive specific IgE test Positive skin test	Not stated
Schubert 2009 Germany [5]	Asthma	Perennial	Single	Dust mites: Unspecified dust mites	Positive specific IgE test Positive skin test	Not stated
Valovirta 1986[6] Valovirta 1984 [7] Denmark- Finland	Asthma	Perennial	Single	Animals: Dogs	Age: 5-18 years No previous immunotherapy Positive specific IgE test Positive skin test	Government Non-profit
Adkinson 1997[8] Limb 2006[9] USA	Asthma	Seasonal and Perennial	Multiple	Dust mites : Dermatophagoides pteronyssinus and farinae Trees : white oak Weeds: Short ragweed and English plantain Grass: Grass mix and Bermuda grass Molds: Alternaria, aspergillus cladosporium	Age: 5-12 years Positive specific IgE test Positive skin test Minimum duration of disease:1 year	Government Industry

b) Table G1b. Study characteristics – SCIT- Pediatrics-**Rhinoconjunctivitis**

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
The PAT study Möller 2002[10] Niggeman 2006[11] Jacobsen 2007[12] Multiple European countries	Rhinoconjunctivitis	Seasonal	Multiple	Trees: Birch Grass: Timothy grass	Age: Children No previous immunotherapy Positive skin test Monosensitized individuals only	Industry

c) Table G1c. Study characteristics – SCIT- Pediatrics-**Asthma and rhinitis**

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Akmanlar 2000 Turkey[13]	Asthma and Rhinitis	Perennial	Multiple	Dust mites:Dermatophagoides pteronyssinus and farinae	Age: children No previous immunotherapy Positive skin test Monosensitized individuals only	Not stated
Hedlin 1999 Denmark-Sweden[14]	Asthma and Rhinitis	Perennial	Multiple	Animals: Cats Dust mites: Dermatophagoides pteronyssinus Weeds	Age: Children Positive skin test Minimum duration of disease: 2 years	Non-profit Industry
Cantani 1997 Italy[15]	Asthma and Rhinitis	Seasonal and Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus Grass: Perennial ryegrass Weeds: Parietaria	No previous immunotherapy Positive skin test	Not stated

d) Table G1d. Study characteristics – SCIT- Pediatrics-**Asthma and rhinoconjunctivitis**

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Dreborg 1986 Multiple European countries[16]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Mold: Cladosporium	No previous immunotherapy Positive specific IgE test Positive skin test	Industry
Kuna 2011 Poland[17]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Mold: Alternaria	Age: Children 5-18 years Positive skin test Positive specific IgE test Duration of disease: 2 years	Not stated

TABLE G2.- PATIENT CHARACTERISTICS SCIT- PEDIATRICS

a) Table G2a. Patient characteristics – SCIT- Pediatrics-**Asthma**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Hill 1982[1]	20	SCIT Placebo	Range 9-14 Range 9-14	Entire study 65/35	11/NR 9/NR	3 3
Altintas 1999[2]	35	Adsorbed Aluminum HydroxideSCIT 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
Pifferi 2002[3]	29	SCIT no treatment	11 +/- 3 10 +/- 2	Entire Study 55/45	15/0 14/4	NR
Van Bever 1990[4]	19	SCIT Placebo (after 1 year of SCIT)	12.2 (Range 8- 16) 12 (Range 9-14)	NR	9/NR 10/NR	NR
Schubert 2009[5]	34	SCIT Cluster SCIT Classic	10 8.5	NR NR	20/2 14/2	NR
Valovirta 1986[6] Valovirta 1984[7]	27	SCIT Placebo	11 (Range 5-18) 10.5 (Range 5-16)	60/40 58/42	15/0 12/0	NR
Adkinson 1997[8] Limb 2006[9]	121	SCIT Placebo	9 +/- 2 9 +/- 2	80/20 76/24	61/8 60/3	greater than 1 greater than 1

b) Table G2b. Patient characteristics – SCIT- Pediatrics-**Rhinoconjunctivitis**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
The PAT study Möller 2002[10] Niggeman 2006[11] Jacobsen 2007[12]	205	SCIT Placebo	Entire study 16 (Range 11-20)	Entire study 66/34	103/NR 102/NR	NR

c) Table G2c. Patient characteristics – SCIT- Pediatrics-**Asthma and Rhinitis**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Akmanlar 2000[13]	18	SCIT Rush SCIT Conventional	7 +/- 2.6 9 +/- 4	NR NR	9/0 9/0	NR

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Hedlin 1999[14]	32 3 dropouts whole study	SCIT SCIT and Placebo	11.7 (Range 7-16) 12 (Range 10-16)	53/57 43/57	15/NR 14/NR	NR
Cantani 1997[15]	300	SCIT Pharmacotherapy	Entire study 4 (Range 3.-7)	Entire study 58/42	151/NR 149/NR	NR

d) Table G2d. Patient characteristics – SCIT- Pediatrics-**Asthma and Rhinoconjunctivitis**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Dreborg 1986[16]	30	SCIT Placebo	11 (Range 5-17) 11 (Range 5-17)	NR	16/NR 14/NR	NR
Kuna 2011[17]	50	SCIT Placebo	12 +/-4 11 +/-4	50/50 50/50	30/NR 20/NR	2 years

TABLE G3. INTERVENTION CHARACTERISTICS -SCIT- PEDIATRICS

a) Table G3a. Intervention characteristics – SCIT- Pediatrics-Asthma

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Hill 1982[1]	SCIT Rye grass Rush Placebo	conventional therapy	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
Altintas 1999[2]	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 ≡ 1/1000w/v)	NR	Every 4 weeks	NR	2 years
Pifferi 2002[3]	SCIT Dust mite HDM No treatment	conventional therapy	800 U	24758.33 U (mean)	4 -6 weeks	NR	3 years

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Van Bever 1990[4]	SCIT Dust mite Cluster SCIT HDM Placebo	conventional therapy	1000 BU	16497 - 28497 (Year1: 16,497 Year 2: 12000) Year1: 16,497 Year 2:placebo	Every 4 weeks	NR	2 year
Schubert 2009[5]	SCIT dust mite Cluster alum-precipitated SCIT dust mite Conventional alum-precipitated	conventional therapy	5000 TUafter 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
Valovirta 1986[6] Valovirta 1984[7]	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
Adkinson 1997[8] Limb 2006[9]	SCIT Multiple allergen Placebo	conventional therapy and rescue therapy	0.7 mL of concentrate	NR	Biweekly for 24 months, every 3 weeks after 24 months	4.3 µg Der p1-5 µg Der f1-26 µg Amb a138 µg group 1 (Grass mix – timothy orchard perennial ryegrass) 6 µg Alt a1Not reported for Bermuda grass English plantain white oak Cladosporium herbarum Aspergillus fumigatus	27 months

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

b) Table G3b. Intervention characteristics – SCIT- Pediatrics-**Rhinoconjunctivitis**

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
The PAT study Möller 2002[10] Niggeman 2006[11] Jacobsen 2007[12]	SCIT Grass and Birch alum-precipitated Placebo	conventional therapy	100,000 SQ U/ml (Alutard SQ)	not specified	every 6 +/- 2 weeks interval	20 µg Phl p5 (grass) and 12 µg Bet v 1 (Birch)	3 years

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

c) Table G3c. Intervention characteristics – SCIT- Pediatrics-**Asthma and Rhinitis**

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Akmanlar 2000[13]	SCIT Dust mite Rush SCIT Dust mite Conventional	conventional therapy	100000 SQ-U 50000- 100000 SQ-U	NR	Biweekly Every 4 weeks		3 years
Hedlin 1999[14]	SCIT-perennial (cat or dust mite) alum-precipitated SCIT-seasonal (birch or timothy) + Placebo	conventional therapy	100,000 SQU 100,000 SQU	NR	Every 6 weeks	15.0 µg Fel d 1; 7.0 µg Der p 1 (maintenance) 20 µg Phl p 5; 23 µg Bet v 1 (maintenance)	3 years
Cantani 1997[15]	SCIT Dust mite Parietaria ryegrass alum-precipitated Pharmacotherapy	conventional therapy	500 BU per month	26000 BU	Every 4 weeks		3 years

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

d) Table G3d. Intervention characteristics – SCIT- Pediatrics-**Asthma and Rhinoconjunctivitis**

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
Dreborg 1986[16]	SCIT Cladosporium Placebo	conventional therapy	100000 BU (reached after 18 weeks	NR	Every 4 weeks		10 months
Kuna 2011[17]	SCIT Placebo	ONLY rescue therapy	2.0 ml (5000 TU/ml) or the highest tolerated dose	24.6 ml =123,000 TU (range, 109,000-158,000 TU).	Every 4 to 6 weeks	8 µg/mL Alt a 1	3 years

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg Ag/ml: major protein unit TU Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: See appendix C for detailed explanation on unitage

TABLE G4.- RISK OF BIAS-SCIT- PEDIATRICS

a) Table G4a. Quality assessment – SCIT- Pediatrics-**Asthma**

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Hill 1982[1]	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
Altintas 1999[2]	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
Pifferi 2002[3]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
Van Bever 1990[4]	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Schubert 2009[5]	Low risk	High risk	High risk	High risk	High risk	No	High risk
Valovirta 1986[6] Valovirta 1984[7]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Adkinson 1997[8] Limb 2006[9]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

b) Table G4b. Quality assessment – SCIT- Pediatrics-**Rhinoconjunctivitis**

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
The PAT study Möller 2002[10] Niggeman 2006[11] Jacobsen, 2007[12]	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

c) Table G4c. Quality assessment – SCIT- Pediatrics-**Asthma and Rhinitis**

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Akmanlar 2000 [13]	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
Hedlin 1999[14]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Cantani 1997[15]	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

d) Table G4d. Quality assessment – SCIT- Pediatrics-**Asthma and Rhinoconjunctivitis**

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Dreborg 1986[16]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
Kuna 2011[17]	Low risk	Low risk	Low risk	Low risk	High risk	Yes or unclear	Medium risk

High risk= inadequately addressed or unclear with a high risk of bias; Low risk= adequately addressed with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

TABLE G5-ASTHMA SYMPTOM SCORES- SCIT-PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Pifferi 2002[3]	Dust mite	SCIT Pharmacotherapy	3 years	Numbers of asthma exacerbations per year		8 8.5	1 4.5	SCIT vs Pharmacotherapy p < 0.01
Hill 1982[1]	Rye grass	SCIT Placebo	Year 1 (preseasonal IT for >4 months)	Median asthma symptom score	Calculated score from 3 domains	3 (before season) 4 (before season)	7 (during season) 5 (during season)	SCIT pre vs post p <0.05 Placebo pre vs post p NS
Hill 1982[1]	Rye grass	SCIT Placebo	Year 2 (No IT given)	Median asthma symptom score	Calculated score from 3 domains	3 (before season) 2 (before season)	3 (during season) 5 (during season)	SCIT pre vs post p NS Placebo pre vs post p significant but value not reported (No report of statistical comparison between year 1 and

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
								year 2)
Dreborg 1986[16]	Cladosporium	SCIT – Cluster Placebo	6 months (2 weeks with highest spore counts)	Bronchial symptoms	0-3	210 240	170 260	SCIT vs Placebo p NS
Adkinson 1997[8] Limb 2006[9]	Multiple	SCIT Placebo	last follow up (18 months or more)	Symptom score		0.34 0.37	-0.08 (change from baseline) -0.16 (change from baseline)	SCIT pre vs post p= 0.02 Placebo pre vs post p= 0.003 SCIT vs Placebo p = 0.5 (Mean difference pre = 0.003; post = -0.08)
Cantani 1997[15]	Dust mites ryegrass and parietaria	SCIT Pharmacotherapy	Year 3	Mean percentage of NIGHTS with asthma		NR NR	40 66	SCIT vs Pharmacotherapy p<0.0005
Cantani 1997[15]	Dust mites ryegrass and parietaria	SCIT control	Year 3	Mean percentage of DAYS with asthma		NR NR	32 56	SCIT vs Control p=0.0001
Kuna 2011[17]	Alternaria	SCIT Placebo	3 years	Mean asthma symptom scores (Visual analog scale)	0-400	88.6 85.5	22.4 42	SCIT vs Placebo p = 0.0005

TABLE G6- ASTHMA MEDICATION SCORES- SCIT- PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Pifferi 2002[3]	Dust mite	SCIT Pharmacotherapy	3 years	Days of therapy/year (Salbutamol)		40 50	7 40	SCIT vs Pharmacotherapy p <0.01
Pifferi 2002[3]	Dust mite	SCIT Pharmacotherapy	3 years	Days of therapy/year (systemic steroids)		22 25	1 12	SCIT vs Pharmacotherapy p <0.01

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Hill 1982[1]	Rye grass	SCIT Placebo	Year 1 (preseason al IT x >4 months)	Median asthma drug score		4 (before season) 1 (before season)	5 (during season) 2 (during season)	SCIT pre vs SCIT post p <0.05 Placebo pre vs Placebo post p NS
Hill 1982[1]	Rye grass	SCIT Placebo	Year 2 (No IT given)	Median asthma drug score		4 (before season) 1 (before season)	4 (during season) 2 during season)	SCIT pre vs SCIT post p NS Placebo pre vs Placebo post p NS
Adkinson 1997[8] Limb 2006[9]	Multiple allergen	SCIT Placebo	27 months	10 point ordinal scale medication score	0-10	4.9 5.0	-1.4 (change from baseline) -1.2 (change from baseline)	SCIT pre vs SCIT post p <0.001 Placebo pre vs Placebo post p <0.001 SCIT vs Placebo p =0.37 (Mean difference pre = 0.11; post = 0.22)
Cantani 1997[15]	Dust mite-Parietaria-ryegrass	SCIT Placebo	3 year	Mean drug usage for asthma attacks		NR	52 180	SCIT vs Placebo p= 0.0003

TABLE G7- ASTHMA COMBINED SYMPTOM AND MEDICATION SCORES- SCIT- PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Akmanlar 2000[13]	Dust mite	SCIT rush SCIT conventional	3 years	Combined total symptoms and Medication score	Symptom 0-3 Medication 0-7	NR NR	NR NR	SCIT rush pre vs post p = 0.0003 SCIT conventional pre vs post p = 0.0003 SCIT vs placebo p NS
Altintas 1999[2]	Dust mite	SCIT-Adsorbed aluminum SCIT-Adsorbed calcium SCIT-aqueous Placebo	2 years	Combined asthma symptom medication score (SMS)	Symptom 0-3 Medication 0-7	6.2 5.1 4.6 4.0	0.7 2.4 1.4 3.2	SMS was significantly reduced after IT period (p <0.05); most significant improvement occurred in Arm 1 and least improvement in Arm 4 (placebo) with no significant difference among the IT group.
Kuna 2011[17]	Alternaria	SIT Placebo	3 years	Combined symptom medication score		75 75	30 62	SCIT vs Placebo p<0.001 (65% reduction when compared to placebo)

TABLE G8.SCIT – ASTHMA STUDIES REPORTING COMBINED ASTHMA AND RHINOCONJUNCTIVITIS MEDICATION SCORES – SCIT- PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Dreborg 1986[16]	Cladosporium	SCIT Placebo	6 months (during 2 weeks with highest spore count)	Total daily medication score	Sum of doses per day	1370 1170	1180 1630	SCIT vs Placebo p<0.01
Kuna 2011[17]	Alternaria	SIT Placebo	Baseline-3yr	Mean daily medication score		13.8 11.2	2.3 21.4	SCIT pre vs Post p<0.001 Placebo pre vs Post p=0.001 SCIT vs Placebo p=0.001

TABLE G9- ASTHMA PFT RESULTS- SCIT-PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
Adkinson 1997[8] Limb 2006[9]	Multiple	SCIT Placebo	last follow up (18 months or more)	PEFR	81.9 84.8	2.5 (change from baseline) -1.4 (change from baseline)	SCIT vs Placebo p = 0.05 (mean difference pre = 2.9; post = -3.8)
Dreborg 1986[16]	Cladosporium	SCIT Placebo	6 months	Mean PEF	290 310	280 340	SCIT vs Placebo p NS

TABLE G10- SCIT-CHALLENGES SCORES- SCIT-PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Adkinson 1997[8] Limb 2006[9]	Cats	SCIT Placebo	last follow up	PEFR		81.9 84.8	2.5 -1.4	SCIT pre vs post p = 0.5
Adkinson 1997[8] Limb 2006[9]	Cats	SCIT Placebo	last follow up	Bronchial provocation to methacholine		0.23 0.32	0.41 0.39	SCIT vs Placebo p = 0.99
Dreborg 1986[16]	Cladosporium	SCIT Placebo	10 week period during peak season	Conjunctival provocation tets		NR NR	NR NR	SCIT pre vs post p=0.01 SCIT vs Placebo p>0.05

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Dreborg 1986[16]	Cladosporium	SCIT Placebo	10 week period during peak season	Bronchial provocation test		NR NR	NR NR	SCIT pre vs post p<0.01 SCIT vs Placebo p<0.05
Akmanlar 2000[13]	Dust mites	SCIT-Rush SCIT-conventional	3 years	Allergen bronchial provocation test		20470 20470		Rush vs conventional p=0.41 (6 months)
Altintas 1999[2]	Dust mite	SCIT-Adsorbed aluminum SCIT-Adsorbed calcium SCIT-aqueous Placebo	2 years	Allergen bronchial provocation test		7244 4786 2137 4786	31622 39810 31153 7100	No significant difference among treatment groups, p>0.05 All SCIT vs Placebo p<0.05
Hedlin 1999[14]	Cat, dust mite, Birch, Timothy	SCIT Placebo	1 year	Allergen bronchial provocation, PC-20		1900 1400	100000 5600 (SQU/ml)	SCIT pre vs post p<0.001 Placebo pre vs post, p<0.01 SCIT vs Placebo p=0.001
Hedlin 1999[14]	Cat, dust mite, Birch, Timothy	SCIT Placebo	1 year	Histamine bronchial provocation		0.18 0.28	1.68 0.54 (mg/ml)	SCIT pre vs post p=0.002 Placebo pre vs post p<0.05 SCIT vs Placebo p=NS
Kuna 2011[17]	Alternaria	SCIT Control	3 years	Nasal Challenge		207 199	67 185	SCIT pre vs post p<0.05

TABLE G11- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES- SCIT-PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
The PAT study Möller 2002[10] Niggeman 2006[11] Jacobsen, 2007[12]	SCIT Grass and Birch	SCIT Placebo	5 years	VAS Nose symptom score		0 0	-21.5 -7.4	SCIT vs Placebo p <0.01
Kuna 2011[17]	Alternaria	SCIT Placebo	3 years	Mean rhinitis symptom scores (Visual analog scale)	0-500	311.1 331.0	78.7 145.0	SCIT vs Placebo p = 0.028
Dreborg 1986[16]	Cladosporium	SCIT Placebo	10 week period during peak season before tx and the following year after 5-7 months of tx	Unspecified nasal symptom score (sneezing, rhinorrhea and occlusion)	0-3	175 200	140 160	SCIT vs Placebo p> 0.05 No significant difference

TABLE G12- OCULAR SYMPTOM SCORES- SCIT-PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
The PAT study Möller 2002[10] Niggeman 2006[11] Jacobsen 2007[12]	Birch and Timothy grass	SCIT Placebo	5 year	VAS- Ocular symptoms	0-100mm		-29.4 mm Change from baseline -11.8 mm Change from baseline	SCIT vs Placebo p<0.01
Dreborg 1986[16]	Cladosporium	SCIT Placebo	10 weeks	None	0-3			SCIT vs Placebo p>0.05
Kuna 2011[17]	Alternaria	SCIT Placebo	3 years	Mean conjunctivitis symptom scores (Visual analog scale)	0-100	71 88	6 49	SCIT vs Placebo p = 0.001

TABLE G13- RHINITIS COMBINED SYMPTOMS AND MEDICATION SCORES-SCIT- PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Kuna 2011[17]	Alternaria	SCIT Placebo	3rd year-peak season Baseline – peak season	Sum of symptom and medication scores recorded daily during allergy season (July, August, and September)	3 yr: Baseline: 75	At baseline SLIT: 75 plac: 75	At 3rd year: SLIT: 28 plac: 62	SLIT vs Placebo Baseline: p=0.73 year 3 p<0.0001 AUC year 1 10.8%, AUC year 2 38.7%, AUC year 3 63.5%

TABLE G14.- ASTHMA QOL -SCIT- PEDIATRICS

Study	ARMS	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Kuna 2011[17]	SCIT Placebo	Baseline and after 1, 2, and 3 years of SIT	Asthma QOL questionnaire score in children up to 12 years	higher score = higher QOL	At baseline SCIT: 4.19 plac: 4.8	At 3rd year: SCIT: 5.8 plac: 3.9	SCIT pre-post: p=0.008 increase in QOL Placebo pre-post: p=0.019 decrease in QOL SCIT vs Plac post: p=0.04
Kuna 2011[17]	SCIT Placebo	Baseline and after 1, 2, and 3 years of SIT	Asthma QOL questionnaire score in adolescents (12-18y)	higher score = higher QOL	At baseline SCIT: 3.9 plac: 4.3	At 3rd year: SCIT: 6.5 plac: 4.2	SCIT pre-post: p=0.005 increase in QOL Placebo pre-post: p=0.715 no change in QOL SCIT vs Plac post: p=0.018

TABLE G15.- RHINITIS/RHINOCONJUNCTIVITIS QOL - SCIT- PEDIATRICS

Study	ARMS	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
Cantani 1997[15]	SCIT Control (drug-treated)	3 year	QOL				No significant difference
Kuna 2011[17]	SCIT Control	Baseline and after 1, 2, and 3 years of SIT	Rhinoconjunctivitis QOL questionnaire score in children up to 12 years	lower score = higher QOL	At baseline SCIT: 1.7 plac: 2.0	At 3rd year: SCIT: 0.7 plac: 2.7	SCIT pre-post: p=0.003 increase in QOL Placebo pre-post: p=0.019 decrease in QOL SCIT vs Plac post: p=0.001
Kuna 2011[17]	SCIT Control	Baseline and after 1, 2, and 3 years of SIT	Rhinoconjunctivitis QOL questionnaire score in adolescents (12-18y)	lower score = higher QOL	At baseline SCIT: 2.7 plac: 2.0	At 3rd year: SCIT: 0.9 plac: 2.2	SCIT pre-post: p=0.0006 increase in QOL Placebo pre-post: p=0.68 no change in QOL SCIT vs Plac post: p=0.03

TABLE G16.- RHINITIS – PREVENTION OF ASTHMA -SCIT- PEDIATRICS

Study	ARMS	Prevention of asthma
The PAT study Möller 2002[10] Niggeman 2006[11] Jacobsen, 2007[12]	SCIT Placebo	After 3 years of SCIT, OR 2.52 (1.3-5.1); p<0.05 in favor of the hypothesis that SIT can prevent the development of asthma in children with pollinosis. N=151 children without asthma at beginning of study. 5 year follow up: No significant increase in the number of patients reporting symptoms of asthma. OR 2.68 (1.3-5.7, p<0.05) in favor of hypothesis that SIT can prevent development of asthma; 39% reported asthma symptoms (p<0.01) 10 year follow up: (7 years after finishing 3 years of SIT) 147 subjects of 205 initially randomized 10 years ago. Among SIT group, 16/64 children developed asthma, compared to 24/53 children in the control group. OR= 2.5 (1.1-5.9) Based on patients without asthma before treatment (n=117)

TABLE G17. SAFETY – SCIT - PEDIATRICS

SCIT LOCAL REACTIONS -Reported as patients

Study	Allergen	Number of patients in arm	Number of events and Description	% of patients	Severity
Akmanlar 2000[13]	Dust mites: Der P and F Rush vs Cluster Cluster	18	3 patients Local swelling > 3 cm: required adjust dosing	17%	Moderate
Altintas 1999[2]	Dust mites: Dermatophagoides pteronyssinus	34	5 patients Local swelling > 3 cm: required adjust dosing	15%	Unspecified
Kuna 2011[17]	Alternaria	30	4 patients /11 reactions (987 injections): Local edema	13%	Mild
Van Bever 1990[4]	Dust mite	9	1 patients with Local swelling	11%	Mild

SCIT LOCAL REACTIONS - Reported as events

Study	Allergen	Number of patients in arm	Number of events and Description	% of injections	Events per Patient	Severity
Schubert 2009[5]	Dust mites (cluster schedule)	20 (341 injections)	185 local events: Redness: 97 (28%), Swelling <5cm: 57 (16%), Swelling > 5cm: 22 (6%), painful swelling >3h: 8 (2%)	54%	9.25	Mild
	Dust mites (classic schedule)	10 (151 injections)	80 local events: Redness: 40 (26%), Swelling <5cm: 20 (13%), Swelling > 5cm: 17 (11%), painful swelling >3h: 3 (2%)	53%	8	Mild
Dreborg 1986[16]	Cladosporium	16	4 local reactions: defined as reaction > 10 cm diameter	NA	0.25	Mild
Valovirta 1986[6]	Dogs	15	309 local reactions: 227<1cm, 71 1-3cm, 11>3cm	NA	20	Mild
	Placebo	12	251 local reactions: 163<1cm, 82 1-3cm, 6>3cm	NA	21	Mild

SCIT CUTANEOUS REACTIONS - Reported as patients

Study	Allergen	Number of Patients in arm	Number of events and Description	% of patients	Severity
Dreborg 1986[16]	Cladosporium	16	3 patients: urticaria	19%	Unspecified
Cantani 1997[15]	Dermatophagoides pteronyssinus Perennial ryegrass Parietaria officinalis	151	3 patients: urticaria	2%	Unspecified

SCIT RESPIRATORY REACTIONS - Reported as patients

Study	Allergen	Number of Patients in arm	Number of events and Description	% of patients	Severity
Akmanlar 2000[13]	Both Der P and F (conventional schedule) Both Der P and F (rush schedule)	9 9	3 patients bronchospasm 2 patients bronchospasm	30% 22%	Severe Severe
Cantani 1997[15]	Multiple: Dermatophagoides pteronyssinus, Perennial ryegrass, Parietaria officinalis	151	2 patients with wheezing	1%	Unspecified

SCIT RESPIRATORY REACTIONS - Reported as events

Study	Allergen	Number of Patients in arm	Number of events and Description	% of injections	Events per Patient	Severity
Schubert 2009[5]	Dust mites (cluster schedule)	20 (341 injections)	12 reactions: 10 cough-2 dyspnea 2 reactions had bronchial asthma)	3.5% 0.6%	0.7	Mild Moderate
	Dust mites (classic schedule)	10 (151 injections)	7 reactions: 6 cough-1 dyspnea 1 reaction had bronchial asthma)	4.6% 0.7%	0.8	Mild Moderate

SCIT SYSTEMIC REACTIONS: GENERAL SYMPTOMS

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Adkinson 1997[8]	Multiple allergens Placebo	61 60	21 patients with systemic reactions 4 patient with systemic reactions	34% 7%	Unspecified Unspecified
Kuna 2011[17]	Alternaria Placebo	30 20	1 patient reported headache 1 hour after injection that continued up to 5 hours, no treatment given. 2 patients with mild facial flushing and redness with placebo injections	3% 10%	Mild Unspecified

SCIT UNSPECIFIED REACTIONS - Reported as patients

Study	Allergen	Number of Patients in Arm	Number of events and Description of the reaction	% of Patients	Severity
Hedlin 1999[14]	Cats Dermatophagoides pteronyssinus White birch Timothy grass (plus pollen extract)	15	5 systemic side effects : 1 patient was excluded due to recurrent asthma and urticaria	33%	Mild

SCIT UNSPECIFIED REACTIONS - Reported as events

Study	Allergen	Number of Patients in Arm	Number of events and Description of the reaction	% of Injections	Events per Patient	Severity
Dreborg 1986[16]	Cladosporium	16	45 unspecified systemic reactions	NA	2.8	Unspecified

ANAPHYLACTIC REACTIONS

Study	Allergen	Number of Patients in arm	Number of events	Definition of anaphylaxis
No study reported Anaphylactic reactions				

% of patients calculated, % of injections given in the article, NA Not available: means % is not given and can not be calculated as denominator is not given.

2. SUBLINGUAL IMMUNOTHERAPY

TABLE G18. - STUDY CHARACTERISTICS SLIT – PEDIATRICS

a) Table G18a. Study characteristics – SLIT- Pediatrics-Asthma

Study, Author, Year, Country	Diagnosis	Seasonal OR Perennial	Single or multiple Allergen	Allergen	Inclusion criteria	Funding source
Pajno 2000 Italy[18]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: Children No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Industry
Lue 2006 Taiwan[19]	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: 6-12 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Other (not industry)
Niu 2006[20] Taiwan	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Positive skin test No previous immunotherapy Positive specific IgE test Monosensitized individuals only Minimum duration of disease: 1 year	Not stated

b) Table G18b. Study characteristics – SLIT- Pediatrics-Rhinitis

Study, Author, Year, Country	Diagnosis	Seasonal OR Perennial	Single or multiple Allergen	Allergen	Inclusion criteria	Funding source
deBot 2011[21] Netherlands	Rhinitis	Perennial	Multiple	Dust mite: Dermatophagoides pterynossum and farinae	Age: Children 6-18 years Positive specific IgE test No previous immunotherapy Minimum duration of disease: 1 year	Industry
Tseng 2008[22] Taiwan	Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: 6-18 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Industry Non-profit

c) Table G18c. Study characteristics – SLIT- Pediatrics-Rhinoconjunctivitis

Study, Author, Year, Country	Diagnosis	Seasonal OR Perennial	Single or multiple Allergen	Allergen	Inclusion criteria	Funding source
la Rosa 1999[23] Leonardi 2009[24] France-Italy	Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Positive specific IgE test Positive skin test Monosensitized individuals only	Industry
Novembre 2004[25] Italy	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Roder 2007[26] The Netherlands	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Age: 6-18 years Positive specific IgE test No previous immunotherapy	Industry
Stelmach 2011 Poland[27]	Asthma/ Rhinitis	Seasonal	Multiple	Grass: Grass mix	Age: Children 6-18 years No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Academia

d) Table G18d. Study characteristics – SLIT- Pediatrics-Asthma and Rhinitis

Study, Author, Year, Country	Diagnosis	Seasonal OR Perennial	Single or multiple Allergen	Allergen	Inclusion criteria	Funding source
Marogna 2008 Italy[28]	Asthma and Rhinitis	Seasonal	Multiple	Trees: White birch Grass: Grass mix	Age: 5-17 years No previous immunotherapy Positive skin test Minimum duration of disease: 2 years	Not stated
Hirsch 1997 Germany[29]	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: children No previous immunotherapy Positive specific IgE test Positive skin test	Not stated
Bahceciler 2001[30] Turkey	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: children >7 years old No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Tari 1990[31]	Asthma and Rhinitis	Perennial	Multiple	Dust mites : Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 3 years	Not stated

e) Table G18e. Study characteristics – SLIT- Pediatrics-Asthma and Rhinoconjunctivitis

Study, Author, Year, Country	Diagnosis	Seasonal OR Perennial	Single or multiple Allergen	Allergen	Inclusion criteria	Funding source
Pajno 2003[32] Pajno 2004[33] Italy	Asthma and Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Age: children Positive skin test Positive specific IgE test No previous immunotherapy	Industry
Vourdas 1998[34] France-Greece	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Olive	Positive specific IgE test Positive skin test	50% of authors are industry
Pajno 2011[35] Italy	Asthma/ Rhinoconjunctivitis	Seasonal	Multiple	Grass mix (Timothy, Sweet Vernal, Rye, Cock's foot, Meadow)	No previous immunotherapy Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Not stated
Valovirta 2006[36] Savolainen 2006[37] Finland	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Trees: Tree mix	Age: 5-14 years Positive specific IgE test Positive skin test Minimum duration of disease: 2 years No previous immunotherapy	Industry
Ippoliti 2003[38] Italy	Asthma and Rhinoconjunctivitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: children No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Government

TABLE G19.- PATIENT CHARACTERISTICS SLIT – PEDIATRICS

a) Table G19a. Patient characteristics – SLIT- Pediatrics-**Asthma**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Gender % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean number of years affected with disease
Pajno 2000[18]	24	SLIT Placebo	11 (Range 8-15) 12 (Range 8-15)	58/42 50/50	12/0 12/3	4.8 years 5.1 years
Lue 2006[19]	20	SLIT Placebo	7.7 +/- 1.8 8.6 +/- 1.8	40/60 40/60	10/0 10/0	1 year 1 year
Niu 2006[20]	110	SLIT Placebo	7.9 +/- 1.6 (Range 5-11) 8.2 +/- 1.7 (Range 5-12)	61/39 58/42	56/7 54/6	1 year 1 year

b) Table G19b. Patient characteristics – SLIT- Pediatrics-**Rhinitis**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Gender % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean number of years affected with disease
deBot 2011[21]	257	SLIT Placebo	11.8 +/- 3.1 11.7 +/- 2.9	61/39 59/41	125/17 126/15	1 year
Tseng 2008[22]	63	SLIT Placebo	9.7 +/- 3.3 9.7 +/- 3	73/27 70/30	30/2 33/2	63%: 2-5 years, 33%: 6-10 years, 3%: 13 years 52% : 2-5 years, 48%: 6-10 years, 0% :13 years

c) Table G19c. Patient characteristics – SLIT- Pediatrics-**Rhinoconjunctivitis**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Gender % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean number of years affected with disease
la Rosa 1999[23] Leonardi 2009[24]	41	SLIT Placebo	10 (Range 6-14) 10 (Range 7-13)	65/35 57/43	20/5 21/4	3 years 4 years
Novembre 2004[25]	113	SLIT Controls	8.96 (Range 5-14) 7.74 (Range 4-16)	70/30 70/30	54/6 59/10	NR NR
Roder 2007[26]	204	SLIT Placebo	12.9 +/- 2.6 (Range 7-17) 12.5 +/- 2.9 (Range 6-17)	67/33 44/56	108/26 96/24	NR NR
Stelmach 2011[27]	60	SLIT pre-coseasonal SLIT continuous Placebo	8.3 (Range 5-17) 10.1 (Range 3-16) 8.1 (Range 4-15)	65/35 74/26 61/39	20/3 20/1 20/2	2 years 2 years 2 years

d) Table G19d. Patient characteristics – SLIT- Pediatrics-**Asthma and Rhinitis**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Gender % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean number of years affected with disease
Marogna 2008[28]	216	SLIT Control	10.7 +/- 0.43 10.0 +/- 0.3	72/38 60/40	144/14 72/6	2 years 2 years
Hirsch 1997[29]	30	SLIT Placebo	11.3 (Range 6-15) 9.92 (Range 6-14)	66/34 66/34	15/1 15/0	4.5 years (asthma),5 years (rhinitis) 2.5 years (asthma),3 years (rhinitis)
Bahceciler 2001[30]	15	SLIT Placebo	Median 12.4 (Range 7.8-18) Median12 (Range 7.3-15)	50/50 57/43	8/0 7/0	Median 1.5 Median 3
Tari 1990[31]	66	SCIT Placebo	Range 5-12 Range 5-12	Entire study 64/36	34/4 32/4	≥3 years ≥3 years

e) Table G19e. Patient characteristics – SLIT- Pediatrics-**Asthma and rhinoconjunctivitis**

Study	Patients randomized	Comparators	Age in years Mean +/- SD (range)	Gender % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean number of years affected with disease
Pajno 2003[32] Pajno 2004[33]	30	SLIT+ fluticasone Placebo+fluticasone	11 (Range 8-14) 11 (Range 8-14)	47/53 40/60	15/1 15/2	4.7 years 3.1 years
Vourdas 1998[34]	66	SLIT Placebo	12 (Range 8-17) 12 (Range 7-17)	74/26 75/25	34/1 32/1	4 years 4 years
Pajno 2011[35]	80	SLIT continuous; SLIT co-seasonal	11 (Range 8-16) 12 (Range 8-16)	60/40 47/53	40/3 40/5	5.2 years 4.1 years
Valovirta2006[36] Savolainen 2006[37]	98	SLIT high dose – gp 2 SLIT low dose – gp 1 Placebo	9.0 +/- 2.7 9.6 +/- 3.1 9.9 +/- 3.0	48/52 59/41 62/38	32/7 33/1 33/6	4.1 years (rhinitis) 5.0 years (rhinitis) 4.6 years (rhinitis)
Ippoliti 2003[38]	86	SLIT Placebo	Median 9 (Range 5-12) Median 9 (Range 7-11)	60/40 56/44	47/0 39/0	1.8 years 1.6 years

TABLE G20. INTERVENTION CHARACTERISTICS –SLIT – PEDIATRICS

a) Table G20a. Intervention characteristics – SLIT- Pediatrics-**Asthma**

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
Pajno 2000[18]	SLIT Dust mite Placebo	ONLY rescue medication	5 drops of 10 BU/ml	NR	3 times a week	2.4 Der p 1, 1.2 Der p 2 (per week)	2 years
Lue 2006[19]	SLIT Dust mite Placebo	conventional therapy	20 drops of 300 IR/mL	41824 IR	Daily	3000 Der F , 1700 Der P (cumulative)	6 months
Niu 2006[20]	SLIT Dust mite Placebo	ONLY rescue medication	20 drops of 300 IR/ml	41824 IR	Daily	3000 Der F , 1700 Der P (cumulative)	24 weeks

b) Table G20b. Intervention characteristics – SLIT- Pediatrics-**Rhinitis**

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
deBot 2011[21]	SLIT Dust mite(DP) placebo	Conventional therapy	20 drops =700 BU	435 µg Der p 1	2 times a week	2.03 µg Der p 1 (maintenance dose)	2 years
Tseng 2008[22]	SLIT Dust Mite Placebo	ONLY rescue medication	20 drops 300 IR/mL	37,312 IR	Daily	1560 Der P 2710 Der f (cumulative)	3 weeks induction therapy, 21 weeks maintenance

c) Table G20c. Intervention characteristics – SLIT- Pediatrics-**Rhinoconjunctivitis**

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
la Rosa 1999[23] Leonardi 2009[24]	SLIT Parietaria Placebo	conventional therapy	20 drops of 300 IR/ml	75,000 IR per year	3 times a week	52.5 Par j 1 (cumulative)	2 years
Novembre 2004[25]	SLIT Grass mix symptomatic therapy	ONLY rescue medication	5 drops of 25 BU/ml	120 µg	Daily	0.5 Group V major grass (maintenance)	3 years
Roder 2007[26]	SLIT Grass mix Placebo	conventional therapy	9500 BU	1976000 BU, 4.5 mg Lol p5	2 times a week	21µg Lol p 5 (maintenance)	2 years
Stelmach 2011[27]	SLIT pre-co-seasonal - grass mix SLIT continuous – grass mix placebo	ONLY rescue medication	300IR	3.6 mg 7.3 mg	Arm 1:Daily for 6 of 12 months Arm 2: daily for 12 of 12 months	10 µg of major allergens (maintenance dose) Dact g 5, Antx 0 5, Lol p 5, Poa p 5, Phl p 5	12 months

d) Table G20d. Intervention characteristics – SLIT- Pediatrics-**Asthma and Rhinitis**

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
Marogna 2008[28]	SLIT Birch /Grass conventional therapy	conventional therapy	5 drops of 10,000 RU/ml	480 µg of Der p1, 480 µg Der p2, 40 µg of Phl p 1, 40 µg Par j 1, 100 µg of Bet v 1 (per year)	3 times a week	480 µg of Der p1, 480 µg Der p2, 40 µg of Phl p 1, 40 µg Par j 1, 100 µg of Bet v 1 (per year)	3 years

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
Hirsch 1997[29]	SLIT Dust mite Placebo	conventional therapy	7 drops of 11.9 µg /ml=3.75 µg g	570 µg (per year)	3 times a week	570 Der p1 (per year)	1 year
Bahceciler 2001[30]	SLIT Dust mite Placebo	conventional therapy	20 drops of 100 IR/mL	7000 IR (560 µg Der P, 980 µg Der F)	daily 4 weeks, then 2 times a week for 4 months	560 Der P, 980 Der F (cumulative)	6 months
Tari 1990[31]	SLIT Placebo	ONLY rescue medication	15 drops of 500 STU/ml or 5BU/ml		3 times per week		18 months

e) Table G20e. Intervention characteristics – SLIT- Pediatrics-**Asthma and rhinoconjunctivitis**

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
Pajno 2003[32] Pajno 2004[33]	SLIT Parietaria Placebo	conventional therapy	5 drops of 10 BU/ml	20.3 µg	every other day	20.3 Par j 1 (cumulative)	13 months
Pajno 2011[35]	continous SLIT co-seasonal SLIT Grass mix	Conventional therapy	6 drops of 300 IR/ml	NR	5 days per week	6 drops of 14 µg /ml Phl p 5 (maintenance dose)	32 months 4 months/year during season, total of 2 years of treatment
Vourdas 1998[34]	SLIT Olive Placebo	conventional therapy	20 drops of 300 IR/ml	30000 IR/year	Daily	4050 Ole e 1 (per year)	seasonal (6 months each year) for 2 years
Valovirta, 2006[36] Savolainen 2006[37]	SLIT Tree mix-High dose SLIT Tree mix-Low dose Placebo	conventional therapy	100,000 SQ-U/ml (per week) 12,000 SQ-U/ml (per week)	200,000 SQ-U/ week =30 µg 24,000 SQ-U/ week or 3.6 µg	5 times a week	30 Bet v1/Aln g 1/Cor a1 (per week) 3.6 Bet v1/Aln g 1/Cor a1 (per week)	5 weeks build-up up to 18 months 18 months maintenance
Ippoliti 2003[38]	SLIT Dust mite Placebo	conventional therapy	5 drops of 10 BU/mL	NR	3 times a week	2.4 Der p 1 1.2 Der p 2 (per week)	6 months

TABLE G21.- QUALITY ASSESSMENT – SLIT – PEDIATRICS

a) Table G21a. Quality assessment – SLIT- Pediatrics-**Asthma**

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Pajno 2000[18]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Lue 2006[19]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Niu 2006[20]	Low risk	Low risk	Low risk	High risk	High risk	No	Medium risk

High= inadequately addressed or unclear, with a high risk of bias; Low= adequately addressed, with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

b) Table G21b. Quality assessment – SLIT- Pediatrics-**Rhinitis**

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
deBot 2011[21]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Tseng 2008[22]	Low risk	Low risk	Low risk	High risk	Low risk	No	Medium risk

High= inadequately addressed or unclear, with a high risk of bias; Low= adequately addressed, with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

c) Table G21c. Quality assessment – SLIT- Pediatrics-**Rhinoconjunctivitis**

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
la Rosa, 1999[23] Leonardi 2009[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Novembre 2004[25]	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Roder 2007[26]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Stelmach 2011[27]	Low risk	Low risk	Low risk	Low risk	High risk	No	Low risk

High= inadequately addressed or unclear, with a high risk of bias; Low= adequately addressed, with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

d) Table G21d. Quality assessment – SLIT- Pediatrics-**Asthma and Rhinitis**

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Marogna 2008[28]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
Hirsch 1997[29]	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
Bahceciler 2001[30]	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Tari 1990[31]	Low risk	High risk	High	Low risk	Low risk	Yes or unclear	Medium risk

High= inadequately addressed or unclear, with a high risk of bias; Low= adequately addressed, with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

e) Table G21e. Quality assessment – SLIT- Pediatrics-**Asthma and rhinoconjunctivitis**

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Pajno 2003[32] Pajno 2004[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
Vourdas 1998[34]	Low risk	High risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
Pajno 2011[35]	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
Valovirta, 2006[36] Savolainen 2006[37]	Low risk	High risk	Low risk	Low risk	Low risk	Yes or unclear	Medium risk
Ippoliti 2003[38]	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk

High= inadequately addressed or unclear, with a high risk of bias; Low= adequately addressed, with a low risk of bias; Yes/Unclear= Sponsor involved in design or unclear involvement; No=sponsor uninvolved in design

TABLE G22-ASTHMA AND ASTHMA COMBINED SYMPTOM SCORES –SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Pajno 2000[18]	Dust mite	SLIT Placebo	2 years	Mean score for nighttime symptoms per month	0-90 per month	14 15	6 13.2	SLIT pre vs post p = 0.001 Placebo pre vs post p= 0.439 SLIT vs Placebo p <0.0001
Pajno 2000[18]	Dust mite	SLIT Placebo	2 years	VAS Asthma Symptoms	0-10/day	5.1 5.3	2.5 6.6	SLIT pre vs post p = 0.001
Lue 2006[19]	Dust mite	SLIT Placebo	6 months	night time asthma score	0-3/day	0.51 +/- 0.24 0.5 +/- 0.38	0.16 +/- 0.15 0.5 +/- 0.47	SLIT pre vs post p< 0.001 Placebo pre vs post p=0. 996 SLIT vs Placebo p = 0.047
Niu 2006[20]	Dust mite	SLIT Placebo	24 weeks	Daily asthma symptom score (Daytime + Nighttime symptoms)	0-3/day	0.11 0.05	0.04 0.06	SLIT vs Placebo p= 0.028
Hirsch 1997[29]	Dust mite	SLIT Placebo	1 year	Mean daily symptom score for pulmonary symptoms	0-3/day	0.36 0.07	0.07 0.28	SLIT pre vs post, p<0.05 SLIT vs Placebo p< 0.05
Tari 1990[31]	Dust mite	SLIT Placebo	18 months	Daily Lung symptom score (sum of individual sx scores)	0-3/sx	10 10	6 9.5	SLIT pre vs post p 0.001 SLIT vs Placebo NS
Bahceciler 2001[30]	Dust mite	SLIT placebo	6 months	Asthma symptoms	0-3	0.64 0.33	0.3 0.26	SLIT pre vs post p <0.05 SLIT vs Placebo NS, p=0.77
Bahceciler 2001[30]	Dust mite	SLIT placebo	6 months	Total # of exacerbations experienced		NR	3 30	SLIT vs placebo, p=0.007
Ippoliti, 2003[38]	Dust mite	SLIT Placebo	6 months	Daily asthma symptom score (sum of individual sx scores)	0-3/sx (scale per Tari, 1990)	3.28 3.08	1.28 3.15	SLIT pre vs post p <0.001 Placebo pre vs post p NS
Pajno 2003[32] Pajno 2004[33]	Parietaria	SLIT Placebo	Pollen season (April-June)	Overall chest symptom score – median weekly sum for whole season	0-3/sx/d 4 sx	NR	5 8	SLIT vs Placebo p =0.191

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Pajno 2003[32] Pajno 2004[33]	Parietaria	SLIT Placebo	Pollen season (April-June)	VAS Chest symptoms – Overall median scores for the whole season, "How has your asthma been for the last 2 weeks?"	0-10/wk, Assessed weekly	NR	1.5 2.0	SLIT vs Placebo p =0.037
Valovirta, 2006[36] Savolainen 2006[37]	Tree mix	SLIT high dose SLIT low dose Placebo	Whole pollen season	Asthma symptoms	0-3/ day	NR NR NR	0.6 (48% reduction) 0.5 (34% reduction) 0.9	High dose vs placebo p=0.02 Low dose vs placebo NS
Valovirta, 2006[36] Savolainen 2006[37]	Tree mix	SLIT high dose SLIT low dose Placebo	Whole pollen season	Asthma and rhinoconjunctivitis symptoms	0-9/ day	NR NR NR	2.9 (40% reduction) 2.9 (31% reduction) 4.3	High dose vs placebo p=0.01, Low dose vs placebo p =0.03,
Stelmach 2011[27]	Grass mix	SLIT pre-coseasonal SLIT continuous Placebo	2 years	Asthma score (cough, wheeze, dyspnea)	0-3/sx 0-9/d	NR	4.3 5.9 13.8	SLIT coseasonal pre vs post: significant SLIT continuous pre vs post: signficant No difference in both active groups compared with placebo
Stelmach 2011[27]	Grass mix	SLIT pre-coseasonal SLIT continuous Placebo	2 years	Total symptom score (Nasal, ocular, asthma symptoms)	0-3/sx 0-30/d	NR	36.9 45.2 65.3	SLIT coseasonal pre vs post: significant SLIT continuous pre vs post: signficant coseasonal vs placebo: significant continuous vs placebo: significant coseasonal vs continuous: NS
deBot 2011[21]*	Dust mite	SLIT placebo	2 years	Dyspnea/wheeze score		NR	0.21+/-0.46 0.11+/-0.24	SLIT vs Placebo p=0.01, favoring placebo
Pajno* 2011[35]	Grass Mix (peds)	Cont SLIT Co-seasonal SLIT	3 yrs	0-3 per Chest symptom, 0-12 per day.	% reduction from baseline	NR	80% reduction 50% reduction	Continuous vs Seasonal NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Pajno* 2011[35]	Grass mix (peds)	Cont SLIT; Co seasonal SLIT	3 years	0-3 per symptom per day. Nasal, chest, eye symptoms	% reduction from baseline		60% reduction 50% reduction	Continuous vs Seasonal NS
Vourdas 1998[34] *	Olive	SLIT Placebo	2 years	Lung symptoms (cough, dyspnea, wheeze)	0-3/sx/d	0.15 0.31	0.05 0.25	Peak season comparison SLIT vs placebo, p<0.03

*In these studies, the diagnosis of asthma did not quality for inclusion in the body of evidence tables

TABLE G23- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES –SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
deBot, 2011[21]	Dust Mite	SLIT placebo	2 years	Total daily mean nose symptom score, based on rhinorrhea, blocked nose, sneezing, itching	0-3/ symptom 0-12/day	3.2 +/- 1.96 3.2 +/- 1.92	2.26 +/- 1.84 2.02 +/- 1.67	SLIT pre vs post: 26% decrease Placebo pre vs post: 37% decrease SLIT vs Placebo NS
Tseng, 2008[22]	Dust mite	SLIT Placebo	24 weeks	Daily rhinitis symptom scores ([Daytime+Nighttime scores] / 2)	0-3	1.79 +/- 1.13 2.33 +/-1.62	1.72+/- 1.78 1.89 +/-1.9	SLIT pre vs post p= 0.826 Placebo pre vs post p= 0.095 SLIT vs Placebo p= 0.608
la Rosa, 1999[23] Leonardi 2009[24]	Parietaria	SLIT Placebo	2 years	Daily means of rhinitis symptom scores (sneezing, rhinorrhea, nasal blockage)	0-3	NR NR	NR NR	SLIT vs Placebo p= 0.02 >30% reduction in rhinitis symptom
Roder, 2007[26]	Grass mix	SLIT Placebo	2 years	Mean daily total of all rhinoconjunctivitis symptoms	0-3/ symptom 0-15/day	8.7 9.0	3.1 3.4	SLIT vs Placebo NS
Hirsch, 1997[29]	Dust mite	SLIT Placebo	1 year	Mean daily nasal symptom score	0-3/d	1.4 0.48	0.84 0.34	SLIT vs Placebo p NS
Tari, 1990[31]	Dust mite	SLIT Placebo	18 months	Nasal symptom score	0-3	14.5 13.5	8.0 12	SLIT pre vs post p = 0.001 SLIT vs Placebo p NR

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Bahceciler, 2001[30]	Dust mite	SLIT Placebo	6 months	Rhinitis score (sneezing, rhinitis or blockage)	1/sx 0-2	1 (median) 0.64 (median)	0.4 (median) 0.38 (median)	SLIT vs Placebo p=0.56, NS
Pajno 2003[32] Pajno 2004[33]	Parietaria	SLIT Placebo	13 months	Median weekly sum Nasal symptoms	0-3/sx/d	NR	NR	SLIT vs Placebo NS p=0.059
Vourdas, 1998[34]	Olive	SLIT Placebo	pollen season Year 2	Rhinitis score	0-4	1.4 1.05	0.75 1.23	SLIT vs Placebo p NS
Valovirta, 2006[36] Savolainen 2006[37]	Tree mix	SLIT high dose SLIT low dose Placebo	Peak season	Nasal symptoms	0-3	NR NR NR	1.5 1.6 2.2	High dose vs Placebo p=0.04, 35% reduction vs placebo Low dose vs Placebo p =0.04, 31% reduction vs placebo
Ippoliti, 2003[38]	Dust mite	SLIT Placebo	6 months	Rhinitis symptom score (scale described by Tari, 1990)	0-3	0.84 0.91	0.39 0.82	SLIT pre vs post p <0.001 Placebo pre vs post p NS
Novembre, 2004[25]	Grass mix	SLIT Placebo	3 years	Rhinoconjunctivitis Symptom score	NR	NR	Mean 60 Mean 60	SLIT vs Placebo NS
Stelmach 2011[27]	Grass mix	SLIT pre-coseasonal SLIT continuous Placebo	2 years	Nasal score (rhinitis, sneezing, itching, nasal congestion)	0-3/sx 0-12/d	NR	20.6 28.0 34.2	Coseasonal pre vs post significant Continuous re vs post signficant coseasonal vs placebo p < 0.001 continuous vs placebo p>0.05 coseasonal vs continuous p<0.05

TABLE G24- CONJUNCTIVITIS SYMPTOM SCORES –SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Tari, 1990[31]	Dust mite	SLIT Placebo	18 months	Ocular symptoms	0-3	10 10	8 9	SLIT pre vs. post p NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
deBot, 2011[21]	Dust mite	SLIT placebo	2 years	0-3/eye score, 0-9 /day		NR	0.49 +/- 0.77 0.57 +/- 1.03	SLIT vs Placebo NS
Valovirta, 2006[36] Savolainen 2006[37]	Tree Mix	SLIT HighDose SLIT LowDose Placebo	Whole pollen season	Total eye symptoms (streaming, swelling, redness, itching)	0-3/sx 0-12/day	NR	0.8 0.9 1.1	High dose vs placebo, p=0.04, 47% reduction Low dose vs placebo, 32% reduction Low dose pre-post, NS p=0.1
Vourdas 1998[34]	Olive	SLIT Placebo	End of pollen season Year 2	4-point scale	0-4	0.13 0.14	0.03 0.23	seasonal peak comparison SLIT vs Placebo p <0.05; only significant week 19
Pajno, 2003[32] Pajno 2004[33]	Parietaria	SLIT Placebo	13 months	Median weekly sum, Conjunctivitis symptom score (itching, redness, streaming, swelling)	0-3/sx/d	NR	NR	SLIT vs Placebo, p=0.340
Stelmach 2011[27]	Grass mix	SLIT pre-coseasonal SLIT continuous Placebo	2 years	Ocular score (ocular pruritis, watery eyes, itching)	0-3/sx 0-9/d	NR	12.0 10.8 17.2	SLIT pre-coseasonal pre vs post significant SLIT continuous pre vs post signficant pre-coseasonal vs Placebo <0.01 continuous vs Placebo: NS >0.05 pre-coseasonal vs continuous NS >0.05

TABLE G25.- MEDICATION SCORES–SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Niu, 2006[20]	Dust mite	SLIT Placebo	24 weeks	Medication scores for oral corticosteroids (tabs/day)		0.11 +/- 0.35 0.04 +/- 0.15	0.03 +/- 0.22 0.04 +/- 0.22	SLIT pre-post p=0.183 Placebo pre-post p=1.00 SLIT vs Placebo p=0.195
Niu 2006[20]	Dust mite	SLIT Placebo	24 weeks	Inhaled corticosteroids (puffs/day)		0.60 +/- 1.14 0.47 +/- 0.84	0.43 +/- 1.09 0.37 +/- 0.86	SLIT pre-post p=0.78 Placebo pre-post p=0.52 SLIT vs Placebo, p=0.215

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Niu, 2006[20]	Dust mite	SLIT Placebo	24 weeks	Inhaled Beta-2 agonist (puffs/day)		0.06 +/- 0.09 0.03 +/- 0.01	0.02 +/- 0.31 0.05 +/- 0.27	SLIT pre-post, p=0.37 Placebo pre-post, p=0.185 SLIT vs Placebo, p=0.951
Niu, 2006[20]	Dust mite	SLIT Placebo	24 weeks	Anti-histamine (tabs/day)		0.23 +/- 0.43 -0.09 +/- 0.46	0.14 +/- 0.32 0.16 +/- 0.30	SLIT pre-post, p=0.174 Placebo pre-post, p=0.417 SLIT vs Placebo, p=0.068
Tseng, 2008[22]	Dust mite	SLIT Placebo	24 weeks	Anti-histamine (tabs/day)		0.38+/-0.44 0.62+/-0.65	0.25 +/- 0.51 0.53 +/- 0.69	SLIT pre-post p=0.826 Placebo pre-post p=0.312 SLIT vs Placebo p=0.462
Tseng, 2008[22]	Dust mite	SLIT Placebo	24 weeks	Beta-2 agonist (puffs per day)		0.04 +/- 0.13 0.05 +/- 0.17	0.04 +/- 0.12 0.04 +/- 0.15	SLIT pre-post p = 0.932 Placebo pre-post p = 0.843 SLIT vs Placebo p= 0.748
deBot, 2011[21]	Dust mite	SLIT; placebo	2 years	Proportion of days with rescue meds		NR	0.21 +/- 0.35 0.26 +/- 0.40	SLIT vs Placebo NS
Pajno 2000[18]	Dust mite	SLIT Placebo	2 years	Unspecified		259.68 296	82.68 205.2	SLIT vs Placebo p <0.0001
Lue 2006[19]	Dust mite	SLIT Placebo	6 months	Unspecified		1.7 +/- 1.08 1.25 +/- 0.72	1.0 +/- 0.94 1.1 +/- 1.15	SLIT pre-post p = 0.034 Placebo pre-post p= 0.432 SLIT vs Placebo p = 0.366
Hirsch 1997[29]	Dust mite	SLIT Placebo	1 year	Pulmonary symptom relief medication (beta-sympathomimetics, theophylline PRN)		NR	5 8	SLIT vs Placebo p NS
Hirsch 1997[29]	Dust mite	SLIT Placebo	1 year	Nasal symptom relief medication (anti-histamines, nasal steroids)		NR	3 1	SLIT vs Placebo p NS
Bahceciler 2001[30]	Dust mite	SLIT Placebo	6 months	Beta-2 mimetic (agonist) use; 2-point scale	0-1	median: 0.17 range: 0-0.77 median: 0.17 range: 0-1	median: 0.03 range: 0-0.48 median: 0.08 range: 0-0.29	SLIT pre vs post p=0.028

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Bahceciler 2001[30]	Dust mite	SLIT Placebo	6 months	Inhaled corticosteroid (ICS) dose; 6-point scale	0-5	median: 3.5 range; 2-4 median: 3 range; 2-5	median: 2 range; 1-3 median: 3 range; 0-5	SLIT pre vs post p=0.06 Placebo pre vs post p = 0.06 SLIT vs Placebo p = 0.06
Bahceciler 2001[30]	Dust mite	SLIT Placebo	6 months	Intranasal budesonide dose		3 (0-3) 2 (0-3)	1 (0-3) 2 (0-3)	SLIT pre vs post p=0.043 SLIT vs Placebo NS
laRosa 1999[23] Leonardi 2009[24]	Parietaria	SLIT Placebo	2 years	Daily mean anti-rhinitis medication score		Could not determine	Could not determine	SLIT vs Placebo p NS
Pajno2003[32] Pajno2004[33]	Parietaria	SLIT Placebo	Pollen season (April-June)	Drug scores, Median weekly sum, overall for the whole season		NR	1 3	SLIT vs Placebo p =0.192
Roder 2007[26]	Grass mix	SLIT Placebo	2 years	% rescue med free days		NR	69.3 (SEM: 3.4) 74.2 (SEM: 3.2)	SLIT vs Placebo p=0.674
Pajno 2011[35]	Grass mix	SLITContinous SLIT Coseasonal	3 years	Percent reduction from baseline (1 pt locally administered med, 2 pts systemic med)		NR	70% reduction 50% reduction	Continuous vs coseasonal NS difference in amount of reduction of medication use
Novembre 2004[25]	Grass Mix	SLIT Conventional therapy	3 years	Medication score	1 per medication	NR	8 21	SLIT vs conventional therapy p=0.02
Vourdas 1998[34]	Olive	SLIT Placebo	Pollen season Year 2	Unspecified		NR	NR	SLIT vs Placebo p NS Oral steroids were the only variables with p-values near significance, p=0.06, in favor of SLIT
Valovirta 2006[36] Savolainen 2006[37]	Tree mix	SLIT high dose SLITlow dose Placebo	Peak season	Mean daily med score (sum of meds administered /day) during whole season	0-8		2.9 +/- 3.4 3.8 +/- 4.4 3.9 +/- 4.6	High dose vs placebo p=0.06 (39% reduction vs placebo) Low dose vs placebo p=0.72 (6.6% reduction vs placebo)

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Stelmach 2011[27]	Grass mix	SLIT pre-coseasonal SLITcontinuous Placebo	2 years	Medication score: 1 pt for each rescue med multiplied by # of tx days during total season		NR	3.8 11.9 10.8	Pre coseasonal pre vs post significant Continuous pre vs postsignficant Pre coseasonal vs Placebo <0.01 Continuous vs Placebo NS >0.05 Pre coseasonal vs Continuous NS >0.05

TABLE G26- COMBINED SYMPTOM AND MEDICATION SCORES –SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Novembre 2004[25]	Grass Mix	SLIT Conventional therapy	3 years	Nasal, eye, bronchial symptoms plus medication	NR	NR	92 92	SLIT vs Placebo NS
Pajno 2011[35]	Grass Mix	SLIT continuous SLIT Co-seasonal	3 yrs	0-3 per symptom (nose, chest, eye), 1 point topical med, 2 point systemic med per day	% reduction from baseline	NR	70% reduction 55% reduction	SLIT continuous vs SLIT coseasonal NS
Marogna 2008[28]	Dust mite, birch, grass mix, parietaria	SLIT Placebo	3 years	Seasonal daily SMS, 7 Nasal, eye, bronchial symptoms, plus meds, 1 pt per each daily med use, reported as mean monthly sum of SMS	0-750	Mean 146.4 Mean 136.7	40 100	Pre SLIT vs Placebo p<0.001 Post SLIT vs Placebo p<0.001

TABLE G27. QUALITY OF LIFE –SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale Description	Value Pre	Value post	Comparative values
deBot, 2011[21]	Dust mite	SLIT placebo	2 years	PRQLQ (6-11 years)	NR NR	0.93 +/- 0.79 0.91 +/- 0.69	SLIT vs placebo NS Lower score indicates better QOL
deBot, 2011[21]	Dust mite	SLIT placebo	2 years	Adolescent RQLQ (12-17 years)	NR NR	0.93 +/- 0.73 0.90 +/- 1.00	SLIT vs placebo NS Lower score indicates better QOL
Roder, 2007[26]	Grass mix	SLIT Placebo	2 years	PRQLQ (6-11 years) Total score 0-6	NR	1.7 (SEM 0.2) 1.4 (SEM 0.1)	SLIT vs placebo, NS p=0.799 SLIT (n=30), placebo (n=26) Lower score indicates better QOL
Roder, 2007[26]	Grass mix	SLIT Placebo	2 years	Adolescent RQLQ (12-17 years) Total score 0-6	NR	1.7 (SEM 0.2) 2.1 (SEM 0.2)	SLIT vs placebo, NS p=0.272 SLIT (n=56), placebo (n=47) Lower score indicates better QOL

TABLE G28. CHALLENGES SCORES –SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Hirsch, 1997[29]	Dust mite	SLIT Placebo	1 year	nasal provocation (acoustic rhinometry)	SBU/ml 40% reduction nasal flow	1240 470	1380 1790	SLIT pre vs post p NS Placebo pre vs post p<0.01 SLIT vs Placebo p<0.05
Hirsch, 1997[29]	Dust mite	SLIT Placebo	1 year	Bronchial histamine provocation test, PC20 FEV1 (mg/mL)	Concentration inducing 20% reduction of FEV1	0.7 1.7	0.52 1.5	SLIT vs Placebo p NS
la Rosa, 1999[23] Leonardi 2009[24]	Parietaria	SLIT Placebo	2 years	ocular conjunctival provocation test	0-3	23 IR/mL18 IR/mL	35 15	SLIT vs Placebo p =0.02

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Lue 2006[19]	Dust mite	SLIT Placebo	6 months	FEV1		75 80	90 82	SLIT pre vs post p = 0.001 Placebo pre vs post p =0.48 SLIT vs Placebo p =0.93
Niu 2006[20]	Dust mite	SLIT Placebo	24 weeks	FEV1		85 90	95 90	SLIT pre vs post p=0.048 Placebo pre vs post p=0.977 SLIT vs Placebo NS
Ippoliti, 2003[38]	Dust mite	SLIT Placebo	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
Lue 2006[19]	Dust mite	SLIT Placebo	6 months	Morning PEFR		185 210	197 225	SLIT pre vs post p=0.244 Placebo pre vs post p=0.086 SLIT vs Placebo p=0.132
Lue 2006[19]	Dust mite	SLIT Placebo	6 months	Evening PEFR		190 225	215 235	SLIT pre vs post p=0.008 Placebo pre vs post p=0.253 SLIT vs Placebo p=0.341
Niu 2006[20]	Dust mite	SLIT Placebo	24 weeks	PEF		65 70	75 77	SLIT pre vs post p=0.001 Placebo pre vs post p=0.075 SLIT vs Placebo NS Pre/post SLIT: FVC p=0.042, FEV1 p=0.048
Stelmach 2011[27]	Grass mix	SLIT pre-coseasonal SLIT continuous placebo	2 years (2010)	FEV1 (% predicted)		98.3(2.8 SEM) 101.9(2.4) 99.7(2.4)	100.2(2.9) 102.8(2.7) 102.3(1.9)	No significant changes within and among all groups throughout study.
Stelmach 2011[27]	Grass mix	SLIT pre-coseasonal SLIT continuous placebo	2 years	Morning PEF (% predicted)	Compare season 2009 to season 2010	NR	99.5 (3.1) 98 (3.9) 90.1 (4.9)	No significant changes within and among all groups throughout study.
Stelmach 2011[27]	Grass mix	SLIT pre-coseasonal SLIT continuous placebo	2 years	PD20 (mg)		NR	0.25 (0.02) 0.19 (0.03) 0.25 (0.02)	No significant changes within and among all groups throughout study.

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Marogna 2008[28]	Birch and Grass	SLIT Pharma-cotherapy	3 years	Methacholine challenge	# of patients with positive Mch test	82 (56.9%) 47 (65.3%)	23 (17.7%) 31 (47.7%)	SLIT pre/post, p<0.001, Controls pre/post, NS p=0.5 Post: SLIT vs control, p<0.001, OR=0.24 (0.12-0.47)
Pajno 2003[32] Pajno 2004[33]	Parietaria	SLIT Placebo	2 years	Methacholine challenge, PC20 (mg/mL)	Compared PC20 in Spring 1999 and Spring 2001	3.37 +/- 2.99 2.44 +/- 2.25	9.10 +/- 7.7 2.46 +/- 2.26	SLIT pre vs post, p=0.01, Placebo pre vs post, p NS Pre: SLIT vs placebo, NS Post: SLIT vs placebo, p=0.001
Pajno 2003[32] Pajno 2004[33]	Parietaria	SLIT Placebo	2 years	FEV1 (% predicted)	Spring 1999 compared to Spring 2001	82.0 (5.4) 78.9 (5.9)	88.4 (3.7) 75.6 (4.9)	SLIT showed trend toward improvement during pollen seasons, although not significant
Bahceciler 2001[30]	Dust Mite	SLIT Placebo	6 months	Peak Expiratory Flow (%)		97 (77-117) 99 (82-128)	99 (75-116) 76 (62-106)	SLIT vs placebo PEF Significant improvement p=0.04 SLIT pre vs post, NS Placebo pre vs post, p=0.028
Bahceciler 2001[30]	Dust Mite	SLIT Placebo	6 months	FEV1 (%)		95 (75-113) 101 (75-115)	100 (78-119) 93 (61-104)	No significant improvement vs placebo
Bahceciler 2001[30]	Dust Mite	SLIT Placebo	6 months	PC20 (mg/ml)		0.28 (0.03-3.8) 0.78 (0.04-1.8)	0.85 (0.17-2.2) 0.98 (0.18-3.9)	No significant improvement vs placebo
Tari, 1990[31]	Dust mite	SLIT Placebo	18 months	Nasal provocation test (NPT)		NR	5.2x increase No increase	SLIT vs Placebo p< 0.01 Provocation dose significantly increased compared with initial values in SLIT (5.2 x increase), which was not observed in placebo
Tari, 1990[31]	Dust mite	SLIT Placebo	12 months	Bronchial provocation challenge	FEV-1 Mch challenge (µg) (aspecific)	SLIT group 280.8 +/- 16.4	SLIT group 502 +/- 26.6	SLIT pre vs post, p< 0.05 Threshold value increased 1.78x
Tari, 1990[31]	Dust mite	SLIT Placebo	12 months	Bronchial provocation challenge	FEV1 Dust mite challenge (specific)	SLIT 170.8 +/-18.4	SLIT 300.3 +/- 28.4	SLIT pre vs post p< 0.05 Threshold value increased 1.76x

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Valovirta, 2006[36] Savolainen 2006[37]	Tree mix	SLIT high dose SLITlow dose Placebo	Peak season	Conjunctival provocation test	Positive test if 2/4 sx present (itch, red, tears, swelling)	NR	NR	No statistically significant differences between treatment groups
Valovirta, 2006[36] Savolainen 2006[37]	Tree mix	SLIT high dose SLITlow dose Placebo	Peak season	Methacholine bronchial provocation test (MBPT)	PD20, continued until fall in FEV1 of ≥20%	NR	NR	No statistically significant differences between treatment groups

TABLE G29 – TOTAL SECONDARY OUTCOMES –SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	OUTCOME	Scale Description	Value Pre	Value post	Comparative values
Niu, 2006[20]	Dust mite	SLIT Placebo	24 weeks	Disease Modification	# of patients with change in asthma classification from mild/moderate to intermittent	Intermitt: 0 Mild/mod: 49 Intermitt: 0 Mild/mod: 48	Intermitt: 26 Mild/mod: 23 Intermitt: 19 Mild/mod: 29	SLIT vs placebo, p=0.043
Marogna, 2008[28]	Birch and Grass	SLIT Pharmacotherapy	3 years	Disease Modification	# of children with intermittent asthma	86 (59.7%) 45 (62.5%)	15 (11.5%) 11 (16.7%)	SLIT vs control in 3rd year, p NS OR 0.65 (95% CI: 0.28-1.51)
Marogna, 2008[28]	Birch and Grass	SLIT Pharmacotherapy	3 years	Disease Modification	Overall # of children with intermittent and mild persistent asthma	86/144(60%) 45/72 (62%)	17/130 (13%) 30/66 (45%)	OR 5.54, CI: 2.74-11.19)
Marogna, 2008[28]	Birch and Grass	SLIT Pharmacotherapy	3 years	Development of New Sensitivities	# of new sensitivities after 3 yrs	0 0	4/130 23/66	OR=0.6 (CI: 0.02-0.17) Prevention of onset of sensitizations in SLIT
Marogna, 2008[28]	Birch and Grass	SLIT Pharmacotherapy	3 years	Prevention of Asthma	# of children with mild persistent ashthma	0 0	2/130 (1.5%) 19/66 (28.8%)	Lower occurrence of mild persistent asthma in SLIT patients vs placebo, significant even after worst case analysis OR=0.04, (95% CI, 0.01-0.17) NNT=4 (95% CI, 3-5)

Study	Allergen	Arms	Time of measure	OUTCOME	Scale Description	Value Pre	Value post	Comparative values
Novembre, 2004[25]	Grass Mix	SLIT Conventional therapy	3 years	Prevention of Asthma	# of patients who developed asthma	0 0	8/45 18/44	SLIT vs placebo, p=0.0412 Relative risk of developing asthma in controls was 3.8 (95%CI:1.5-10)
Hirsch, 1997[29]	Dust mite	SLIT Placebo	1 year	Adherence	# patients reporting completely regular intake of SLIT over 1 whole year		8/15 (53%) 10/15 (67%)	
la Rosa, 1999[23] Leonardi 2009[24]	Parietaria	SLIT Placebo	8 years (tx for 2 yrs)	Disease Modification				At 8 year follow up, similar report of rhinitis symptoms during Parietaria pollen season in SLIT and placebo groups.
la Rosa, 1999[23] Leonardi 2009[24]	Parietaria	SLIT Placebo	8 years (tx for 2 yrs)	Prevention of Asthma	Mean FEV1 (SD)		97.5 (11.2) 92.6 (16.4)	No difference in FEV1 or # of asthmatics was noted between groups. At 8 year follow up, 21 patients were reevaluated (10 SLIT, 11 placebo).
la Rosa, 1999[23] Leonardi 2009[24]	Parietaria	SLIT Placebo	8 years (tx for 2 yrs)	Prevention of Asthma	# patients with asthma (intermittent/mild persistent)		6 (4/2) 7 (5/2)	No difference in # of asthmatics was noted between groups. At 8 year follow up, 21 patients were reevaluated (10 SLIT, 11 placebo).
la Rosa, 1999[23] Leonardi 2009[24]	Parietaria	SLIT Placebo	2 years	Development of New Sensitivities	# of new sensitizations after 8 years		19 in 10 patients 20 in 11 patients	Monosensitized patients developed new sensitizations in both groups. At 8 year follow up, 21 patients were reevaluated (10 SLIT, 11 placebo).

- Outcomes not reported Maintenance control, Prevention of Sinusitis, Prevention of Otitis and Convenience

TABLE G30 – BIOMARKERS –SLIT– PEDIATRICS

Study	Arms	IgG - IgG4	Mean baseline Ig E –Change IgE	Other markers
Bahceciler 2001[30]	SLIT		IgE: pre: median 420 (range 42-2751); post: 295 (40-1701) Total IgE levels reported but no significant difference was found	
Bahceciler 2001[30]	Placebo		IgE:pre: median 405 (range:197-5967); post: 536 (166-3948)	
Hirsch, 1997[29]	SLIT (D.pt)	IgG: No significant change IgG4: NR	IgE:Pre: 39.1 kU/l, post: 78.9 Total IgE increased, pre vs post: p<0.01 sIgE D.f. increased in SLIT group (p<0.01)	

Study	Arms	IgG - IgG4	Mean baseline Ig E –Change IgE	Other markers
Hirsch, 1997[29]	Placebo	IgG: No significant change IgG4:Decreased, p<0.05	IgE:Pre: 33.3 kU/I, post: 47.7 Total IgE pre vs post increased, p<0.01 Greater increase in total IgE in SLIT vs placebo, p<0.05	
Ippoliti, 2003 [38]	SLIT			No variation in CD40+ and ACTH. Significant decrease in serum ECP, IL-13, and prolactin levels.
la Rosa, 1999[23] Leonardi 2009[24]	SLIT	IgG4:SLIT pre: 7% (graph) SLIT post: 12% (graph) Significant increase in levels after 2 yrs (p=0.02)	IgE:No significant difference between the groups	
la Rosa, 1999[23] Leonardi 2009[24]	Placebo	IgG4:Placebo pre: 10% (graph) Placebo post: 10%(graph) No significant change in levels	IgE:No significant change in levels	
Lue, 2006[19]	SLIT	IgG4:Statistically significant increase within group and when compared to placebo p=0.026, after 6 months	IgE:Pre: 500 IU/L (from graph) Increased within group, not statistically significant when compared with placebo	
Lue, 2006[19]	Placebo	IgG4:no major change	IgE:Pre: 400 IU/L (from graph) no major change	
Niu, 2006[20]	SLIT		IgE:Pre: 829.8 +/- 582.0 Change in total IgE from baseline to 24 weeks: 129.7 +/- 460.6 (Pre-post SLIT, p=0.057) IgE: SLIT vs Placebo, p=0.063 Specific IgE was also reported: no significant change comparing SLIT vs placebo	
Niu, 2006[20]	Placebo		IgE:Pre: 780.6 +/- 592.0 Change in total IgE from baseline to 24 weeks: - 85.1 +/- 59.8 (Pre-post placebo, p=0.221)	
Pajno, 2000[18]	SLIT	IgG: Mean at baseline: 33.0, after 2 years: 31.3 IgG4:Mean at baseline: 2.85, after 2 years: 2.53 No significant changes in D. pter specific IgG or IgG4 concentrations were detected in either group	IgE:Mean at baseline: 45.4 After 2 years: 52.6 SLIT vs placebo group differences: NS No significant changes in D. pter specific IgE concentrations	
Pajno, 2000[18]	Placebo	IgG: Mean at baseline: 26.0, after 2 years: 31.9 Between group differences: NS IgG4:Mean at baseline: 2.7, after 2 years: 2.66, Between group differences: NS	IgE:Mean IgE baseline: 52.2 After 2 years: 65.3 Between group differences: NS	

Study	Arms	IgG - IgG4	Mean baseline Ig E –Change IgE	Other markers
Tari, 1990[31]	SLIT	IgG: Significant increase after 12 and 18 months p<0.001. IgG4: Pre: 2.49 +/- 1.10 Post: 10.71 +/- 3.81 p<0.01	IgE:No significant change	
Tari, 1990[31]	Placebo	IgG: No change after 12 and 18 months IgG4:Pre: 2.04 +/- 1.03 Post: 2.78 +/- 2.02	IgE:Significant rise (p<0.01)	
Tseng, 2008[22]	SLIT	IgG4:Der p baseline: 591.4 +/- 476.9 IgG4: change from baseline, p<0.001Change from baseline to 24th week: 772.9 +/- 1002.8, p<0.001	IgE:Der p baseline: 129 +/- 91, Change from baseline to 24th week: 40.8 +/- 76.1, p=0.008 D. pteronyssinus IgE: SLIT vs placebo change from baseline, NS, p=0.12	
Tseng, 2008[22]	Placebo	IgG4:Der p baseline: 520.1 +/- 308.2; Change from baseline to 24th week: -92.4 +/- 290.1, p=0.018	IgE:Der p baseline: 98.8 +/- 71.5 Change from baseline to 24th week: 21.0 +/- 46.7, p=0.018	
Tseng, 2008[22]	SLIT	IgG4:Der f baseline: 425.0 +/- 392.1; Change from baseline to 24th week: 710 +/- 990.9, p=0.002 IgG4: SLIT vs placebo change from baseline, p<0.001	IgE:Der f baseline: 170.5 +/- 88.8 Change from baseline to 24th week: 49.0 +/- 73.9, p=0.002 D. farinae IgE: SLIT vs placebo change from baseline, NS, p=0.087	
Tseng, 2008[22]	Placebo	IgG4:Der f baseline: 386.1 +/- 285.8; Change from baseline to 24th week: -6.4 +/- 280.1, p=0.889	IgE:Der f baseline: 83.3 +/- 62.9 Change from baseline to 24th week: 24.2 +/- 43.3, p=0.004 D. farinae	
[36]Valovirta, 2006 [37]Savolainen 2006				Reported in Savolainen: At 2 years: Increased IL-10 values. Decreased IL-5 values in high dose vs placebo. (Subset of the original study, with 10 patients from each arm)
Vourdas 1998[34]	SLIT	IgG4:no significant change	IgE:no significant change No significant changes in specific IgE was detected. After an initial increase in specific IgG4 during the first pollen season, the values decreased in both groups. Actual values not reported.	
Vourdas 1998[34]	Placebo	IgG4:no significant change	IgE:no significant change	
Pajno 2011[35]		IgG4:Baseline specific IgG4: Continous SLIT: 0.9 Coseasonal SLIT: 0.8	IgE:Baseline Timothy specific IgE: Continuous SLIT: 11.2 Coseasonal SLIT: 9.9	

Study	Arms	IgG - IgG4	Mean baseline Ig E –Change IgE	Other markers
		Season 3 IgG4: Continuous SLIT: 22.7 Coseasonal SLIT: 11.9 IgG4:Both groups had significant increase in specific IgG4 at end of study compared to baseline (p<0.05)	IgE remained unchanged from beginning to end of study	

TABLE G31. SAFETY–SLIT– PEDIATRICS

SLIT LOCAL REACTIONS

Study	SLIT Allergen	Number of Patients in Arm	Number of events and description	% of patients	Severity
Pajno, 2000[18]	Dust mite	12	2 patients presented local delayed reactions: one case of swelling of the mouth, lips, and face (at 2 h) and one case of itching of the mouth (at 3 h). Resolved spontaneously without drugs	16%	Mild
Marogna, 2008[28]	Dust mite, Birch, Parietaria, Grass mix	144	1 dropout because of oral itching	0.6%	Unspecified
deBot 2011[21]	Dust mite placebo	125 126	14 patients reported oral pharyngeal irritation/swelling 18 patients reported oral pharyngeal irritation/swelling	11.2% 14.3%	Unspecified Unspecified
Hirsch, 1997[29]	Dust mite Placebo	15 15	5 patients reported local events. 1 patient required dose reduction. 1 patient reported local events. Local events defined as swelling, reddening, and tingling of the tongue, buccal mucosa and/or gingiva within less than 30 minutes of application.	33% 6%	Mild Mild
Stelmach 2011[27]	Grass mix (SLIT arms reported together) placebo	40 20	18 patients reported local reactions such as sublingual itching 3 patients reported local reactions such as sublingual itching	45% 15%	Unspecified Unspecified
Novembre, 2004[25]	Grass mix	54	1 patient had itching in the throat that resolved without requiring treatment discontinuation.	0.2%	Mild
Vourdas, 1998[34]	Olive Placebo	34 32	8 patients presented local symptoms: 8 patients had buccal itching or oropharyngeal pruritus, 1 patient had labial swelling 2 patients presented buccal itching, labial swelling.	45% 7%	Mild Mild
Valovirta, 2006[36] Savolainen 2006[37]	 Tree mix-high Tree mix-low Placebo	 32 33 32	Oral local reactions 16 patients 12 patients 8 patients	 50% 36% 25%	 Unspecified Unspecified Unspecified

Study	SLIT Allergen	Number of Patients in Arm	Number of events and description	% of patients	Severity
La Rosa, 1999[23] Leonardi 2009[24]	Parietaria Placebo	20 21	5 patients with local symptoms: 3 had oral itching, 2 had labial swelling 4 patients with local symptoms: 2 had oral itching, 2 had labial swelling	25% 19%	Unspecified Unspecified
Roder 2007[30]	Grass mix Placebo	108 96	42 patients with oral pharyngeal irritation/swelling 16 patients with oral pharyngeal irritation/swelling	39% 17%	Unspecified Unspecified
Pajno 2004[50]	Parietaria	15	1 patient with itching in mouth and throat – maintenance dose decreased	7%	Mild
Pajno 2011	Coseasonal grass mix Continuous grass mix	40 40	Local side effects (itching/burning in mouth, gastrointestinal symptoms) were frequent. 5 patients with local symptoms led to discontinuation of SLIT.	At least 6%	Unspecified

SLIT SYSTEMIC REACTIONS: UPPER RESPIRATORY EVENTS: Rhinitis/Nasal Reactions

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Tari, 1990[31]	Dust mite	30	8 patients presented severe nasal symptoms	25%	Severe-subjects exceeded max dose
deBot 2011[21]	Dust mite placebo	125 126	115 patients reported nasal complaints / rhinitis 118 patients reported nasal complaints / rhinitis	92% 94%	Unspecified Unspecified
Valovirta, 2006[36] Savolainen 2006[37]	Tree mix-high Tree mix-low Placebo	32 33 32	- - 1 patient Rhinitis 1 patient Rhinitis	— 3% 3%	 Unspecified Unspecified
La Rosa, 1999[23] Leonardi 2009[24]	Parietaria Placebo	20 21	1 patient: Rhinitis 1 patient: Rhinitis	5% 5%	Unspecified Unspecified
Roder 2007[30]	Grass mix Placebo	108 96	89 patients with rhinitis 76 patients with rhinitis	82% 79%	Unspecified Unspecified

SLIT SYSTEMIC REACTIONS: LOWER RESPIRATORY REACTIONS

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Tari, 1990[31]	Dust mite	32	8 patients had mild asthma 3 patients presented severe asthma	25% 9%	Mild Severe: patients exceeded max dose
deBot 2011[21]	Dust mite placebo	125 126	84 patients reported shortness of breath / cough 87 patients reported shortness of breath / cough	67% 69%	Unspecified Unspecified

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Marogna, 2008[28]	Birch and Grass mix	144	1 dropouts due to asthma	0.6	Unspecified
La Rosa, 1999[23] Leonardi 2009[24]	Parietaria Placebo	20 21	0 patients 2 patients: 1 mild asthma attack, 1 severe asthma attack	0% 10%	Mild; severe
Roder 2007[30]	Grass mix Placebo	108 96	29 patients with shortness of breath/cough 28 patients with shortness of breath/cough	27% 29%	Unspecified Unspecified

SLIT SYSTEMIC REACTIONS: CUTANEOUS: (rash/urticaria/angioedema)

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Tari, 1990[31]	Dust mite	30	3 patients presented urticaria.	10%	Unspecified
deBot 2011[21]	Dust mite placebo	125 126	71 patients reported cutaneous adverse events 82 patients reported cutaneous adverse events Cutaneous events : Eczema, itch, rash	57% 65%	Unspecified Unspecified
Novembre, 2004[25]	Grass mix Placebo	54 59	1 patient with cutaneous rash, which spontaneously resolved without any intervention. 1 patient had cutaneous rash	2% 2%	Mild Mild
Marogna, 2008[28]	Birch and Grass mix	130	1 patient reported 1 episode of generalized itching (without skin lesions) within 30 minutes of taking the dose. This adverse event appeared during the maintenance phase, self-resolved without therapy	0.7%	Mild
Roder 2007[30]	Grass mix Placebo	108 96	42 patients with eczema/itch/rash 34 patients with eczema/itch/rash	39% 35%	Unspecified Unspecified

SLIT SYSTEMIC REACTIONS: GASTROINTESTINAL (nausea/pain/diarrhea)

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Tari, 1990[31]	Dust mite	32	4 patients with GI symptoms: abdominal swelling and/or pain, and/or diarrhea	12%	Unspecified
Novembre, 2004[25]	Grass mix	54	1 patient experienced mild gastrointestinal complaints that spontaneously resolved without requiring treatment	2%	Mild
Valovirta, 2006[36] Savolainen 2006[37]	 Tree mix-high Tree mix-low Placebo	 32 33 32	Abdominal pain 1 patient 2 patient --	 3% 6% --	 Unspecified Unspecified

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
La Rosa 1999[23] Leonardi 2009[24]	Parietaria Placebo	20 21	19 patients (12 in the active group and 7 in the placebo group) had gastrointestinal complaints. These complaints led to withdrawal from the trial in 4 cases in the active group and in 1 case in the placebo group.	60% 33%	Unspecified Unspecified
Marogna, 2008[28]	Birch, Grass mix	144	1 dropout due to abdominal pain.	0.7%	Unspecified
Stelmach 2011[27]	Dust mite (arm 1 + 2 reported together) placebo	40 20	Stomach aches in the first year of immunotherapy, 3.5% vs. %0.5% and 6% vs. 5.6% in the second year of immunotherapy.	NC	Unspecified Unspecified
Roder 2007[30]	Grass mix Placebo	108 96	80 patients with gastrointestinal complaints 70 patients with gastrointestinal complaints	74% 73%	Unspecified Unspecified
deBot 2011[21]	Dust mite Placebo	125 126	85 patients with gastrointestinal complaints 76 patients with gastrointestinal complaints	68% 60.3%	Unspecified Unspecified

SLIT SYSTEMIC REACTIONS: CARDIOVASCULAR

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
NO study described any cardiovascular reaction					

SLIT SYSTEMIC REACTIONS: OCULAR REACTIONS

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
Vourdas, 1998[34]	Olive	34	1 patient presented conjunctivitis symptoms	3%	Mild
La Rosa, 1999[23] Leonardi 2009[24]	Parietaria Placebo	20 21	1 patient with conjunctivitis 1 patient with conjunctivitis	5% 5%	Unspecified Unspecified
Roder 2007[30]	Grass mix Placebo	108 96	53 patients with conjunctivitis 54 patients with conjunctivitis	49% 56%	Unspecified Unspecified
Tari, 1990[31]	Dust mite	30	6 patients with severe eye symptoms	20%	Severe
deBot 2011[21]	Dust mite Placebo	125 126	69 patients with conjunctivitis 82 patients with conjunctivitis	55% 65%	Unspecified Unspecified

SLIT SYSTEMIC REACTIONS: GENERAL SYMPTOMS

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity

Pajno, 2000[18]	Dust mite Placebo	12 12	4 patients : reported tiredness 1 patient : reported tiredness These side-effects resolved spontaneously without drugs	30% 8%	Unspecified Unspecified
Hirsch, 1997[29]	Dust mite	15	1 patient dropped out after 8 weeks of therapy (14 years old), complaining of local swelling under the tongue and a subjective feeling of weakness after having reached the maintenance dose.	7%	Unspecified
Valovirta 2006[36] Savolainen 2006[37]	Tree mix-high	32	1 patient had flushing, 2 patients had allergic reaction	9%	Unspecified
Stelmach 2011[27]	Dust mite (arm 1 + 2 reported together) placebo	40 20	Headaches in first year of immunotherapy, 4.1% vs 4% and 0 vs .2% in the second year of immunotherapy	NC	Unspecified Unspecified
Roder 2007[30]	Grass mix Placebo	108 96	10 patients with allergy (not specified) 9 patients with allergy (not specified)	9% 9%	Unspecified Unspecified
Pajno 2004[50]	Parietaria Placebo	15 15	3 patients with tiredness after drop ingestion- 1 dropout due to abdominal pain, shortness of breath, and wheezing 20 mins after drops ingestion 2 patients with tiredness after drop ingestion	27% 13%	Mild Mild
deBot 2011[21]	Dust mite Placebo	125 126	75 patients with allergy (not specified) 84 patients with allergy (not specified)	60% 67%	Unspecified Unspecified
Tseng 2008[22]	Dust mite Placebo	30 33	19 patients with side effects including tongue numbness, as most common AE, and epistaxis, mouth ulceration, asthma attacks 7 patients with side effects including tongue numbness, as most common AE, and epistaxis, mouth ulceration, asthma attacks	63% 21%	Mild Mild
Niu 2006	Dust mite	56	5 patients with 10 incidences of mild-moderate local reactions (tongue disorder, vomiting, abdominal pain, circumoral paresthesia)	9%	Mild-moderate

NC not calculated

SLIT ANAPHYLACTIC REACTIONS

Study	SLIT Allergen	Number of Patients in Arm	Description	% of patients	Severity
NO study described any anaphylactic reaction					

3. SUBCUTANEOUS vs SUBLINGUAL IMMUNOTHERAPY

TABLE G32.- STUDY CHARACTERISTICS - SCIT vs SLIT - PEDIATRICS

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Eifan 2010[39]	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Non-profit
Yukselen 2011[40] Turkey	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: children No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only Minimum duration of disease: 1 year	Industry
Keles 2011[41] Turkey	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: 5-12 years Minimum duration of disease: 2 years Positive skin test	Industry

TABLE G33.- PATIENT CHARACTERISTICS- SCIT vs SLIT - PEDIATRICS

Study	Patients randomized	Comparators	Age (years) (mean+/- SD)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Eifan, A.O., 2010[39]	48	SLIT 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
Yukselen 2011[40]	32	SCIT + placebo drops SLIT + 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
Keles 2011[41]	60	SCIT SLIT 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

TABLE G34.- INTERVENTION CHARACTERISTICS- SCIT vs SLIT - PEDIATRICS

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Eifan, 2010[39]	SLIT Dust mite (D. Per-D. Far) SCIT Dust mite (D. Per-D. Far) 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
Yukselen 2011[40]	SCIT (plus placebo sublingual drops) SLIT (plus placebo subcutaneous injections) Placebo (sublingual and subcutaneous)	Conventional	0.2-0.8 ml of 5000 TU/ml 28 drops of 1000 TU/ml	43,770 TU (21,885 of TU D.pt and 21885 TU of D.f) 173733 TU (86866.5 TU of D.pt and 86,866.5 TU of D.F)	Every 4th week Three times a week	NR NR	1 year
Keles 2011[41]	SCIT SLIT SCIT (build-up) + SLIT (maintenance) Pharmacotherapy	Rescue	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

TABLE G35.- QUALITY ASSESSMENT- SCIT vs SLIT - PEDIATRICS

Study	Random allocation of subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other Biases	Sponsor company involved in design	Overall Risk of Bias
Eifan, A.O., 2010[39]	Low	Low	High	High	Low	Yes or unclear	Medium
Yukselen 2011[40]	Low risk	High risk	High risk	Low risk	Low risk	No	Moderate risk
Keles 2011[41]	Low risk	High risk	High risk	Low risk	Low risk	No	Moderate risk

TABLE G36.- ASTHMA AND ASTHMA COMBINED SCORES- SCIT vs SLIT - PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan, 2010[39]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Total asthma symptom score	0-12	1.4±1.5 0.9±0.7 0.95±0.62	0.2±0.4 0.4±0.6 2.5±1.6	SCIT versus Pharmacotherapy, p=0.04 SLIT versus Pharmacotherapy, p=0.02
Yukselen 2011[40]	Dust mites	SCIT SLIT Placebo	1 year	Asthma symptom score	0-12	2.4 3.7 2.7	1.0 (100% improvement) 2.7 (3.3% improvement) 2.6	SCIT pre vs post, p=0.005 SLIT, pre vs post, p= 0.012 SCIT vs SLIT, P=0.01
Keles 2011[41]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Asthma symptom score	NR	0.25 0.12 0.12 0.13	0 0 0 0.23	SCIT vs Pharmacotherapy, p=significant SCIT+SLIT vs Pharmacotherapy, p=SIgnificant

TABLE G37.- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES SCIT vs SLIT - PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan, A.O 2010[39]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Total rhinitis symptom score	0-12	1.3±0.9 1.8±0.9 1.56±1.05	1.5±1.0 1.2±0.9 2.9±0.7	SCIT vs Pharmacotherapy, p=0.01 SLIT vs Pharmacotherapy, p=0.03
Yukselen 2011[40]	Dust mites	SCIT SLIT Placebo	1 year	Rhinitis symptom score	0-12	4.6 4.3 4.0	3.0 (31% improvement) 3.8 (6.6% improvement) 4.1	SCIT pre vs post, p=0.005 SLIT, pre vs post, p= 0.008 SCIT vs placebo, p=0.03 SLIT vs placebo, p= NS SCIT vs SLIT, P= 0.28
Keles 2011[41]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Rhinitis symptom score	NR	0.21 0.36 0.49 0.22	0.06 0.27 0.04 0.41	SCIT+SLIT vs Pharmacotherapy, p=SIgnificant

NS: Not significant

TABLE G38.- OTHER CLINICAL SCORES, SCIT vs SLIT- PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan, A.O., 2010[39]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Total symptom score	0-24	2.8±2.2 2.8±1.3 2.5±1.3	1.4±1.5 1.6±1.5 5.4±1.7	SCIT vs Pharmacotherapy, p=0.01 SLIT vs Pharmacotherapy, p=0.01
Yukselen 2011[40]	Dust mites (D.pt and D.f)	SCIT SLIT Placebo	1 year	Total symptom score	0-24	NR	NR	SCIT pre vs post, p=0.005 SLIR, pre vs post, p=0.005 SCIT vs Placebo, p=0.009
Keles 2011[41]	Dust mites (D.pt and D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Total symptom score	NR	0.38 0.17 0.38 0.28	0.05 0.18 0.04 0.36	SCIT vs Pharmacotherapy, p=significant SCIT+SLIT vs Pharmacotherapy, p=SIgnificant
Yukselen 2011[40]	Dust mites (D.pt and D.f)	SCIT SLIT Placebo	1 year	Visual Analog Score	NR	NR	NR	SCIT (rhinitis score), pre vs post, p=0.005 SCIT (asthma score), pre vs post, p=0.007 SLIT (both scores), pre vs post, p=0.02 SCIT vs Placebo, p= 0.05 (rhinitis), 0.02(asthma) SLIT vs Placebo, p=NS

NS: Not significant

TABLE G39.- MEDICATION SCORES SCIT vs SLIT - PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan 2010[39]	Dust mites	SLIT SCIT Pharmacotherapy	1 year	Total medication score	1-3	2.8±1.2 2.4±1.4 2.5±1.5	1.2±0.9 1.7±1.4 2.8±1.1	SCIT versus Pharmacotherapy, p=0.26 SLIT versus Pharmacotherapy, p=0.03
Yukselen 2011[40]	Dust mites (D.pt and D.f)	SCIT SLIT Placebo	1 year	Rhinitis medication score	NR	2.3 2.3 1.9	1.0 1.7 1.9	SCIT vs Placebo, p= 0.05 SCIT, pre vs post, p=0.005 SLIT, pre vs post, p= 0.03 SCIT vs SLIT, p=0.18
Yukselen 2011[40]	Dust mites (D.pt and D.f)	SCIT SLIT Placebo	1 year	Asthma medication score	NR	1.38 1.1 1.24	1.0 1.1 1.4	SCIT vs Placebo, p= 0.05 SCIT, pre vs post, p=0.02 SLIT, pre vs post, p= 0.18 SCIT vs SLIT, p=0.31

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Keles 2011[41]	Dust mites (D.pt and D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Asthma medication score	NR	1.02 1.06 1.1 1.13	0.065 0.91 0.085 0.8	SCIT vs Pharmacotherapy, p=significant SLIT vs Pharmacotherapy, p=significant SCIT+SLIT vs Pharmacotherapy, p=SIgnificant
Keles 2011[41]	Dust mites (D.pt and D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Rhinitis medication score	NR	0.33 0.18 0.49 0.14	0 0.067 0 0.096	SCIT vs Pharmacotherapy, p=significant SCIT+SLIT vs Pharmacotherapy, p=SIgnificant
Keles 2011[41]	Dust mites (D.pt and D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Total medication score	NR	0.52 0.69 0.92 0.8	0.06 0.23 0.16 0.73	SCIT vs Pharmacotherapy, p=significant SCIT+SLIT vs Pharmacotherapy, p=SIgnificant

TABLE G40.- ALLERGY CHALLENGES AND FUNCTIONAL OUTCOMES: SCIT vs SLIT - PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Eifan, 2010[39]	Dust mite	SLIT SCIT Pharmacotherapy	1 year	Titrated allergen specific nasal provocation test		NR NR NR	NR NR NR	Significant increase in nasal provocative dose in SLIT (p=0.01) and SCIT (p=0.005) when compared to pharmacotherapy group at the end of 12 months. No significant differences between SLIT and SCIT were observed.
Yukselen 2011[40]	Dust mites	SCIT SLIT Placebo	1 year	HDM-Specific Nasal provocation	NR	NR	NR	SCIT, pre vs post, p=0.05 SLIT, pre vs post, p=0.01 SCIT vs SLIT, p= 0.31
Yukselen 2011[40]	Dust mites	SCIT SLIT Placebo	1 year	HDM-Specific Bronchial provocation	NR	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 SLIT, p= 0.91
Keles 2011[41]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Allergen specific nasal provocation dose	NR	4.9 5 5 7	3 4 4 7.5	SCIT vs Pharmacotherapy, p=0.005 SLIT vs Pharmacotherapy, p=0.044 SCIT+SLIT vs Pharmacotherapy, p=0.035

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
Keles 2011[41]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Methacholine PC20	NR	NR	NR	No significant change was detected in any of the groups

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

TABLE G41.- BIOMARKERS – SCIT vs SLIT – PEDIATRICS - IgE

Study	Allergen	Arms	Time of measure	Biomarker	Value Pre	Value post	Units	Comparative values
Eifan 2010 [39]	Dust mite	SLIT SCIT Pharmacotherapy	1 year	IgE D.f/ D.pt specific	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	IU/ml	D.f 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.pt specific: SCIT versus Pharmacotherapy, p=0.03
Yukselen 2011[40]	Dust mites	SCIT SLIT Placebo	1 year	HDM specific IgE	80 68 80	42 48 75	IU/ml	SCIT, pre vs post, p=0.01 SLIT, pre vs post, p=0.02 Placebo,pre vs post, p=0.65
Keles 2011[41]	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Derp1 specific IgE	62+/-52 67+/- 33 83+/-27 73+/- 37	61+/- 53 44+/-32 85+/-34 75+/-41	IU/ml	No significant differences pre vs post in all groups. No significant differences between IT groups and pharmacotherapy
Yukselen 2011[40]	Dust mites (D.pt and D.f)	SCIT SLIT Placebo	1 year	D.pt and D.f specific IgG4	NR	NR		SCIT, pre vs post D.pt sIgG4, p=0.007 SCIT, pre vs post D.f sIgG4, p=0.005 SCIT vs SLIT, p=0.003
Keles 2011[41]	Dust mites (D.pt and D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Derp1 specific IgG4	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	Ua/ML	SCIT vs Pharmacotherapy, p<0.05 SCIT+SLIT vs Pharmacotherapy, p<0.05

TABLE G42. SAFETY - SCIT vs SLIT - PEDIATRICS

LOCAL REACTIONS

SLIT ARM **Reported as a Percent of Patients- Oral cavity or Oropharynx Itching**

Study	Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Yukselen, 2011[40]	Dust mite	10	3	30	NR

SLIT ARM **Reported as a Percent of Patients - Injection site reaction**

Study	Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Yukselen, 2011[40]	Dust mite	10	2	20	NR

SLIT ARM **Reported as Number of Events - Injection site reaction**

Study	Allergen	Number of patients in arm	Number of events	Number of events per patient	Severity
Eifan,A.O.,2010[39]	Dust mite	16	1	0.06	mild

SYSTEMIC REACTIONS

SCIT ARM

Study	Allergen	Number of patients in arm	Number of patients with reactions	Percent of Patients with reactions	Severity
Respiratory (rhinitis/asthma)					
Eifan, 2010[39]	Dust mite	16	1	6.2	severe
Keles 2011[41]	Dust mite	11	2	18.2	moderate
Cutaneous (rash/urticaria/angioedema) No study reported Cutaneous reactions					
Gastrointestinal (nausea/pain/diarrhea) No study reported GI reactions					
Cardiovascular reactions No study reported cardiovascular reactions					
Unspecified No study reported Unspecified reactions					
Anaphylaxis One study (Eifan, 2010[39]) reported 1 anaphylactic reaction (flushing, wheezing and dyspnea requiring adrenaline					

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Appendix H. Excluded Articles

A trial of house dust mite extract in bronchial asthma. Mite Allergy Subcommittee of the Research Committee of the British Thoracic Association. Br J Dis Chest 79; 73 (3): 260-70. **It does not meet ALL the inclusion criteria**

A. Assa'ad Allergy, asthma, and immunology. Pediatric Annals 2011 40 (4): 179-180. **It does not meet ALL the inclusion criteria**

A. Iglesias-Cadarso, P. Hernandez-Weigand, M. Reano, A. Perez-Pimiento, J. A. Vargas Nunez and F. De La Torre Risk factors for systemic reactions to allergen- specific subcutaneous immunotherapy. Journal of Investigational Allergology and Clinical Immunology 2010 20 (7): 621-622. **No original dataOther reason for exclusion (specify):case report**

A. Malet, M. Lluch, A. L. Valero and M. Casanovas Clinical and immunological effects of immunotherapy with glutaraldehyde modified house dust mite extract. Allergol Immunopathol (Madr) 1994 22 (5): 226-32. **Not an RCT**

Aabel, S. No beneficial effect of isopathic prophylactic treatment for birch pollen allergy during a low-pollen season: a double-blind, placebo-controlled clinical trial of homeopathic Betula 30c. Br Homeopath J 2000; 89 (4): 169-73. **It does not meet ALL the inclusion criteria dose not quantifiable**

Aabel, S. Prophylactic and acute treatment with the homeopathic medicine, Betula 30c for birch pollen allergy: a double-blind, randomized, placebo-controlled study of consistency of VAS responses. Br Homeopath J 2001; 90 (2): 73-8. **It does not meet ALL the inclusion criteriaTherapy NOT AVAILABLE in the U.S**

Aabel, S., Laerum, E., Dolvik, S., and Djupesland, P. Is homeopathic 'immunotherapy' effective? A double-blind, placebo-controlled trial with the isopathic remedy Betula 30c for patients with birch pollen allergy. Br Homeopath J 2000; 89 (4): 161-8. **It does not meet ALL the inclusion criterianot a quantifiable dose**

AARONSON, A. L., FRANKEL, D. B., and EHRLICH, N. J. REPOSITORY THERAPY FOR AIRBORNE ALLERGENS. Chic Med Sch Q 62; 22 45-8. **It does not meet ALL the inclusion criteria**

Aaronson, D. W. and Gandhi, T. K. Incorrect allergy injections: allergists' experiences and recommendations for prevention. J Allergy Clin Immunol 2004; 113 (6): 1117-21. **It does not meet ALL the inclusion criteriaNo SIT**

Aas, K. Adequate clinical trials of immunotherapy. Allergy 82; 37 (1): 1-14. **No original dataOther reason for exclusion (specify): review on methodology of clinical trials**

Aas, K. Bronchoprovocative tests (BPT) in clinical and experimental allergy. Ann Allergy 74; 33 (6): 320-4. **No original dataOther reason for exclusion (specify): review**

Aas, K. Hyposensitization in house dust allergy asthma. A double-blind controlled study with evaluation of the effect on bronchial sensitivity to house dust. Acta Paediatr Scand 71; 60 (3): 264-8. **Therapy NOT AVAILABLE in the U.S**

Aas, K. Hyposensitization: action and immunological procedure. Arb Paul Ehrlich Inst Georg Speyer Haus Ferdinand Blum Inst Frankf A M 78; 73 7-16. **No original data**

Aberer W and Von Weikersthal Drachenberg F European outcomes amongst allergic rhinoconjunctivitis patients participating in a placebo-controlled study of ultra short course subcutaneous immunotherapy (USCIT) conducted during the 2007 grass pollen season. Allergy ; **It does not meet ALL the inclusion criteria**

Acquistapace, F., Agostinis, F., Castella, V., Kantar, A., Novembre, E., Perrone, M. R., Pietrasanta, M., Sambugaro, R., and Milani, M. 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; 20 (7): 660-4. **It does not meet ALL the inclusion criteria dose**

Adamek-Guzik, T., Szczeklik, A., and Woloszynski, J. Multicenter controlled trial of desensitization treatment of pollen-induced hay fever and asthma with pollinex vaccine. Pol Tyg Lek 79; 34 (28): 1111-3. **Therapy NOT AVAILABLE in the U.S**

Adamic, K., Zidarn, M., Bajrovic, N., Erzen, R., Kopac, P., and Music, E. The local and systemic side-effects of venom and inhaled-allergen subcutaneous immunotherapy. Wien Klin Wochenschr 2009; 121 (9-10): 357-60. **It does not meet ALL the inclusion criteria**

Addition of specific immunotherapy in patients with grass-pollen allergic asthma treated with inhaled steroid therapy **Library unable to locate**

Adelsberg, B. R. Review: allergen-specific immunotherapies reduce symptoms, medication requirements, and bronchial hyperreactivity in asthma. ACP J Club 2004; 141 (1): 18. **No original dataOther reason for exclusion (specify): quick summary of cochrane 2003 review**

Adinoff, A. D. Environmental controls and immunotherapy in the treatment of chronic asthma. J Asthma 90; 27 (5): 277-89. **No original dataOther reason for exclusion (specify): review**

Adkinson, N. F. Jr Con: Immunotherapy is not clinically indicated in the management of allergic asthma. Am J Respir Crit Care Med 2001; 164 (12): 2140-1; discussion 2141-2. **Other reason for exclusion (specify):editorial**

Adkinson, N. F. Jr Immunotherapy for allergic rhinitis. N Engl J Med 99; 341 (7): 522-4. **Other reason for exclusion (specify):editorial**

Adler, T. R., Beall, G. N., Heiner, D. C., Sabharwal, U. K., and Swanson, K. Immunologic and clinical correlates of bronchial challenge responses to Bermuda grass pollen extracts. J Allergy Clin Immunol 85; 75 (1 Pt 1): 31-6. **Does not apply to any of the key questions**

Agati, G., Sacco, E., and Riscica, G. Treatment of bronchial asthma in children and chronic asthmatic bronchitis in adults by use of nonspecific immunodensensitization with bacterial vaccines. Minerva Med 79; 70 (41): 2805-10. **It does not meet ALL the inclusion criteria case series**

Agostinis, F., Foglia, C., Bruno, M. E., and Falagiani, P. 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; 41 (6): 177-80. **Therapy NOT AVAILABLE in the U.S**

Agostinis, F., Foglia, C., Landi, M., Cottini, M., Lombardi, C., Canonica, G. W., and Passalacqua, G. The safety of sublingual immunotherapy with one or multiple pollen allergens in children. Allergy 2008; 63 (12): 1637-9. **It does not meet ALL the inclusion criteria**

Agostinis, F., Forti, S., and Di Berardino, F. Grass transcutaneous immunotherapy in children with seasonal rhinoconjunctivitis. Allergy 2010; 65 (3): 410-1. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):patch**

Agrawal, S. and Kandimalla, E. R. Medicinal chemistry and therapeutic potential of CpG DNA. Trends Mol Med 2002; 8 (3): 114-21. **Therapy NOT AVAILABLE in the U.S**

Ahlstedt, S., Belin, L., Eriksson, N. E., and Hanson, L. A. Quantity and avidity of antibodies against birch pollen in atopic patients during hyposensitization. A preliminary study. Int Arch Allergy Appl Immunol 75; 48 (5): 632-41. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):comparison group has not the same allergy**

Ajduk, J., Marinic, I., Aberle, N., Rabatic, S., and Gagro, A. Effect of house dust mite immunotherapy on transforming growth factor beta1-producing T cells in asthmatic children. Ann Allergy Asthma Immunol 2008; 100 (4): 314-22. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):no harms**

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Akdis, C. A., Barlan, I. B., Bahceciler, N., and Akdis, M. Immunological mechanisms of sublingual immunotherapy. Allergy 2006; 61 Suppl 81 11-4. **No original data**

Akdis, M., Blaser, K., and Akdis, C. A. T regulatory cells in allergy: novel concepts in the pathogenesis, prevention, and treatment of allergic diseases. J Allergy Clin Immunol 2005; 116 (5): 961-8; quiz 969. **No original data**

Alemany-Vall, R. Sensitization against mould fungi. Allerg Asthma (Leipz) 68; 14 (3): 84-9. **No original data**

Alfaro V., Juan Manuel Eficacia de la inmunoterapia subcutbnea en el manejo de la rinitis alqrgica al polvo y/o acaro. CES med 92; 6 (2): 149-157. **Not an RCT**

Ali, I., Goksal, K., Ozan, B., and Gulsen, D. Long-term allergen-specific immunotherapy correlates with long-term allergen-specific immunological tolerance. Adv Ther 2008; 25 (1): 29-36. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):no doses**

Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 2003; 90 (1 Suppl 1): 1-40. **No original data**

Allergen-specific low-dose immunotherapy in perennial allergic rhinitis: a double-blind placebo-controlled crossover study **Excluded at data abstraction**

Allergen-specific sublingual immunotherapy for patients with grass pollen induced respiratory disease **Meeting abstract**

Allergen-specific sublingual immunotherapy in patients season respiratory allergy symptoms **Meeting abstract**

Allergic rhinitis and quality of life after one year of allergen immunotherapy Abstract **Abstract only**

Allergic rhinitis to ragweed pollen. I. Reassessment of the effects of immunotherapy on cellular and humoral responses **Oral IT**

Allergic rhinitis. Treating symptoms or desensitization?. MMW Fortschr Med 2003; 145 (5): 52. **No original data**

Almagro, E., Asensio, O., Bartolome, J. M., Bosque, M., de la Hoz, B., Dolz, I., Elorza, J., Ferreiro, M., Garcia, J. M., Losada, E., and et, a. l. Multicenter drug surveillance of sublingual immunotherapy in allergic patients. Allergol Immunopathol (Madr) 95; 23 (4): 153-9. **It does not meet ALL the inclusion criteria**

Al-Nahdi, M. S. Effect of immunotherapy in allergic bronchial asthma. Allerg Immunol (Paris) 96; 28 (1): 4-6. **It does not meet ALL the inclusion criteria**Method of asthma diagnosis not addressed

Alonso, A., Albonico, J. F., Mouchian, K., Scavini, L. M., Iraneta, S. G., and Pionetti, C. H. Immunological changes during cockroach immunotherapy. J Investig Allergol Clin Immunol 99; 9 (5): 299-304. **Observational case series**

Alvarez J M N Costs of specific immunotherapy (Brief record). Journal of Investigational Allergology and Clinical Immunology ; **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions No SITNo original data**

Amin, H. S., Liss, G. M., and Bernstein, D. I. Evaluation of near-fatal reactions to allergen

immunotherapy injections. J Allergy Clin Immunol 2006; 117 (1): 169-75. **Not an RCT**
Anaphylaxis-rhinitis-hyposensitization. Hautarzt 97; 48 (8 Suppl): 4-6. **No original data**
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Andre, C., Vatrinet, C., Galvain, S., Carat, F., and Sicard, H. Safety of sublingual-swallow immunotherapy in children and adults. Int Arch Allergy Immunol 2000; 121 (3): 229-34. **It does not meet ALL the inclusion criteria**
Andri, L. and Falagiani, P. Symptomatic relief after grass nasal immunotherapy: lasting efficacy after 4-5 years. J Investig Allergol Clin Immunol 2003; 13 (4): 228-31. **Therapy NOT AVAILABLE in the U.S**
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Anon Homoeopathy ineffective for treating asthma triggered by dust-mite allergy. Pharmaceutical Journal ; **No SIT**
Ansari, A. A., Killoran, E. A., and Marsh, D. G. An investigation of human immune response to perennial ryegrass (Lolium perenne) pollen cytochrome c (Lol p X). J Allergy Clin Immunol 87; 80 (2): 229-35. **Study evaluates outcomes in animals only or in vitro**
Anthracopoulos, M. B., Mantzouranis, E., Paliatsos, A. G., Tzavelas, G., Lagona, E., Nicolaidou, P., and Priftis, K. N. Different effects of sensitization to mites and pollens on asthma symptoms and spirometric indices in children: a population-based Cohort study. Ann Allergy Asthma Immunol 2007; 99 (2): 122-9. **No SIT**
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ARBESMAN, C. E. and REISMAN, R. E. HYPOSENSITIZATION THERAPY INCLUDING REPOSITORY: A DOUBLE-BLIND STUDY. J Allergy Clin Immunol 64; 35 12-7. **Observational case series**
ARGABRITE, J. W., MORROW, M. B., and MEYER, G. H. ALLERGIC BRONCHIAL ASTHMA AND PULMONARY INFECTION DUE TO ASPERGILLUS FUMIGATUS TREATED BY INJECTIONS OF EMULSIFIED ALLERGEN. Ann Allergy 63; 21 583-7. **Therapy NOT AVAILABLE in the U.S**
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Ariano, R., Kroon, A. M., Augeri, G., Canonica, G. W., and Passalacqua, G. Long-term treatment with allergoid immunotherapy with Parietaria. Clinical and immunologic effects in a randomized, controlled trial. Allergy 99; 54 (4): 313-9. **Therapy NOT AVAILABLE in the U.S**
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Arikan, C., Bahceciler, N. N., Deniz, G., Akdis, M., Akkoc, T., Akdis, C. A., and Barlan, I. B. Bacillus Calmette-Guerin-induced interleukin-12 did not additionally improve clinical and immunologic parameters in asthmatic children treated with sublingual immunotherapy. Clin Exp Allergy 2004; 34 (3): 398-405. **Other reason for exclusion (specify):compares BCG**
Armentia, A., Fernandez, A., Tapias, J. A., Mendez, J., de la Fuente, R., Sanchez-Palla, P., and Sanchis, E. Immunotherapy with allergenic extracts in geriatric patients: evaluation of effectiveness and safety. Allergol Immunopathol (Madr) 93; 21 (5): 193-6. **It does not meet ALL the inclusion criteria**
Armentia-Medina, A., Blanco-Quiros, A., Martin-Santos, J. M., Alvarez-Cuesta, E., Moneo-Goiri, I., Carreira, P., and Losada-Cosmes, E. Rush immunotherapy with a standardized Bermuda grass pollen extract. Ann Allergy 89; 63 (2): 127-35. **No SIT**
Asai, S. Effect of hyposensitization therapy on nasal allergy (author's transl). Nippon Jibiinkoka Gakkai Kaiho 76; 79 (8): 850-61. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):no control group**
Asaoku, Y. Clinical study of immunotherapy for bronchial asthma using purified mite feces antigen. Nihon Kokyuki Gakkai Zasshi 2000; 38 (2): 92-9. **Other reason for exclusion (specify):**no cotnrol group**Not an RCT**
Asaoku, Y., Jyo, T., Mochiduki, N., Kodomari, Y., Kuwabara, M., Yoshizane, T., Shigeta, S., Ono, K., Tsuboi, S., Ootsuka, T., and et, a. l. Desensitization

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Ascione, E., De Lucia, A., Imperiali, M., Varricchio, A., and Motta, G. Nasal application of immunotherapy. Chem Immunol Allergy 2003; 82 89-98. **Therapy NOT AVAILABLE in the U.S**
Asero, R. Efficacy of injection immunotherapy with ragweed and birch pollen in elderly patients. Int Arch Allergy Immunol 2004; 135 (4): 332-5. **It does not meet ALL the inclusion criteria**. **dose is half a vial**
Asero, R. Pollen specific immunotherapy is not a risk factor for de novo sensitization to cross-reacting allergens in monosensitized subjects. J Investig Allergol Clin Immunol 2006; 16 (4): 253-7. **No SIT**
Assem, E. S. and McAllen, M. K. Changes in challenge tests following hyposensitization with mite extract. Clin Allergy 73; 3 (2): 161-75. **It does not meet ALL the inclusion criteria**
Atwater, J. S. Jr Allergen immunotherapy. Ann Allergy Asthma Immunol 2003; 91 (1): 97; author reply 97-8. **No original data**
Avila Castanon, L., Lerma-Ortiz, L., Velazquez Armenta, Y., del Rio Navarro, B. E., and Sienra Monge, J. J. Adverse reactions to immunotherapy in pediatric patients. Rev Alerg Mex 2003; 50 (5): 182-6. **Not an RCT**
Aydogan M, Keles S, Eifan A, Akkoc T, Yildiz A, Gursoy MA, Bahceciler N, and Barlan I Impact of sublingual immunotherapy on development of asthma in children with allergic rhinitis sensitised to house-dust-mite: A double blind placebo controlled study. Abstracts of the XXVI Congress of the European Academy of Allergology and Clinical Immunology (EAACI) ; **It does not meet ALL the inclusion criteria**
Bachert, C. Allergic rhinitis and its impact on asthma (ARIA)--what does it mean for the future of SIT?. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 2003; (94): 229-35. **No original data**
Badan, M., Fasel-Felley, J., Kolly, M., Frei, P. C., and Pecoud, A. Prospective study of the undesirable effects of allergic desensitization. Schweiz Med Wochenschr 86; 116 (8): 243-5. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):no dose**
BAGRATUNI, L. A comparative study of topical steroids, antihistamines and pollen vaccine in the treatment of hay fever and hay asthma. Ann Allergy 60; 18 859-65. **It does not meet ALL the inclusion criteriaNo SITOther reason for exclusion (specify):**no concentration
Bahceciler, N. N., Arikan, C., Taylor, A., Akdis, M., Blaser, K., Barlan, I. B., and Akdis, C. A. Impact of sublingual immunotherapy on specific antibody levels in asthmatic children allergic to house dust mites. Int Arch Allergy Immunol 2005; 136 (3): 287-94. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):control group is healthy**
Bakanov, M. I. Development of bronchial asthma attacks in children under the effect of prophylactic immunization. Vopr Okhr Materin Det 68; 13 (4): 78-9. **Non-English article: Russian- Not and RCT**
Bakulin, M. P. Several problems in specific desensitization in children with bronchial asthma. Vopr Okhr Materin Det 70; 15 (7): 52-5. **Non-English article: Russian - Not and RCT**
Balabolkin, I. I., Botvin'eva, V. V., Abdyldaev, T. T., Imanalieva, C. h. A., Ryleeva, N. V., and Ivanov, V. G. Bronchial asthma in children with sensitization to mites. Pediatriia 92; (3): 22-6. **Non-English article: Russian – Not original data**
Balabolkin, I. I., Stasii, E. D., Dzhunelov, A. B., Abdyldaev, T. T., Imanalieva, C. h. A., Guseva, N. V., Babaeva, S. B., and Strigan, V. A. Use of anti-allergic immunoglobulin in children with allergic diseases. Pediatriia 92; (1): 76-8. **No SIT Other reason for exclusion (specify):it is about use o IG not allergen Non-English article**
Balli, F., Bergamini, B. M., Marcolini, C., De Palma, M., Marchioni, C. F., and Baldini, E. V. Asthma due to Dermatophagoides in children. Peroral desensitization. Pediatr Med Chir 92; 14 (5): 523-7. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify): no control group**
Barbero, S., Catapane, M. R., and Lorenzi, L. Clinical and immunoglobulinic behavior of asthmatic children treated by desensitization with bronchoasthmatic vaccine. Minerva Pediatr 69; 21 (16): 665-78. **No SIT**
Bauer, C. P. Therapy control of hyposensitization treatment in inhalation allergies. Monatsschr Kinderheilkd 84; 132 (6): 488-93. **It does not meet ALL the inclusion criteriaNot an RCT**
Bauer, P. and Schwager, R. The effect of hyposensitization in bronchial asthma of childhood with regard to the histamine reactivity of the bronchial tract. Monatsschr Kinderheilkd 83; 131 (3): 140-4. **It does not meet ALL the inclusion criteria**
Baur X Is hyposensitization still an adequate treatment of bronchial asthma?. <ORIGINAL> IST DIE HYPOSENSIBILISIERUNG NOCH EIN ADAQUATES VERFAHREN ZUR BEHANDLUNG DES ASTHMA BRONCHIALE?. PNEUMOLOGIE ; **Non-English article – No original data**
Baur, X. Hyposensitization in bronchial asthma--still a current therapeutic procedure?. Med Klin (Munich) 89; 84 (9): 439-44. **Not an RCT**
Baur, X. Is hyposensitization still an adequate procedure in treatment of bronchial asthma?. Pneumologie 92; 46 (3): 89-91. **No original data**
Beato Martinez, A., Ayala Mejias, S., Molina Quiros, C., Colmenero Ruiz, M., and Sanz Fernandez, R. Sublingual immunotherapy in seasonal allergic rhinitis. Review of 30 cases. Acta Otorrinolaringol Esp 2005; 56 (3): 112-5. **It does not meet ALL the inclusion criteria**

Belli, E. and Riccardino, N. Variations in serum immunoglobulins during specific hyposensitization. G Batteriol Virol Immunol 72; 65 (5): 178-81. **Does not apply to any of the key questions**

BELLI, N. Further contribution to the therapy of bronchial asthma.. Praxis 52; 41 (52): 1128-30. **No SIT**

Bellussi, L., Bologna, M., Di Stanislao, C., Lauriello, M., Mezzedimi, C., Muzi, P., Passali, G. C., and Passali, D. Simplified local nasal immunotherapy in mite dust allergic rhinitis. J Investig Allergol Clin Immunol 2002; 12 (1): 42-7. **Therapy NOT AVAILABLE in the U.S**

Berbis, P., Carena, M. C., Auffranc, J. C., and Privat, Y. Cutaneo-systemic necrotizing vasculitis occurring during desensitization. Ann Dermatol Venereol 86; 113 (9): 805-10. **It does not meet ALL the inclusion criteria**

Berek-Pyzikowa, B. Protective vaccinations in children with severe allergic reactions. Przegl Epidemiol 69; 23 (1): 135-8. **Does not apply to any of the key questions**

Berg, T., Nordvall, S. L., and Lanner, A. Clinical studies of a purified timothy pollen extract. Desensitization therapy with a purified timothy pollen preparation compared to a crude timothy pollen extract. I. Results of tests in vivo. Int Arch Allergy Appl Immunol 80; 63 (3): 266-74. **It does not meet ALL the inclusion criteria no clinical outcomes**

Bernard, R., Maurel, P., Raquet, J., and Richez, P. Pollinosis in children. Their treatment with delayed allergens. Pediatrie 70; 25 (8): 883-6. **Therapy NOT AVAILABLE in the U.S**

Bernardis, P., Agnoletto, M., Puccinelli, P., Parmiani, S., and Pozzan, M. Injective versus sublingual immunotherapy in Alternaria tenuis allergic patients. J Investig Allergol Clin Immunol 96; 6 (1): 55-62. **Not an RCT**

Bernstein, D. I., Epstein, T., Murphy-Berendts, K., and Liss, G. M. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. Ann Allergy Asthma Immunol 2010; 104 (6): 530-5. **It does not meet ALL the inclusion criteria**

Bernstein, D. I., Wanner, M., Borish, L., and Liss, G. M. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004; 113 (6): 1129-36. **No SIT**

Bernstein, I. L., Michael, J. G., Malkiel, S., Sweet, L. C., and Brackett Immunoregulatory function of specific IgG. II. Clinical evaluation of combined active and passive immunotherapy. Int Arch Allergy Appl Immunol 79; 58 (1): 30-7. **Therapy NOT AVAILABLE in the U.S**

Bernstein, J. A. Pharmacoeconomic considerations for allergen immunotherapy. Clin Allergy Immunol 2004; 18 151-64. **It does not meet ALL the inclusion criteria**

Berto, P., Bassi, M., Incorvaia, C., Frati, F., Puccinelli, P., Giaquinto, C., Cantarutti, L., and Ortolani, C. Cost effectiveness of sublingual immunotherapy in children with allergic rhinitis and asthma. Eur Ann Allergy Clin Immunol 2005; 37 (8): 303-8. **It does not meet ALL the inclusion criteria**

Berto, P., Frati, F., and Incorvaia, C. Economic studies of immunotherapy: a review. Curr Opin Allergy Clin Immunol 2008; 8 (6): 585-9. **It does not meet ALL the inclusion criteria**

Berto, P., Frati, F., Incorvaia, C., Cadario, G., Contiguglia, R., Di Gioacchino, M., Puccinelli, P., Senna, G. E., and Valle, C. Comparison of costs of sublingual immunotherapy and drug treatment in grass-pollen induced allergy: results from the SIMAP database study. Curr Med Res Opin 2008; 24 (1): 261-6. **It does not meet ALL the inclusion criteria**

Berto, P., Passalacqua, G., Crimi, N., Frati, F., Ortolani, C., Senna, G., and Canonica, G. W. 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; 97 (5): 615-21. **It does not meet ALL the inclusion criteria**

Bigoni, A. Report of an unusual case of a phenomenom of the Arthus type following specific desensitization. Arcisp S Anna Ferrara 68; 21 Suppl:901-6. **Other reason for exclusion (specify):case report Not an RCT**

Blair, H. Hyposensitization for hay fever. Clin Allergy 77; 7 (3): 291-4. **Other reason for exclusion (specify): letter**

Blaiss, M. S. Allergic rhinitis: Direct and indirect costs. Allergy Asthma Proc 2010; 31 (5): 375-80. **It does not meet ALL the inclusion criteria**

Blaiss, M. S. Important aspects in management of allergic rhinitis: compliance, cost, and quality of life. Allergy Asthma Proc 2003; 24 (4): 231-8. **It does not meet ALL the inclusion criteriaNo original data**

Blazowski, L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. Allergy 2008; 63 (3): 374. **Other reason for exclusion (specify):case report**

Bleda, C., Soler, R., Romaguera, A., Mas, S., and Juan, J. M. Immunotherapy is effective in the treatment of allergic rhinitis. Retrospective study of 67 cases. Acta Otorrinolaringol Esp 98; 49 (5): 369-72. **Not an RCT**

Bodtger, U., Poulsen, L. K., and Malling, H. J. Retrospective assessment of seasonal allergic symptoms: over-rating but useful. Clin Exp Allergy 2003; 33 (4): 496-500. **Does not apply to any of the key questions**

Bohle, B. Immunological mechanisms in sublingual immunotherapy. Drugs Today (Barc) 2008; 44 Suppl B 95-6. **No original data**

Bonifazi, F. Immunotherapy in pollen and mould asthma. Monaldi Arch Chest Dis 94; 49 (2): 150-3. **It does not meet ALL the inclusion criteriaNo original data**

Bonneau, J. C., Drouet, M., Le Sellin, J., and Sabbah, A. Type III (Arthus) reaction during desensitization. Allerg Immunol (Paris) 86; 18 (4): 13-6. **Other reason for exclusion (specify):**

Bonnin, A. J. and Zacharias, D. M. Sublingual immunotherapy. N Engl J Med 2008; 359 (8): 869-70; author reply 870. **It does not meet ALL the inclusion criteria**

Boquete, M., Carballada, F., Exposito, F., and Gonzalez, A. Preventive immunotherapy. Allergol Immunopathol (Madr) 2000; 28 (3): 89-93. **Other reason for exclusion (specify): review**

Borchers, A. T., Keen, C. L., and Gershwin, M. E. Fatalities following allergen immunotherapy. Clin Rev Allergy Immunol 2004; 27 (2): 147-58. **No original data**

Bordignon, V. and Burastero, S. E. Multiple daily administrations of low-dose sublingual immunotherapy in allergic rhinoconjunctivitis. Ann Allergy Asthma Immunol 2006; 97 (2): 158-63. **It does not meet ALL the inclusion criteria**

Botey, J., Eseverri, J. L., and Marin, A. M. Do nasal and conjunctival provocation tests represent a trustworthy parameter for the follow-up of childhood IgE-dependent bronchial asthma?. Allerg Immunol (Paris) 96; 28 (2): 52-4. **It does not meet ALL the inclusion criteria**

Bousquet, J. and Malling, H. J. Immunotherapy vs inhaled budesonide in bronchial asthma: an open, parallel comparative trial. Clin Exp Allergy 98; 28 (6): 778. **No original data**

Bousquet, J., Braquemond, P., Feinberg, J., Guerin, B., Maasch, H., and Michel, F. B. Specific IgE response before and after rush immunotherapy with a standardized allergen or allergoid in grass pollen allergy. Ann Allergy 86; 56 (6): 456-9. **It does not meet ALL the inclusion criteria**d

Bousquet, J., Hejjaoui, A., Dhivert, H., Clauzel, A. M., and Michel, F. B. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. Systemic reactions during the rush protocol in patients suffering from asthma. J Allergy Clin Immunol 89; 83 (4): 797-802. **It does not meet ALL the inclusion criteria**

Bousquet, J., Hejjaoui, A., Skassa-Brociek, W., Guerin, B., Maasch, H. J., Dhivert, H., and Michel, F. B. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. J Allergy Clin Immunol 87; 80 (4): 591-8. **Therapy NOT AVAILABLE in the U.S**

Bousquet, J., Scheinmann, P., Guinnepain, M. T., Perrin-Fayolle, M., Sauvaget, J., Tonnel, A. B., Pauli, G., Caillaud, D., Dubost, R., Leynadier, F., Vervloet, D., Herman, D., Galvain, S., and Andre, C. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. Allergy 99; 54 (3): 249-60. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):no lung function**

Bowser, C., Erstein, D. P., Silverberg, J. I., Nowakowski, M., and Joks, R. Correlation of plasma complement split product levels with allergic respiratory disease activity and relation to allergen immunotherapy. Ann Allergy Asthma Immunol 2010; 104 (1): 42-9. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):no comp gr**

Bradding, P. Allergen immunotherapy and mast cells. Clin Exp Allergy 99; 29 (11): 1445-8. **No original data**

Branco Ferreira, M., Spinola Santos, A., Pereira Santos, M. C., Palma Carlos, M. L., Pereira Barbosa, M. A., and Palma Carlos, A. G. Efficacy and safety of specific immunotherapy with a modified mite extract. Allergol Immunopathol (Madr) 2005; 33 (2): 80-5. **Therapy NOT AVAILABLE in the U.S**

Branco-Ferreira, M., Clode, M. H., and Palma-Carlos, A. G. Distal digital vasculitis induced by specific immunotherapy. Allergy 98; 53 (1): 102-3. **Other reason for exclusion (specify):case report**

Brechter, C. and Rorsman, H. Basophil leukocytes in hyposensitisation. Int Arch Allergy Appl Immunol 65; 28 (1): 35-40. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**

Bringel, H., Vela, C., Urena, V., Gurbindo, D., Garcia, R., and Lahoz, C. IgG antibodies: in vitro blocking activity of IgE mediated reactions. Clin Allergy 82; 12 (1): 37-46. **It does not meet ALL the inclusion criteria**

Broman, P. and Moller, E. Lymphocyte transformation by grass pollen allergens. A study of atopic patients receiving immunotherapy. Allergy 84; 39 (4): 297-308. **Therapy NOT AVAILABLE in the U.S**

Broman, P. and Moller, E. Lymphocyte transformation by grass pollen allergens: a study of atopic patients receiving immunotherapy. Part II. Patients during maintenance treatment. Allergy 88; 43 (5): 321-31. **Does not apply to any of the key questions Other reason for exclusion (specify):No asthma or rhinitis**

Bronchial asthma in children. Sublingual immunotherapy treatment alternative with dermatofhagoides pteronyssinus **Library unable to locate**

Brostoff, J. and Ganderton, M. A. Co-seasonal prick desensitization in summer hay fever. Acta Allergol 68; 23 (1): 35-8. **It does not meet ALL the inclusion criteria**

Brostoff, J. Cellular and humoral effects of hyposensitization in patients with summer hay fever. Int Arch Allergy Appl Immunol 73; 45 (1): 162-9. **Does not apply to any of the key questions**

BROWN, E. A. RAGWEED POLLINOSIS. THE TREATMENT OF POLLINOSIS BY MEANS OF EMULSIFIED EXTRACTS XXVII. A STUDY OF 1809 PATIENTS STUDIED FOR THE 1962 RAGWEED POLLEN SEASON. Ann Allergy 63; 21 505-27. **Therapy NOT AVAILABLE in the U.S**

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Modulation of histamine-releasing factor production by specific immunotherapy. J Allergy Clin Immunol 92; 89 (1 Pt 1): 87-94. **It does not meet ALL the inclusion criteria**d**Not an RCT**

Brunner, F. X. Allergic rhinitis in childhood--therapy and therapeutic success in a 5-year observation period. Laryngol Rhinol Otol (Stuttg) 86; 65 (5): 260-3. **It does not meet ALL the inclusion criteria**

Bruttmann, G. and Agnius-Delord, C. IgE changes in pollinosis after desensitization. Nouv Presse Med 76; 5 (38): 2544, 2547. **It does not meet ALL the inclusion criteria**

Bruun, E. Treatment of hay fever with an aluminum--precipitated pyridine grass pollen extract ("Allpyral grass mix"). Ugeskr Laeger 67; 129 (26): 874-6. **Therapy NOT AVAILABLE in the U.S**

Buchanan, D. J., Hillis, A., and Williams, P. N. A double blind controlled trial of Bencard house dust mite (Migen) hyposensitisation in Zambian asthmatics. Med J Zambia 80-81; 15 (1): 14-6. **It does not meet ALL the inclusion criteria**

Buenfil Lopez, J. A. Immunotherapy in childhood asthma. Rev Alerg Mex 97; 44 (3): 67-9. **It does not meet ALL the inclusion criteria**

Bulakhova, E. K. The efficacy of specific hyposensitization in bronchial asthma and pollinosis. Vrach Delo 91; (2): 89-91. **Other reason for exclusion (specify):**

Bunnag, C. and Dhorranintra, B. A preliminary study of circulating immune complexes during allergen immunotherapy in Thai patients. Asian Pac J Allergy Immunol 89; 7 (1): 15-21. **It does not meet ALL the inclusion criteria**

Burgi, H. and Regli, J. Experiences with the immunotherapy of chronic asthmatic bronchitis. Schweiz Med Wochenschr 67; 97 (31): 1007-8. **It does not meet ALL the inclusion criteria**

Businco, L., Zannino, L., Cantani, A., Corrias, A., Fiocchi, A., and La Rosa, M. Systemic reactions to specific immunotherapy in children with respiratory allergy: a prospective study. Pediatr Allergy Immunol 95; 6 (1): 44-7. **It does not meet ALL the inclusion criteria**

Bystrzanowska, T., Majchrzak, M., and Poplawski, B. Results of desensitization treatment in allergic rhinitis. Pol Tyg Lek 76; 31 (21): 881-4. **Other reason for exclusion (specify):**

C. Antunez, C. Mayorga, J. L. Corzo, A. Jurado and M. J. Torres Two year follow-up of immunological response in mite-allergic children treated with sublingual immunotherapy. Comparison with subcutaneous administration. Pediatr Allergy Immunol 2008 19 (3): 210-8. **It does not meet ALL the inclusion criteria**

C. J. Wen, M. F. Zhu, W. M. Ren, X. Y. Liu and H. Qian Clinical efficacy and safety of sublingual immunotherapy using standardized dermatophagoides farinae extract for children with combined allergic rhinitis and asthma syndrome. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011 46 (5): 393-6. **Not an RCT**

C. K. Naspitz and J. O. Warner Children are pharmaco-therapeutic orphans. Pediatric Allergy and Immunology 2010 21 (2 PART 1): 249-250. **Does not apply to any of the key questions No SITOther reason for exclusion (specify):Editorial**

C. Rondon, N. Blanca-Lopez, A. Aranda, R. Herrera, J. L. Rodriguez-Bada, G. Canto, C. Mayorga, M. J. Torres, P. Campo and M. Blanca Local allergic rhinitis: Allergen tolerance and immunologic changes after preseasonal immunotherapy with grass pollen. Journal of Allergy and Clinical Immunology 2011 127 (4): 1069-1071. **Other reason for exclusion (specify):**correspondence with pilot observational data**Not an RCT**

C. S. Hankin and R. F. Lockey Patient characteristics associated with allergen immunotherapy initiation and adherence. Journal of Allergy and Clinical Immunology 2011 127 (1): 46-48.e3. **Not an RCT**

C. S. Wang, W. Zhang, X. D. Wang, L. Xi, Y. H. Ouyang, Y. Zhao, Y. Wang and L. Zhang Clinical efficacy and immunological changes in children with allergic rhinitis receiving specific immunotherapy with Dermatophagoides pteronyssinus. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011 46 (1): 36-9. **Other reason for exclusion (specify):chinese**

C. Vidal, A. I. Tabar, J. Figueroa, J. A. Navarro, C. Sanchez, A. Orovitg, M. Armisen, S. Echechipia, A. Joral, S. Lizarza, M. T. Lizaso, V. Rodriguez and F. de la Torre Assessment of short-term changes induced by a Dermatophagoides pteronyssinus extract on asthmatic patients. Randomised, double-blind, placebo-controlled trial. Current drug delivery 2011 8 (2): 152-158. **It does not meet ALL the inclusion criteria**

Cabrera, G. E., Citera, G., Gutierrez, M., Scopelitis, E., and Espinoza, L. R. Digital vasculitis following allergic desensitization treatment. J Rheumatol 93; 20 (11): 1970-2. **It does not meet ALL the inclusion criteria**

Calvo, M., Marin, F., Grob, K., Sanhueza, M., Kylling, L., Albornoz, C., and Strickler, A. Ten-year follow-up in pediatric patients with allergic bronchial asthma: evaluation of specific immunotherapy. J Investig Allergol Clin Immunol 94; 4 (3): 126-31. **It does not meet ALL the inclusion criteria**

Cambri, S., Tarantino, G., and Cambri, V. Is the diagnostic differentiation between Parietaria officinalis and Parietaria judaica important for the specific immunotherapy?. Clin Ter 86; 119 (4): 269-73. **It does not meet ALL the inclusion criteria**

Campbell, J. D., Buchmann, P., Kesting, S., Cunningham, C. R., Coffman, R. L., and Hessel, E. M. Allergen-specific T cell responses to immunotherapy monitored by CD154 and intracellular cytokine expression. Clin Exp Allergy 2010; 40 (7): 1025-35. **Does not apply to any of the key questionsStudy evaluates outcomes in animals only or in vitro**

Can allergy shots provide relief from hay fever even after the shots are discontinued?. Mayo Clin Health Lett 2000; 18 (6): 8. **No original data**

Can nasal ECP help to predict clinical outcome of specific immunotherapy in mite-allergic rhinitis patients? **Library unable to locate**
Can serum specific IgE/total IgE ratio predict clinical response to allergenspecific immunotherapy in children monosensitised to house dust mite? **Meeting abstract**
Can, D., Demir, E., Tanac, R., Gulen, F., and Yenigun, A. Immediate adverse reactions to immunotherapy. J Investig Allergol Clin Immunol 2003; 13 (3): 177-80. **Not an RCT**
Can, D., Tanac, R., Demir, E., Gulen, F., and Veral, A. Efficacy of pollen immunotherapy in seasonal allergic rhinitis. Pediatr Int 2007; 49 (1): 64-9. **It does not meet ALL the inclusion criteria**
Canonica, G. W., Mingari, M. C., Melioli, G., Colombatti, M., and Moretta, L. Imbalances of T cell subpopulations in patients with atopic diseases and effect of specific immunotherapy. J Immunol 79; 123 (6): 2669-72. **Therapy NOT AVAILABLE in the U.S**
Canos Molinos, J. and Munoz-Lopez, F. Value of serum IgG subclasses in the prognosis of asthma in children with immunotherapy treatment. Allergol Immunopathol (Madr) 97; 25 (1): 10-7. **Does not apply to any of the key questions**
Cantani, A. and Ciaschi, V. Epidemiology of alternaria alternata allergy: a prospective study in 6840 Italian asthmatic children. Eur Rev Med Pharmacol Sci 2004; 8 (6): 289-94. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**
Cantani, A. and Micera, M. A prospective study of asthma desensitization in 1182 children, 592 asthmatic children and 590 nonatopic controls. Eur Rev Med Pharmacol Sci 2005; 9 (6): 325-9. **Does not apply to any of the key questions**
Cantani, A. and Micera, M. Is specific immunotherapy safe and effective in children?. Eur Rev Med Pharmacol Sci 2000; 4 (5-6): 139-43. **No original data**
Cantani, A. and Micera, M. Significant decrease of IgE antibodies after a three-year controlled study of specific immunotherapy to pollen allergens in children with allergic asthma. Eur Rev Med Pharmacol Sci 2005; 9 (2): 103-11. **It does not meet ALL the inclusion criteria**
Cantani, A., Arcese, G., Di Rienzo, A., and Lucenti, P. Immunotherapy for asthma. Ann Allergy Asthma Immunol 98; 80 (2): 213-4. **No original data**
Cantani, A., Arcese, G., Gagliesi, D., and Lucenti, P. Specific immunotherapy in children is safe and effective. Eur Rev Med Pharmacol Sci 98; 2 (1): 41-4. **No original data**
Cantani, A., Businco, E., and Maglio, A. Alternaria allergy: a three-year controlled study in children treated with immunotherapy. Allergol Immunopathol (Madr) 88; 16 (1): 1-4. **It does not meet ALL the inclusion criteria**
Cantani, A., Businco, E., Benincori, N., de Angelis, M., di Fazio, A., and Businco, L. A three year controlled study in children with pollinosis treated with immunotherapy. Ann Allergy 84; 53 (1): 79-84. **Therapy NOT AVAILABLE in the U.S**
Cao, L. F., Lu, Q., Gu, H. L., Chen, Y. P., Zhang, Y., Lu, M., Qian, Y. Q., Li, L., and Xu, Y. P. Clinical evaluation for sublingual immunotherapy of allergic asthma and atopic rhinitis with Dermatophagoides Farinae Drops. Zhonghua Er Ke Za Zhi 2007; 45 (10): 736-41. **Non-English article**
Capristo, A., Comune, V., Maiello, N., and Miraglia Del Giudice, M. Long-term studies of respiratory function during hyposensitization therapy of childhood asthma. Pediatria (Napoli) 79; 87 (2): 183-95. **No original data**
Capristo, A., Maiello, N., Barra, R., Salzano, V., and Miraglia Del Giudice, M. Long-term clinical and laboratory findings in a group of asthmatic children treated for 3 years with a specific desensitizing therapy. Pediatria (Napoli) 80; 88 (2): 171-87. **It does not meet ALL the inclusion criteria**
Carbone, R., Luppi, F., Monselise, A., and Bottino, G. Bronchial hyperresponsiveness in asthmatic adults--a long-term correlation study. Eur Rev Med Pharmacol Sci 2005; 9 (2): 125-31. **It does not meet ALL the inclusion criteria**
Carnimeo, N., Valerio, G., Resta, O., and Lopez, M. Computerized analysis of methodological data and clinical reports concerning a group of 400 asthmatic patients undergoing immunotherapy. Arch Monaldi 79; 34 (1-2): 42-8. **It does not meet ALL the inclusion criteria**
Carron, R., Tuaillon, C., Brodschi, M., and Chalamelle, M. J. Allergic asthma in children treated by desensitization: 12 years experience; results, considerations. Lyon Med 70; 223 (2): 111-25. **It does not meet ALL the inclusion criteria**
Casale, T. B., Busse, W. W., Kline, J. N., Ballas, Z. K., Moss, M. H., Townley, R. G., Mokhtarani, M., Seyfert-Margolis, V., Asare, A., Bateman, K., and Deniz, Y. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006; 117 (1): 134-40. **Does not apply to any of the key questions**
Casgrain, G., Leger, J., and Leger, F. A slowly absorbed pollen extract: follow-up of a clinical study. Union Med Can 65; 94 (6): 808-10. **It does not meet ALL the inclusion criteria**
CASGRAIN, G., LEGER, J., and LEGER, F. CLINICAL STUDY OF A NEW POLLEN EXTRACT OF SLOW ABSORPTION.. Union Med Can 64; 93 302-4. **It does not meet ALL the inclusion criteria**
Castell, M., Castellote, C., and Barbera, G. Detection of blocking antibodies after hyposensitization. Immunobiology 85; 169 (1): 30-6. **It does not meet ALL the inclusion criteria**
Castellote, M. C., Duran, N., Barbera, G., and Torralba, A. Levels of complement factors and immunoglobulins in asthmatic children undergoing hyposensitization. Allergol Immunopathol (Madr) 84; 12 (4): 259-66. **Does not apply to any of the key questions**

Castellote, M. C., Munoz Lopez, F., Barbera, G., and Torralba, A. Urinary excretion of cyclic-AMP and cyclic-GMP in allergic children throughout seven months of hyposensitization treatment. Ann Allergy 81; 46 (5): 281-3. **It does not meet ALL the inclusion criteria**, C, D

Castracane, J. M. and Rocklin, R. E. Detection of human auto-anti-idiotypic antibodies (Ab2). II. Generation of Ab2 in atopic patients undergoing allergen immunotherapy. Int Arch Allergy Appl Immunol 88; 86 (3): 295-302. **It does not meet ALL the inclusion criteria**

Cengizlier, R., Saraclar, Y., Adalioglu, C., and Tuncer, A. Changes in nasal metachromatic cells during allergen immunotherapy in children. Allergol Immunopathol (Madr) 95; 23 (3): 111-6. **It does not meet ALL the inclusion criteria**

Cengizlier, R., Saraclar, Y., and Tomac, N. Evaluation of immunotherapy by nasal antigen challenge. J Otolaryngol 99; 28 (4): 185-8.

Centanni, G. Comparison of the therapeutic results obtained with alum-pyridine pollen extracts and aqeuous extracts. Folia Allergol (Roma) 70; 17 (3): 309-26. **Therapy NOT AVAILABLE in the U.S**

Cernelc, D. and Cernelc, M. Prognosis of bronchial asthma in children after specific subcutaneous hyposensitization (SSH) and nonspecific treatment (NT). Allerg Immunol (Leipz) 72; 18 (3): 167-76. **It does not meet ALL the inclusion criteria**

Cernelc, D., Bohinjec, M., and Cernelc, P. Some results of various methods of specific hyposensitization in asthmatic children. Monatsschr Kinderheilkd 76; 124 (5): 250-1. **It does not meet ALL the inclusion criteria**

Cernelc, D., Vozelj, M., and Wraber, T. Immunotherapy of pollinosis caused by Ambrosia artemisiifolia (author's transl). Plucne Bolesti Tuberk 78; 30 (1-2): 70-6. **Non-English article: serb**

Cernelc, V. D., Bobinjec, M., and Cernelc, S. Epidemiology, diagnosis and treatment of the house-dust-mite allergy in asthmatic children. Allerg Immunol (Leipz) 74-75; 20-21 (1): 1-6. **It does not meet ALL the inclusion criteria**

Cevit, O., Kendirli, S. G., Yilmaz, M., Altintas, D. U., and Karakoc, G. B. Specific allergen immunotherapy: effect on immunologic markers and clinical parameters in asthmatic children. J Investig Allergol Clin Immunol 2007; 17 (5): 286-91. **It does not meet ALL the inclusion criteria**

Chang, H., Han, D. H., Mo, J. H., Kim, J. W., Kim, D. Y., Lee, C. H., Min, Y. G., and Rhee, C. S. Early compliance and efficacy of sublingual immunotherapy in patients with allergic rhinitis for house dust mites. Clin Exp Otorhinolaryngol 2009; 2 (3): 136-40. **obs case series**

Chang, J. and Hong, C. S. The effect of immunotherapy on nonspecific bronchial hyperresponsiveness in bronchial asthma and allergic rhinitis. Yonsei Med J 2001; 42 (1): 106-13. **It does not meet ALL the inclusion criteria**

Changes in bronchial reactivity to histamine in the course of allergen immunotherapy in seasonal allergic rhinitis patients -are they really caused by the treatment? Comparison of two schedules, Maintenance versus pre-seasonal **Meeting abstract**

CHARPIN, J. and ROCCA-SERRA, J. P. Vaccinations in the asthmatic patient.. J Fr Med Chir Thorac 61; 15 667-71. **No SIT**

Charpin, J., Aubert, J., Roccaserra, J. P., and Zafiropoulo, A. Treatment of Graminaceae pollinosis by Allpyral. Mars Med 66; 103 (12): 967-70. **Therapy NOT AVAILABLE in the U.S**

CHARPIN, J., ZAFIROPOULO, A., and AUBERT, J. SPECIFIC DESENSITIZATION IN THE TREATMENT OF BRONCHIAL ASTHMA.. Minerva Med 64; 55 1243-6. **No original data**

Check, W. A. Modified antigen therapy aids allergy victims. JAMA 82; 247 (16): 2202-3. **No original data**

Chen LL, Li AS, Tao JN, Chen WX, and Tang RF Clinical and experimental studies on preventing and treating anaphylactic asthma with Zusanli(ST36) point immunotherapy. Journal of Integrated Traditional and Western MedicineZhong Xi Yi Jie He Za Zhi ; **Does not apply to any of the key questions**

Chen, J., Kong, W., Xiang, J., Lu, Z., and Zhou, Y. Compliance analysis of sublingual immunotherapy and countermeasures. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2010; 24 (5): 203-6. **It does not meet ALL the inclusion criteria**d

Chen, J., Kong, W., Xiang, J., Shu, H., Shi, Q., Tan, H., Lu, Z., Zhou, Y., and Zhang, X. Efficacy evaluation of specific immunotherapy with standardized dermatophagoides pteronyssinus extract for allergic rhinitis accompanied with asthma. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2010; 24 (2): 57-9. **Not an RCT**

Chen, W. Y., Yu, J., and Wang, J. Y. Decreased production of endothelin-1 in asthmatic children after immunotherapy. J Asthma 95; 32 (1): 29-35. **It does not meet ALL the inclusion criteria**d

Chen, W. Y., Yu, J., and Wang, J. Y. The effect of immunotherapy on bronchial hyperresponsiveness in asthmatic children. Asian Pac J Allergy Immunol 94; 12 (1): 15-20. **Does not apply to any of the key questions**

Chen, Z. G., Chen, Y. F., Li, M., Ji, J. Z., Chen, F. H., and Chen, H. Effects of Dermatophagoides pteronyssinus allergen-specific immunotherapy on the prognosis of asthmatic children. Nan Fang Yi Ke Da Xue Xue Bao 2009; 29 (6): 1179-81. **Not an RCT**

Chen, Z. G., Li, M., Chen, Y. F., Ji, J. Z., Li, Y. T., Chen, W., Chen, F. H., and Chen, H. Effects of dermatophagoides pteronyssinus allergen-specific immunotherapy on the serum interleukin-13 and pulmonary functions in asthmatic children. Chin Med J (Engl) 2009; 122 (10): 1157-61. **It does not meet ALL the inclusion criteria**

Cheng, L. and Li, H. B. Specific immunotherapy of allergic rhinitis. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2008; 43 (1): 73-6. **Non-English article**

Cheng, Z., Wang, X., Wang, G., Shu, C., and Cheng, Y. An experimental study on the regulation of

expression of Thq/Th2 cytokines by allergen vaccine atomization inhalation in patients with asthma. Lin Chuang Er Bi Yan Hou Ke Za Zhi 2006; 20 (17): 790-2. **Does not apply to any of the key questions**
Chernokhvostova, E. V., Kotova, T. S., Atovmian, O. I., Arsen'eva, E. L., Bogacheva, G. T., and Rokhlin, O. V. Immunoenzyme test system with monoclonal antibodies to human IgG4 in the determination of allergen-specific antibodies in pollinosis. Biull Eksp Biol Med 89; 108 (11): 574-7. **Does not apply to any of the key questions**
Chiang, B. L., Lu, F. M., Chuang, Y. H., Chou, C. C., and Hsieh, K. H. Change of chemokines during immunotherapy in asthmatic children. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 96; 37 (5): 324-32. **Number of subjects in study is 6 or fewer on active treatment (Unless it reports harms)**
Chiang, B. L., Tsai, M. J., Chou, C. C., and Hsieh, K. H. In vitro production of cytokines and allergen-specific IgE in bronchial asthmatic children with different disease activity. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 98; 39 (3): 173-9. **Does not apply to any of the key questionsStudy evaluates outcomes in animals only or in vitro**
Chien, Y. K., Anfosso, F., and Charpin, J. IgE and IgG1, 2, 4 in desensitization of pollen asthma. Hawaii Med J 84; 43 (11): 410, 412. **It does not meet ALL the inclusion criteria**
Chien, Y. K., Yang, W. P., Xue, Z. L., and Massey, D. G. House dust mite asthma in China: a review. Ann Allergy 87; 59 (2): 147-8. **No original data**
Chikamatsu, K., Sakakura, K., Matsuoka, T., Endo, S., Takahashi, G., Matsuzaki, Z., and Masuyama, K. Analysis of T-helper responses and FOXP3 gene expression in patients with Japanese cedar pollinosis. Am J Rhinol 2008; 22 (6): 582-8. **Does not apply to any of the key questions Not an RCT**
Choi, I. S., Koh, Y. I., Chung, S. W., Wi, J. O., and Sim, D. S. Late local urticaria as a long-term sequela of allergen-specific immunotherapy. Korean J Intern Med 2004; 19 (3): 202-4. **It does not meet ALL the inclusion criteria**
Choovoravech, P. Effect of immunotherapy: treatment with mite and other aeroallergens in Thai allergic patients. J Med Assoc Thai 80; 63 (9): 506-11. **Does not apply to any of the key questions**
Choovoravech, P. Effects of immunotherapy on Thai asthmatic children. Asian Pac J Allergy Immunol 84; 2 (1): 32-6. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**
Choquet, P. H., Nguyen, B., Vai, F., Guerin, B., and Sauvaget, J. Accelerated desensitization in asthma caused by cat fur. Presse Med 87; 16 (3): 126-7. **It does not meet ALL the inclusion criteria**
Chowdhury, I. and Chatterjee, B. The immunological and clinical effects of immunotherapy in patients suffering from house dust allergy. Ann Agric Environ Med 99; 6 (2): 91-7. **It does not meet ALL the inclusion criteria**
Chu, J. C., Wun, T. H., and Chen, X. J. Treatment of asthmatic patients sensitive to mites (Dermatophagoides farinae); a four-year study of immunotherapy with an extract of Dermatophagoides farinae. Ann Allergy 81; 47 (2): 107-9. **It does not meet ALL the inclusion criteria**
Chuchalin, A. G., Raudla, L. A., Tatarskii, A. R., Shurkalin, B. K., and Evseev, N. G. Extracorporeal specific immunosorption in the complex treatment of patients with bronchial asthma and hypersensitivity to house dust allergen. Ter Arkh 84; 56 (6): 24-8. **Does not apply to any of the key questions**
Cingi, C., Aynaci, S., Cakli, H., Cingi, E., Ozudogru, E., Kecik, C., Altin, F., and Bal, C. Efficacy of long-term sublingual-oral immunotherapy in allergic rhinitis. Acta Otorhinolaryngol Ital 2005; 25 (4): 214-9. **It does not meet ALL the inclusion criteria**
Ciprandi, G., Cadario, G., Di Gioacchino, G. M., Gangemi, S., Gasparini, A., Isola, S., Marengo, F., Minelli, S., Ricciardi, L., Ridolo, E., Pravettoni, V., Valle, C., Verini, M., Zambito, M., Incorvaia, C., Puccinelli, P., Scurati, S., Frati, F., and Simonetta, M. Sublingual immunotherapy in children with allergic polysensitization. Allergy Asthma Proc 2010; 31 (3): 227-31. **It does not meet ALL the inclusion criteria**
Ciprandi, G., Cadario, G., Di Gioacchino, M., Gangemi, S., Minelli, M., Ridolo, E., Valle, C., Verini, M., Boccardo, R., Incorvaia, C., Puccinelli, P., Scurati, S., and Frati, F. Sublingual immunotherapy in polysensitized allergic patients with rhinitis and/or asthma: allergist choices and treatment efficacy. J Biol Regul Homeost Agents 2009; 23 (3): 165-71. **It does not meet ALL the inclusion criteria**
Ciprandi, G., Cadario, G., Valle, C., Ridolo, E., Verini, M., Di Gioacchino, M., Minelli, M., Gangemi, S., Sillano, V., Colangelo, C., Pravettoni, V., Pellegrino, R., Borrelli, P., Fiorina, A., Carosso, A., Gasparini, A., Riario-Sforza, G. G., Incorvaia, C., Puccinelli, P., Scurati, S., and Frati, F. Sublingual immunotherapy in polysensitized patients: effect on quality of life. J Investig Allergol Clin Immunol 2010; 20 (4): 274-9. **It does not meet ALL the inclusion criteria**
Ciprandi, G., Cirillo, I., Fenoglio, D., Marseglia, G., and Tosca, M. A. Sublingual immunotherapy induces spirometric improvement associated with IL-10 production: preliminary reports. Int Immunopharmacol 2006; 6 (8): 1370-3. **Therapy NOT AVAILABLE in the U.S**
Ciprandi, G., Cirillo, I., Tosca, M. A., Marseglia, G., and Fenoglio, D. Sublingual immunotherapy-induced IL-10 production is associated with changed response to the decongestion test: preliminary results. Allergy Asthma Proc 2007; 28 (5): 574-7. **It does not meet ALL the inclusion criteria**
Ciprandi, G., Colombo, B. M., Murdaca, G., and De Amici, M. Serum vascular endothelial growth factor and sublingual immunotherapy. Allergy 2008; 63 (7): 945-6. **It does not meet ALL the inclusion criteria**
Ciprandi, G., Contini, P., Pistorio, A., Murdaca, G., and Puppo, F. Sublingual immunotherapy reduces soluble HLA-G and HLA-A,-B,-C serum levels in patients with allergic rhinitis. Int Immunopharmacol 2009; 9 (2): 253-7. **It does not meet ALL the inclusion criteria; control healthy**

Ciprandi, G., Continia, P., Fenoglio, D., Sormani, M. P., Negrini, S., Puppo, F., and Indiveri, F. Relationship between soluble HLA-G and HLA-A,-B,-C serum levels, and interferon-gamma production after sublingual immunotherapy in patients with allergic rhinitis. Hum Immunol 2008; 69 (7): 409-13. **Does not apply to any of the key questions**

Ciprandi, G., De Amici, M., and Marseglia, G. Serum adipsin levels in patients with seasonal allergic rhinitis: preliminary data. Int Immunopharmacol 2009; 9 (12): 1460-3. **It does not meet ALL the inclusion criteria**

Ciprandi, G., De Amici, M., Murdaca, G., Colombo, B. M., Quaglini, S., Marseglia, G., and Di Gioacchino, M. Serum IL-4 as a marker of immunological response to sublingual immunotherapy. J Biol Regul Homeost Agents 2008; 22 (2): 117-23. **It does not meet ALL the inclusion criteria**

Ciprandi, G., De Amici, M., Murdaca, G., Filaci, G., Fenoglio, D., and Marseglia, G. L. Adipokines and sublingual immunotherapy: preliminary report. Hum Immunol 2009; 70 (1): 73-8. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**

Ciprandi, G., De Amici, M., Negrini, S., Marseglia, G., and Tosca, M. A. TGF-beta and IL-17 serum levels and specific immunotherapy. Int Immunopharmacol 2009; 9 (10): 1247-9. **Does not apply to any of the key questions**

Ciprandi, G., De Amici, M., Tosca, M. A., Pistorio, A., and Marseglia, G. L. Sublingual immunotherapy affects specific antibody and TGF-beta serum levels in patients with allergic rhinitis. Int J Immunopathol Pharmacol 2009; 22 (4): 1089-96. **Does not apply to any of the key questions**

Ciprandi, G., De Amici, M., Tosca, M., and Marseglia, G. Serum transforming growth factor-beta levels depend on allergen exposure in allergic rhinitis. Int Arch Allergy Immunol 2010; 152 (1): 66-70. **Does not apply to any of the key questions**

Ciprandi, G., De Amici, M., Tosca, M., Negrini, S., Murdaca, G., and Marseglia, G. L. Two year sublingual immunotherapy affects serum leptin. Int Immunopharmacol 2009; 9 (10): 1244-6. **It does not meet ALL the inclusion criteria**

Ciprandi, G., Fenoglio, D., Cirillo, I., Vizzaccaro, A., Ferrera, A., Tosca, M. A., and Puppo, F. Induction of interleukin 10 by sublingual immunotherapy for house dust mites: a preliminary report. Ann Allergy Asthma Immunol 2005; 95 (1): 38-44. **Does not apply to any of the key questions**

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Ciprandi, G., Sormani, M. P., Cirillo, I., and Tosca, M. Upper respiratory tract infections and sublingual immunotherapy: preliminary evidence. Ann Allergy Asthma Immunol 2009; 102 (3): 262-3. **It does not meet ALL the inclusion criteria**

Ciprandi, G., Sormani, M. P., Filaci, G., and Fenoglio, D. Carry-over effect on IFN-gamma production induced by allergen-specific immunotherapy. Int Immunopharmacol 2008; 8 (12): 1622-5. **It does not meet ALL the inclusion criteria**

Cirla, A. M., Cirla, P. E., Parmiani, S., and Pecora, S. A pre-seasonal birch/hazel sublingual immunotherapy can improve the outcome of grass pollen injective treatment in bisensitized individuals. A case-referent, two-year controlled study. Allergol Immunopathol (Madr) 2003; 31 (1): 31-43. **It does not meet ALL the inclusion criteria**

Citron, K. M. Hyposensitization: assessment of results. Br J Dis Chest 77; 71 (4): 241-2. **Does not apply to any of the key questions**

Citron, K. M. Injection treatment for desensitization in asthma, hay fever, and allergic rhinitis. Br J Dis Chest 66; 60 (1): 1-9. **No original data**

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Clark, R. B. and Burdett, B. R. Allergy immunotherapy. Am Fam Physician 82; 26 (5): 219-23. **No original data**

Clark, T. J. Efficacy and safety of anti-asthma treatment. Allergy 88; 43 Suppl 8 32-5. **No original data**

Clarke, P. S. Dangers of immunotherapy for the treatment of asthma in children. Med J Aust 90; 153 (11-12): 744. **No original data**

Clarke, P. S. Immunotherapy in allergic asthma. Med J Aust 81; 1 (8): 432. **No original data**

Clarke, P. S. Improved diagnosis and treatment of allergic rhinitis by the use of nasal provocation tests. Ann Allergy 88; 60 (1): 57-60. **It does not meet ALL the inclusion criteria**

Clarke, P. S. Titration of immunotherapy by periodical nasal allergic challenges in the treatment of allergic rhinitis. Med J Aust 92; 157 (1): 11-3. **Does not apply to any of the key questions**

Clarke, P. S. Titration of immunotherapy. Med J Aust 93; 158 (2): 142. **No original data**

Clasen, I. and Wuthrich, B. Recent results of peroral hyposensitization in infantile bronchial asthma. Monatsschr Kinderheilkd 76; 124 (5): 248. **It does not meet ALL the inclusion criteria**

Clemmensen, O. and Knudsen, H. E. Contact sensitivity to aluminium in a patient hyposensitized

with aluminium precipitated grass pollen. Contact Dermatitis 80; 6 (5): 305-8. **It does not meet ALL the inclusion criteria**,d

CLINICAL AND IMMUNOLOGIC EVALUATION OF A PURIFIED FRACTION OF RAGWEED POLLEN (DELTA). A DOUBLE-BLIND STUDY **Excluded at data abstraction**

Clinical data and inflammation parameters in patients with cypress allergy treated with sublingual swallow therapy and subcutaneous immunotherapy **Excluded at abstract level**

Clinical effect of sublingual immunotherapy in allergic rhinitis patients **Meeting abstract**

Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial **Duplicate**

Clinical efficacy and side effects of sublingual immunotherapy versus placebo in children with perennial allergic rhinitis and asthma, sensitised to house dust mites **Abstract only**

Clinical efficacy of grass-pollen immunotherapy **Duplicate**

Clinical efficacy of house dust mite-specific immunotherapy in asthmatic children **Excluded at data abstraction**

Clinical efficacy of sublingual immunotherapy in seasonal allergic asthma **Meeting abstract**

Clinical efficacy of sublingualimmunotherapy in patients with grass pollen induced respiratory allergy symptoms **Meeting abstract**

Clinical outcome and IL-17, IL-23, IL-27 and FOXP3 expression in peripheral blood mononuclear cells of pollen-allergic children during sublingual immunotherapy **Part of** 5734

Cloninger, P. N., Stein, H. L., Nagy, S. M., Kemp, J. P., and Turk, A. The role of immunotherapy in asthma. Am Rev Respir Dis 78; 118 (2): 447-8. **No original data**

Cochard, M. M. and Eigenmann, P. A. Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy. J Allergy Clin Immunol 2009; 124 (2): 378-9. **Other reason for exclusion (specify):case report**

Cohen, G. N. Asthma management includes desensitization injections. Am J Med 95; 98 (5): 517-8. **It does not meet ALL the inclusion criteriaNo original data**

Cohen, S. G. Lowell and Franklin on double-blind hyposensitization therapy for ragweed hay fever: the people. J Allergy Clin Immunol 2004; 113 (6): 1227-31. **Does not apply to any of the key questions**

Cohen, S. G., Frankland, A. W., and Dworetzky, M. Noon and Freeman on prophylactic inoculation against hay fever. J Allergy Clin Immunol 2003; 111 (5): 1142-50. **No original data**

Cohn, J. R. and Pizzi, A. Determinants of patient compliance with allergen immunotherapy. J Allergy Clin Immunol 93; 91 (3): 734-7. **It does not meet ALL the inclusion criteria**

Cohon, A., Arruda, L. K., Martins, M. A., Guilherme, L., and Kalil, J. Evaluation of BCG administration as an adjuvant to specific immunotherapy in asthmatic children with mite allergy. J Allergy Clin Immunol 2007; 120 (1): 210-3. **Therapy NOT AVAILABLE in the U.S**

Coifman, R. E. and Cox, L. S. 2006 American Academy of Allergy, Asthma & Immunology member immunotherapy practice patterns and concerns. J Allergy Clin Immunol 2007; 119 (4): 1012-3. **Does not apply to any of the key questions**

Collins-Williams, C. Non-allergic bronchial hyperreactivity in asthmatic children decreases with age and increases with mite immunotherapy. Ann Allergy 86; 56 (2): 190-1. **Other reason for exclusion (specify): letter**

Combination of immunotherapy and inhaled steroid therapy increase efficacy of the treatment in patient with allergic asthma to house dust mites. **Library unable to locate**

Compalati, E., Passalacqua, G., Bonini, M., and Canonica, G. W. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. Allergy 2009; 64 (11): 1570-9. **Other reason for exclusion (specify):meta-analysis**

Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children **Library unable to locate**

Comparative Efficacy of Subcutaneous Immunotherapy, Sublingual Immunotherapy and Combined Subcutaneous and Sublingual Immunotherapy in Patients with Seasonal Allergic Rhinitis and Cross-Reactive Food Allergy Abstract **Abstract only**

Comparative study of the effectiveness of 2 methods of specific immunotherapy of pollinoses **Library unable to locate**

Comparison of clinical efficacy and preventive role between subcutaneous and sublingual immunotherapy in children with seasonal allergic rhinitis **Meeting abstract**

Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study **Duplicate** of 3490

Comparison of nasal immunohistology in patients with seasonal rhinoconjunctivitis treated with topical steroids or specific allergen immunotherapy **Part of** 4625

Comparison of specific sublingual immunotherapy to homeopathic therapy in children with allergic rhinitis **Meeting abstract**

Comparisons of alum-precipitated and unprecipitated aqueous ragweed pollen extracts in the treatment of hay fever **Excluded at data abstraction**

Confino-Cohen, R. and Goldberg, A. Allergen immunotherapy-induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective study. Ann Allergy Asthma Immunol 2010; 104 (1): 73-8. **Not an RCT**

Connell, J. T. and Sherman, W. B. Changes in skin-sensitizing antibody titer after injections of aqueous

pollen extract. J Allergy 69; 43 (1): 22-32. **It does not meet ALL the inclusion criteria**
CONNELL, J. T. and SHERMAN, W. B. SKIN-SENSITIZING ANTIBODY. II. RELATIONSHIP OF HAY FEVER SYMPTOMS TO THE SKIN-SENSITIZING ANTIBODY TITER IN PATIENTS TREATED WITH RAGWEED EMULSION INJECTIONS, AQUEOUS RAGWEED INJECTIONS, OR NO INJECTION TREATMENT. J Allergy Clin Immunol 64; 35 18-26. **Therapy NOT AVAILABLE in the U.S**
Cook, N. Pre-seasonal local nasal desensitization in hay fever. J Laryngol Otol 74; 88 (12): 1169-74. **It does not meet ALL the inclusion criteria**
Cook, P. R. Allergic rhinitis. Outcomes of immunotherapy on symptom control. Otolaryngol Clin North Am 98; 31 (1): 129-40. **No original data**
Cools, M., Van Bever, H. P., Weyler, J. J., and Stevens, W. J. Long-term effects of specific immunotherapy, administered during childhood, in asthmatic patients allergic to either house-dust mite or to both house-dust mite and grass pollen. Allergy 2000; 55 (1): 69-73. **It does not meet ALL the inclusion criteria**
Coop, C. A. and Tankersley, M. S. Dose adjustment practices among allergists for local reactions to immunotherapy. Ann Allergy Asthma Immunol 2007; 99 (1): 77-81. **Does not apply to any of the key questions**
Cooper, B. Migen in the treatment of perennial rhinitis. Br J Clin Pract 79; 33 (11-12): 323-4. **It does not meet ALL the inclusion criteria**
Cooper, P. J., Darbyshire, J., Nunn, A. J., and Warner, J. O. A controlled trial of oral hyposensitization in pollen asthma and rhinitis in children. Clin Allergy 84; 14 (6): 541-50. **Therapy NOT AVAILABLE in the U.S**
Corbetta, L., Pesiri, P., Ferro, G., and Mander, A. Improvement of fog and exercise-induced bronchoconstriction after local and subcutaneous immunotherapy in mite asthma. Allergol Immunopathol (Madr) 92; 20 (2): 61-6. **It does not meet ALL the inclusion criteria**
Corrigan, C. Sublingual immunotherapy. J Allergy Clin Immunol 2007; 119 (2): 515; author reply 515-7. **No original data**
Cousergue, J. L. Results of allergenic desensitization in asthmatics in Morocco. Study of 200 cases. Maroc Med 70; 537 437-42. **Other reason for exclusion (specify):I observational data - Non-English article**
Cox, L. Accelerated immunotherapy schedules: review of efficacy and safety. Ann Allergy Asthma Immunol 2006; 97 (2): 126-37; quiz 137-40, 202. **No original data**
Cox, L. Allergen immunotherapy. Ann Allergy Asthma Immunol 2003; 91 (1): 96-7; author reply 97-8. **No original data**
Cox, L. S., Larenas Linnemann, D., Nolte, H., Weldon, D., Finegold, I., and Nelson, H. S. Sublingual immunotherapy: a comprehensive review. J Allergy Clin Immunol 2006; 117 (5): 1021-35. **No original data**
Cox, L., Larenas-Linnemann, D., Lockey, R. F., and Passalacqua, G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010; 125 (3): 569-74, 574.e1-574.e7. **No original data**
Craig, T. J., Moeckli, J. K., and Donnelly, A. Noncompliance with immunotherapy secondary to adverse effects. Ann Allergy Asthma Immunol 95; 75 (3): 290. **Other reason for exclusion (specify): letter**
Creticos, P. S. Immunotherapy with allergens. JAMA 92; 268 (20): 2834-9. **No original data**
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Creticos, P. S., Chen, Y. H., and Schroeder, J. T. New approaches in immunotherapy: allergen vaccination with immunostimulatory DNA. Immunol Allergy Clin North Am 2004; 24 (4): 569-81, v. **No original data**
Creticos, P. S., Marsh, D. G., Proud, D., Kagey-Sobotka, A., Adkinson, N. F. Jr, Friedhoff, L., Naclerio, R. M., Lichtenstein, L. M., and Norman, P. S. Responses to ragweed-pollen nasal challenge before and after immunotherapy. J Allergy Clin Immunol 89; 84 (2): 197-205. **It does not meet ALL the inclusion criteria**
Criado Molina, A., Guerra Pasadas, F., Daza Munoz, J. C., Moreno Aguilar, C., Almeda Llamas, E., Munoz Gomariz, E., Font Ugalde, P., Alonso Diaz, C., German Cardenas, M., and Sanchez Guijo, P. Immunotherapy with an oral Alternaria extract in childhood asthma. Clinical safety and efficacy and effects on in vivo and in vitro parameters. Allergol Immunopathol (Madr) 2002; 30 (6): 319-30. **It does not meet ALL the inclusion criteria**d
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Crimi, E., Voltolini, S., Troise, C., Gianiorio, P., Crimi, P., Brusasco, V., and Negrini, A. C. Local immunotherapy with Dermatophagoides extract in asthma. J Allergy Clin Immunol 91; 87 (3): 721-8. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**local inhalation IT
Cross-reactivity between deciduous trees during immunotherapy. I. In vivo results **Excluded at data abstraction**
Cserhati, E. and Mezei, G. Nasal immunotherapy in pollen-sensitive children. Allergy 97; 52 (33 Suppl): 40-4. **Therapy NOT AVAILABLE in the U.S**
Cvitanovic, S. Allergy to Parietaria officinalis pollen. Croat Med J 99; 40 (1): 42-8. **It does not meet ALL the inclusion criteria**

Cvitanovic, S., Zekan, L., Capkun, V., and Marusic, M. Specific hyposensitization in patients allergic to Parietaria officinalis pollen allergen. J Investig Allergol Clin Immunol 94; 4 (6): 283-90. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**allergoid product

Czarnecka-Operacz, M., Jenerowicz, D., and Silny, W. Oral allergy syndrome in patients with airborne pollen allergy treated with specific immunotherapy. Acta Dermatovenerol Croat 2008; 16 (1): 19-24. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):**OAS: food allergy

D AG, Lobefalo G, Liccardi G, and Cazzola M A double-blind, placebo-controlled trial of local nasal immunotherapy in allergic rhinitis to Parietaura pollen.. Clinical and Experimental Allergy ; **Other reason for exclusion (specify):**LNIT

D. Price Asthma and allergic rhinitis: Linked in treatment and outcomes. Annals of Thoracic Medicine 2010 5 (2): 63-64. **No original data**

D. Srivastava, S. N. Gaur, N. Arora and B. P. Singh Clinico-immunological changes post-immunotherapy with Periplaneta americana. European Journal of Clinical Investigation 2011 41 (8): 879-888. **Not an RCT**

D. Vita, L. Caminiti, P. Ruggeri and G. B. Pajno Sublingual immunotherapy: Adherence based on timing and monitoring control visits. Allergy: European Journal of Allergy and Clinical Immunology 2010 65 (5): 668-669. **No original dataOther reason for exclusion (specify): review**

Dal Bo, S. On repository therapy of grass hay fever: a seven years' experience. Acta Allergol 68; 23 (3): 252-64. **Therapy NOT AVAILABLE in the U.S**

DALBO, S. EXPERIENCE WITH REPOSITORY THERAPY OF POLLINOSIS IN NORTHERN ITALY. Ann Allergy 64; 22 670-7. **Therapy NOT AVAILABLE in the U.S**

Dam Petersen, K., Gyrd-Hansen, D., Kjaergaard, S., and Dahl, R. Clinical and patient based evaluation of immunotherapy for grass pollen and mite allergy. Allergol Immunopathol (Madr) 2005; 33 (5): 264-9. **Other reason for exclusion (specify):**retrospective

Damanik, M. P., Wahab, A. S., Suminta, Ediyono, and Ismangoen The influence of desensitization on the recovery of allergy, in particular asthma. Paediatr Indones 84; 24 (9-10): 203-10. **It does not meet ALL the inclusion criteria**

Dantzler, B. S., Tipton, W. R., Nelson, H. S., and O'Barr, T. P. Tissue threshold changes during the first months of immunotherapy. Ann Allergy 80; 45 (4): 213-6. **It does not meet ALL the inclusion criteria**

Davis, W. E., Cook, P. R., McKinsey, J. P., and Templer, J. W. Anaphylaxis in immunotherapy. Otolaryngol Head Neck Surg 92; 107 (1): 78-83. **It does not meet ALL the inclusion criteria**

De Amici, M., Puggioni, F., Casali, L., and Alesina, R. Variations in serum levels of interleukin (IL)-1beta, IL-2, IL-6, and tumor necrosis factor-alpha during specific immunotherapy. Ann Allergy Asthma Immunol 2001; 86 (3): 311-3. **It does not meet ALL the inclusion criteria**d

de Bot, C. M., Moed, H., Berger, M. Y., Roder, E., de Groot, H., de Jongste, J. C., van Wijk, R. G., and van der Wouden, J. C. Randomized double-blind placebo-controlled trial of sublingual immunotherapy in children with house dust mite allergy in primary care: study design and recruitment. BMC Fam Pract 2008; 9 59. **It does not meet ALL the inclusion criteria**

de Bot, C., Moed, H., and van der Wouden, J. C. Sublingual immunotherapy in children. Re: Marcucci et al. Pediatr Allergy Immunol 2006; 17 (4): 315; author reply 316-7. **No original data**

de la Cuesta, C. G., Garcia, B. E., Sanz, M. L., Feliu, X., and Oehling, A. The value of total IgE determination in mite allergy. Allergol Immunopathol (Madr) 89; 17 (5): 233-5. **It does not meet ALL the inclusion criteria**

DeCastro, F. J. Delayed reaction to aqueous hyposensitization material. JAMA 70; 212 (6): 1069. **Other reason for exclusion (specify):**Harms

Degara, P. F. Clinical study of allergy therapy with alum-precipitated pyridine suspensions. Special usefulness for highly sensitive patients. N Y State J Med 65; 65 (21): 2682-4. **Therapy NOT AVAILABLE in the U.S**

Dehlink, E., Eiwegger, T., Gerstmayr, M., Kampl, E., Bohle, B., Chen, K. W., Vrtala, S., Urbanek, R., and Szepfalusi, Z. Absence of systemic immunologic changes during dose build-up phase and early maintenance period in effective specific sublingual immunotherapy in children. Clin Exp Allergy 2006; 36 (1): 32-9. **It does not meet ALL the inclusion criteria**

Deitmer, T. Hyposensitization in allergic rhinoconjunctivitis. HNO 99; 47 (7): 601. **It does not meet ALL the inclusion criteria**

Del Prete, A., Chiosi, E., Magli, A., Calandriello, M., Bernardo, B., and Bracale, G. Surgical treatment and desensitization therapy of giant papillary allergic conjunctivitis. Ophthalmic Surg 92; 23 (11): 776-9. **It does not meet ALL the inclusion criteria**

Del Prete, A., Loffredo, C., Carderopoli, A., Caparello, O., Verde, R., and Sebastiani, A. Local specific immunotherapy in allergic conjunctivitis. Acta Ophthalmol (Copenh) 94; 72 (5): 631-4. **It does not meet ALL the inclusion criteria**

Delaunois, L., Salamon, E., and Prignot, J. Influence of hyposensitization with Dermatophagoides pteronyssinus extract on clinical score, total and specific IgE levels, and skin test in asthmatic patients. Ann Allergy 85; 55 (2): 150-2. **It does not meet ALL the inclusion criteria**

Della Casa, R. and Di Scianni, N. Bronchial asthma in childhood with special reference to vaccine therapy. Minerva Pediatr 69; 21 (34): 1598-603. **It does not meet ALL the inclusion criteria**

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Delthil, P. and Cany, J. A new trend in the treatment of juvenile asthma: combined crenotherapy, climatotherapy and desensitization. Pediatrie 66; 21 (2): 245-50. **No original data**

Dermatophagoides pteronyssinus cluster immunotherapy. A controlled trial of safety and clinical efficacy **Excluded at data abstraction**

Des Roches, A., Paradis, L., and Paradis, J. Immunotherapy for asthma. N Engl J Med 97; 336 (26): 1912. **No original data**

Des Roches, A., Paradis, L., Knani, J., Hejjaoui, A., Dhivert, H., Chanez, P., and Bousquet, J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation. Allergy 96; 51 (6): 430-3.

Des Roches, A., Paradis, L., Menardo, J. L., Bouges, S., Daures, J. P., and Bousquet, J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 97; 99 (4): 450-3. **It does not meet ALL the inclusion criteria**

Descriptive study of tolerance of two different high dose modified allergen extracts **Meeting abstract**

Desensitization for those afflicted with hay fever. With 4 pricks hyposensitized to pollen. MMW Fortschr Med 2004; 146 (11): 58. **No original data**

Detection of human auto-anti-idiotypic antibodies (Ab2). I. Isolation and characterization of Ab2 in the serum of a ragweed immunotherapy-treated patient **Library unable to locate**

Devey, M. E., Wilson, D. V., and Wheeler, A. W. The IgG subclasses of antibodies to grass pollen allergens produced in hay fever patients during hyposensitization. Clin Allergy 76; 6 (3): 227-36. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**modified allergen

Di Bernardino, C., Di Bernardino, F., Colombo, R., and Angrisano, A. A case control study of dermatophagoides immunotherapy in children below 5 years of age. Allerg Immunol (Paris) 2002; 34 (2): 56-9. **Therapy NOT AVAILABLE in the U.S**

Di Bona, D., Plaia, A., Scafidi, V., Leto-Barone, M. S., and Di Lorenzo, G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. J Allergy Clin Immunol 2010; 126 (3): 558-66. **No original data**

Di Lorenzo, G., Mansueto, P., Pacor, M. L., Rizzo, M., Castello, F., Martinelli, N., Ditta, V., Lo Bianco, C., Leto-Barone, M. S., D'Alcamo, A., Di Fede, G., Rini, G. B., and Ditto, A. M. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. J Allergy Clin Immunol 2009; 123 (5): 1103-10, 1110.e1-4. **It does not meet ALL the inclusion criteria**

Di Rienzo, V., Marcucci, F., Puccinelli, P., Parmiani, S., Frati, F., Sensi, L., Canonica, G. W., and Passalacqua, G. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy 2003; 33 (2): 206-10. **It does not meet ALL the inclusion criteria**

Di Rienzo, V., Pagani, A., Parmiani, S., Passalacqua, G., and Canonica, G. W. Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients. Allergy 99; 54 (10): 1110-3. **Other reason for exclusion (specify):**surveillance**Not an RCT**

Di Rienzo, V., Puccinelli, P., Frati, F., and Parmiani, S. Grass pollen specific sublingual/swallow immunotherapy in children: open-controlled comparison among different treatment protocols. Allergol Immunopathol (Madr) 99; 27 (3): 145-51. **It does not meet ALL the inclusion criteria**

Di Stanislao, C., Angelini, F., Gagliardi, M. C., Di Bernardino, L., Fundaro', C., Galli, E., and Rossi, P. Beta glucuronidase short-term immunotherapy. Allergy 2003; 58 (5): 459. **Therapy NOT AVAILABLE in the U.S**

Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology **Abstract only**

Diamond, M. T. and Joffe, B. Reaction at old vaccination site. JAMA 65; 194 (12): 1325-6. **No SIT**

Dieges, P. H. A method for demonstration of blocking antibodies in desensitized hay fever patients. Acta Allergol 72; 27 (3): 179-85. **Does not apply to any of the key questions**

Dieges, P. H. A prospective study on some immunological changes occurring in the first year of grass pollen desensitization. Acta Allergol 76; 31 (2): 130-40. **It does not meet ALL the inclusion criteria**dose not specified

Dieges, P. H. Clinical evaluation of desensitization therapy in hay fever. Acta Otorhinolaryngol Belg 79; 33 (4): 522-7. **No original data**

Dieguez, I., Sanz, M. L., and Oehling, A. Influence of immunotherapy on histamine release and other immunological parameters of immediate hypersensitivity in pollinosis. J Investig Allergol Clin Immunol 93; 3 (2): 64-71. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**

Dinakar, C., Van Osdol, T. J., Barnes, C. S., Dowling, P. J., and Zeigler, A. W. Changes in exhaled nitric oxide levels with immunotherapy. Allergy Asthma Proc 2006; 27 (2): 140-4. **Does not apply to any of the key questions**

Dominguez, M. A., Sanz, M. L., Lobera, T., and Oehling, A. T helper and T suppressor subpopulations in pollinosis. Effect of specific immunotherapy. Allergol Immunopathol (Madr) 83; 11 (6): 415-20. **It does not meet ALL the inclusion criteria**

Donahue, J. G., Greineder, D. K., Connor-Lacke, L., Canning, C. F., and Platt, R. Utilization and cost of immunotherapy for allergic asthma and rhinitis. Ann Allergy Asthma Immunol 99; 82 (4): 339-47. **Does not apply to any of the key questions**

Donovan, J. P., Buckeridge, D. L., Briscoe, M. P., Clark, R. H., and Day, J. H. Efficacy of

immunotherapy to ragweed antigen tested by controlled antigen exposure. Ann Allergy Asthma Immunol 96; 77 (1): 74-80. **It does not meet ALL the inclusion criteria**

Dorward, A. J., Waclawski, E., and Kerr, J. W. A comparison of the clinical and immunological effects of an alum-precipitated five-grass extract with a conjugated two-grass extract in the desensitization of hay fever. Clin Allergy 84; 14 (6): 561-70. **Therapy NOT AVAILABLE in the U.S**

Double blind placebo controlled study of specific immunotherapy (ITS) with alginate conjugated mite alpha fraction in perennial allergic rhinitis **Library unable to locate**

Double blind trial of hyposensitization to Dermatophagoides farinae and D. pteronyssinus in asthmatic children. **Library unable to locate**

Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis **Duplicate** of 2999

Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization **Duplicate** of 5875

Drachenberg KJ, Pfeiffer P, and Urban E Sublingual immunotherapy - Results from a multi-centre, randomised, double-blind, placebo-controlled study with a standardised birch and grass/rye pollen extract.. Allergologie ; german **Non-English article**

Drazhnevskaia, L. D. Specific hyposensitization of the atopic form of bronchial asthma. Vrach Delo 74; (6): 16-7. **Not an RCT**

Drira, I., Belhabib, S., Trojjet, S., Souissi, R., and Chebbi, M. L. Observance in specific desensitization in allergic asthmatics. Tunis Med 96; 74 (10): 411-3. **It does not meet ALL the inclusion criteria**

Droszcz, W. and Pawlowicz, A. Controlled immunotherapy of bronchial asthma. Pol Tyg Lek 83; 38 (27): 829-30. **Other reason for exclusion (specify):**

Droszcz, W., Lech, B., and Madalinska, M. Results of desensitization with Migen of patients with bronchial asthma caused by hypersensitivity to the mite Dermatophagoides pteronyssinus. Pneumonol Pol 78; 46 (8): 613-5. **Other reason for exclusion (specify):Not an RCT**

Droszcz, W., Wronska, J., Lech, B., and Madalinska, M. 3-year experience with desensitization of paptients with pollenosis using grass pollen extract of depot type. Pol Arch Med Wewn 77; 58 (4): 334-8. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**

Drouet, M., Sabbah, A., Bonneau, J. C., and Le Sellin, J. Renal complications due to desensitization. Allerg Immunol (Paris) 86; 18 (4): 17-9. **Not an RCT**

Dubois, O. and Derambure, S. Treatment of bronchial asthma in children by emulsified allergens. Pediatrie 66; 21 (2): 219-32. **Therapy NOT AVAILABLE in the U.S**

Duce Gracia, F. and Fraj Lazaro, J. Desensitizing treatment in bronchial asthma. Arch Bronconeumol 96; 32 (8): 414-20. **No original data**

Ducommun, J., Morel, V., Ribi, C., and Hauser, C. Localized cold-induced urticaria associated with specific immunotherapy for tree pollen allergy. Allergy 2008; 63 (6): 789-90. **Other reason for exclusion (specify):**not significant harm reported

Duflo, V. Results of Allerglobulin in asthma or eczema in a group of children. Lyon Med 71; 226 (20): 891-3. **It does not meet ALL the inclusion criteria**

Dunsky, E. H., Goldstein, M. F., Dvorin, D. J., and Belecanech, G. A. Anaphylaxis to sublingual immunotherapy. Allergy 2006; 61 (10): 1235. **Other reason for exclusion (specify):case report**

During nasal challenge test with aqueous phleum pratense, measurements of nasal peakflow and total nasal symptom score are normalised 6 H post challenge **Meeting abstract**

Dursun, A. B., Sin, B. A., Oner, F., and Misirligil, Z. The safety of allergen immunotherapy (IT) in Turkey. J Investig Allergol Clin Immunol 2006; 16 (2): 123-8. **Not an RCT**

Dworetzky, M. Lowell and Franklin on double-blind hyposensitization therapy for ragweed hay fever: the paper. J Allergy Clin Immunol 2004; 113 (6): 1231-3. **No original data**

Early effects of rush immunotherapy with Dermatophagoides pteronyssinus in asthmatics **Excluded at data abstraction**

Ebner, C., Kraft, D., and Ebner, H. Booster immunotherapy (BIT). Allergy 94; 49 (1): 38-42. **It does not meet ALL the inclusion criteria**

Ebner, H., Neuchrist, C., Havelec, L., and Kraft, D. Comparative studies of the effectiveness of specific immunotherapy in house dust mite allergy. Wien Klin Wochenschr 89; 101 (15): 504-11. **Therapy NOT AVAILABLE in the U.S**

Echechipia, S., Tabar, A. I., Lobera, T., Munoz, D., Rodriguez, A., Blasco, A., Olaguibel, J. M., Casanovas, M., and Fernandez de Corres, L. Immunotherapy with a standardized Dermatophagoides pteronyssinus glutaraldehyde-modified extract against an unmodified extract: a comparative study of efficacy, tolerance and in vivo and in vitro modification of parameters. J Investig Allergol Clin Immunol 95; 5 (6): 325-32. **Therapy NOT AVAILABLE in the U.S**

Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma **Excluded at data abstraction**

Economic evaluation of sublingual vs subcutaneous allergen immunotherapy **Excluded at data abstraction**

Effect of allergen specific immunotherapy (IT) on natural killer cell activity (NK), IgE, IFN-gamma levels and clinical response in patients with allergic rhinitis and asthma **Excluded at data abstraction**

Effect of grass pollen immunotherapy on asthma quality of life Abstract **Meeting abstract**

Effect of grass pollen immunotherapy with Alutard SQ on quality of life in seasonal allergic rhinoconjunctivitis **Part of** 1840

Effect of immunotherapy in bronchial asthma: treatment with extracts of house dust and mite **Excluded at data abstraction**

Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: A randomized, placebo-controlled, double-blind, double-dummy study **Duplicate** of 10246

Effect of pretreatment with fexofenadine on the safety of immunotherapy in patients with allergic rhinitis **Excluded at data abstraction**

Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma **Excluded at data abstraction**

Effect of subcutaneous and sublingual immunotherapy on clinical improvement and quality of life in children with rhinitis and asthma monosensitised to house dust mite: a randomised, placebo-controlled, double-blind, double-dummy study **Library unable to locate**

Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite **Part of** 3525

Effectiveness of hyposensitization therapy in ragweed hay-fever in children **Excluded at data abstraction**

Effects of allergen specific immunotherapy on functions of Th and Treg cells in patients with seasonal allergic rhinitis **Meeting abstract**

Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: changes in inflammatory mediators and cells **Part of** 3835

Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients **Duplicate** of 3403

Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen **Excluded at data abstraction**

Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis **Part of** 10070

Efficacy and safety of sublingual immunotherapy in adults with allergic rhinoconjunctivitis: results after 2 years of a controlled trial **Library unable to locate**

Efficacy and tolerability of high dose sublingual immunotherapy in patients with rhinoconjunctivitis **Duplicate**

Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study **Duplicate**

Efficacy of grass-maize pollen oral immunotherapy in patients with seasonal hay-fever: a double-blind study **Oral IT**

Efficacy of specific desensitization with mites standartization extract in asthma **Library unable to locate**

Efficacy of sublingual specific immunotherapy drops in patients with respiratory allergy to Alternaria alternata: A randomised, Assessor-blinded, Patientreported outcome, Controlled 3-year trial **Duplicate** of 10483

Egeskjold, E. M., Permin, H., Nielsen, I., Sorensen, H. J., Osterballe, O., and Kallerup, H. E. Anti-IgG antibodies and antinuclear antibodies in allergic patients. Allergy 81; 36 (8): 573-81. **It does not meet ALL the inclusion criteria**

Eifan, A. O., Keles, S., Bahceciler, N. N., and Barlan, I. B. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. Allergy 2007; 62 (5): 567-8. **Not an RCT**

Einecke, D. Minor rhinitis. Consequent therapy protects against asthma. MMW Fortschr Med 2002; 144 (13): 14. **No original data**

Einecke, U. From wheezing to anaphylactic shock: allergology for your practice. MMW Fortschr Med 2008; 150 (13): 12-4, 16. **No original data**

El Jundi, O., Karakaya, G., and Fuat Kalyoncu, A. Sarcoidosis following specific immunotherapy: more than just coincidence?. Allergol Immunopathol (Madr) 2007; 35 (1): 32-4. **Other reason for exclusion (specify):**harms**Not an RCT**

el-Hefny, A. Hyposensitization therapy in asthmatic children. J Egypt Med Assoc 66; 49 (11): 728-35. **Not an RCT**

el-Hefny, A. Hyposensitization therapy in asthmatic children. J Egypt Med Assoc 66; 49 (11): 728-35. **Not an RCT**

El-Mehairy, M. M. and el-Tarabishi, M. M. House dust sensitivity in respiratory allergy and the effect of its treatment by desensitization. Allerg Asthma (Leipz) 67; 13 (1): 19-25. **It does not meet ALL the inclusion criteria**

Eng, P. A., Borer-Reinhold, M., Heijnen, I. A., and Gnehm, H. P. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006; 61 (2): 198-201. **Therapy NOT AVAILABLE in the U.S**

Eng, P. A., Reinhold, M., and Gnehm, H. P. Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy 2002; 57 (4): 306-12. **Therapy NOT AVAILABLE in the U.S**

Eng, P. A., Reinhold, M., and Gnehm, H. P. Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy 2002; 57 (4): 306-12. **Therapy NOT AVAILABLE in the U.S**

Engel, P., Malet, A., Sanosa, J., Fajas, L., and Garcia-Calderon, P. A. The histamine liberation test as a diagnostic parameter and its possible modification following specific immunotherapy. Allergol Immunopathol (Madr) 85; 13 (2): 93-100. **It does not meet ALL the inclusion criteria**

Enzyme potentiated hyposensitization: IV. effect of protamine on the immunological behavior of beta glucuronidase in mice and patients with hay fever **Kirwan/Cochrane 2009**

Eriksson, N. E. Allergy diagnosis and specific therapy in asthma--when, where and how?. Eur J Respir Dis Suppl 84; 136 139-59. **No original data**

Eriksson, N. E., Ahlstedt, S., and Lovhagen, O. Immunotherapy in spring-time hay fever. A clinical and immunological study comparing two different

treatment extract compositions. Allergy 79; 34 (4): 233-47. **Therapy NOT AVAILABLE in the U.S**
Eriksson, N. E., Ahlstedt, S., and Lovhagen, O. Immunotherapy in spring-time hay fever. A clinical and immunological study comparing two different treatment extract compositions. Allergy 79; 34 (4): 233-47. **It does not meet ALL the inclusion criteria**
Esch, R. E., Bush, R. K., Peden, D., and Lockey, R. F. Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results. Ann Allergy Asthma Immunol 2008; 100 (5): 475-81. **It does not meet ALL the inclusion criteria**
Eusebius, N. P., Papalia, L., Suphioglu, C., McLellan, S. C., Varney, M., Rolland, J. M., and O'Hehir, R. E. Oligoclonal analysis of the atopic T cell response to the group 1 allergen of Cynodon dactylon (bermuda grass) pollen: pre- and post-allergen-specific immunotherapy. Int Arch Allergy Immunol 2002; 127 (3): 234-44. **It does not meet ALL the inclusion criteria**
Evans, R., Pence, H., Kaplan, H., and Rocklin, R. E. The effect of immunotherapy on humoral and cellular responses in ragweed hayfever. J Clin Invest 76; 57 (5): 1378-85. **Does not apply to any of the key questions Not an RCT**
Evans, R., Pence, H., Kaplan, H., and Rocklin, R. E. The effect of immunotherapy on humoral and cellular responses in ragweed hayfever. J Clin Invest 76; 57 (5): 1378-85. **Does not apply to any of the key questions Not an RCT**
Ewan, P. W. Anaphylactic reaction to desensitisation. Br Med J 80; 281 (6247): 1069. **No original data**
Ewan, P. W. Anaphylactic reaction to desensitisation. Br Med J 80; 281 (6247): 1069. **No original data**
F. Angelini, V. Pacciani, S. Corrente, R. Silenzi, A. Di Pede, A. Polito, C. Riccardi, S. Di Cesare, M. L. Yammine, P. Rossi, V. Moschese and L. Chini Dendritic cells modifi cation during sublingual immunotherapy in children with allergic symptoms to house dust mites. World Journal of Pediatrics 2011 7 (1): 24-30. **Not an RCT**
F. C. Lowell and W. Franklin A double-blind study of the effectiveness and specificity of injecton therapy in ragweed hay fever. N Engl J Med 1965 273 (13): 675-9. **It does not meet ALL the inclusion criteria**no dose
Fadal, R. G. and Nalebuff, D. J. A study of optimum dose immunotherapy in pharmacological treatment failures. Arch Otolaryngol 80; 106 (1): 38-43. **It does not meet ALL the inclusion criteria no comparison**
Fadel, R. Report of the Stallergenes symposium. Eur Ann Allergy Clin Immunol 2004; 36 (3): 104. **It does not meet ALL the inclusion criteria**
Fagerberg, E., Nilzen, A., and Wiholm, S. Studies in hyposensitisation with Allpyral. Objective evaluation of the results. Acta Allergol 72; 27 (1): 1-14. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**Allpyral
Failure hyposensitisation in treatment of children with grass-pollen asthma. Br Med J (Clin Res Ed) 82; 284 (6326): 1402-3. **No original data**
Fargetton, B., Blandin, G., and Latil, F. Hypo-sensitization by oral administration of aqueous pollen extracts. Allerg Immunol (Paris) 87; 19 (4): 165-6. **It does not meet ALL the inclusion criteria**
Farid, R., Ghasemi, R., Baradaran-Rahimi, M., Jabbari, F., Ghaffari, J., and Rafatpanah, H. Evaluation of six years allergen immunotherapy in allergic rhinitis and allergic asthma. Iran J Allergy Asthma Immunol 2006; 5 (1): 29-31. **It does not meet ALL the inclusion criteria no comparator drug**
Farrerons-Co, F. J., Echevarne, F., and Velasco, M. F. The role of cyclic amp in the process of specific hyposensitization. Ann Allergy 80; 45 (3): 180-4. **It does not meet ALL the inclusion criteria**,d**Not an RCT**
Feliziani, V., Marfisi, R. M., and Parmiani, S. Rush immunotherapy with sublingual administration of grass allergen extract. Allergol Immunopathol (Madr) 93; 21 (5): 173-8. **It does not meet ALL the inclusion criteria**
Fell, P. and Brostoff, J. A single dose desensitization for summer hay fever. Results of a double blind study-1988. Eur J Clin Pharmacol 90; 38 (1): 77-9. **Therapy NOT AVAILABLE in the U.S**
Fell, P. and Brostoff, J. A single dose desensitization for summer hay fever. Results of a double blind study-1988. Eur J Clin Pharmacol 90; 38 (1): 77-9. **Therapy NOT AVAILABLE in the U.S**
Feng, H., Xiang, L., and Shen, K. L. Dynamical changes of lung function and immunologic markers in asthmatic children receiving specific immunotherapy with standardized house dust mite extract.. Zhongguo Dang Dai Er Ke Za Zhi 2010; 12 (9): 715-9. **Not an RCT**
Fennerty, A. G., Jones, K. P., Davies, B. H., Fifield, R., and Edwards, J. Immunological changes associated with a successful outcome of pollen immunotherapy. Allergy 88; 43 (6): 415-9. **Not an RCT**
Fenton, M. M. Critical evaluation of optimal dosage in pollen therapy in children. J Asthma Res 66; 4 (1): 53-6. **It does not meet ALL the inclusion criteria**
Fernandez de Corres, L. and Oehling, A. Specific hyposensitization using inhalation antigens. Allerg Immunol (Leipz) 71; 17 (2): 111-6. **It does not meet ALL the inclusion criteria**
Fernandez-Tavora, L., Rico, P., and Martin, S. Clinical experience with specific immunotherapy to horse dander. J Investig Allergol Clin Immunol 2002; 12 (1): 29-33. **It does not meet ALL the inclusion criteria**
Ferreira, M. B., Santos, A. S., Santos, M. C., Carlos, M. L., Barbosa, M. A., and Carlos, A. G. Nasal ECP patterns and specific immunotherapy in mite-allergic rhinitis patients. Eur Ann Allergy Clin Immunol 2005; 37 (3): 96-102. **It does not meet ALL the inclusion criteria**modified extract**Therapy NOT AVAILABLE in the U.S**
Ferreira, M. B., Santos, M. C., Pregal, A. L., Alonso, E., Santos, A. S., Palma-Carlos, M. L., and Palma-Carlos, A. G. Effect of specific immunotherapy versus loratadine on serum adhesion molecules. Allerg

Immunol (Paris) 2001; 33 (8): 319-22. **It does not meet ALL the inclusion criteria**iomarker study w/out cx**Not an RCT**

Ferreira, N. and Trindade, J. C. Specific immunotherapy 3 years follow-up in asthmatic children. Allergol Immunopathol (Madr) 93; 21 (5): 185-92. **It does not meet ALL the inclusion criteria**

Ferrer, A. and Garcia-Selles, J. Significant improvement in symptoms, skin test, and specific bronchial reactivity after 6 months of treatment with a depigmented, polymerized extract of Dermatophagoides pteronyssinus and D. farinae. J Investig Allergol Clin Immunol 2003; 13 (4): 244-51. **It does not meet ALL the inclusion criteria**modified allergen**Therapy NOT AVAILABLE in the U.S**

Ferrer, A. and Garcia-Selles, J. SIT with a depigmented, polymerized mite extract. Allergy 2002; 57 (8): 754-5. **It does not meet ALL the inclusion criteria**modified allergen**Therapy NOT AVAILABLE in the U.S**

Ferres, J., Justicia, J. L., Garcia, M. P., Munoz-Tuduri, M., and Alva, V. Efficacy of high-dose sublingual immunotherapy in children allergic to house dust mites in real-life clinical practice. Allergol Immunopathol (Madr) 2010; **It does not meet ALL the inclusion criteria**

Filiaci, F., Di Filippo, S., Lucarelli, N., and Zambetti, G. Specific local immunotherapy in the treatment of hay fever. Rhinology 84; 22 (4): 261-8. **It does not meet ALL the inclusion criteria**

Filiaci, F., Zambetti, G., Romeo, R., Ciofalo, A., Luce, M., and Germano, F. Non-specific hyperreactivity before and after nasal specific immunotherapy. Allergol Immunopathol (Madr) 99; 27 (1): 24-8. **No SIT**

Filiaci, F., Zambetti, G., Romeo, R., Ciofalo, A., Luce, M., and Germano, F. Non-specific hyperreactivity before and after nasal specific immunotherapy. Allergol Immunopathol (Madr) 99; 27 (1): 24-8. **It does not meet ALL the inclusion criteria**no comparator

Fiocchi, A., Pajno, G., La Grutta, S., Pezzuto, F., Incorvaia, C., Sensi, L., Marcucci, F., and Frati, F. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. Ann Allergy Asthma Immunol 2005; 95 (3): 254-8. **It does not meet ALL the inclusion criteria**

Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children **Part of** 2555

Foucard, T. and Johansson, S. G. Allergen-specific IgE and IgG antibodies in pollenallergic children given immunotherapy for 2-6 years. Clin Allergy 78; 8 (3): 249-57. **Other reason for exclusion (specify):**allpyral

Foucard, T. and Johansson, S. G. Immunological studies in vitro and in vivo of children with pollenosis given immunotherapy with an aqueous and a glutaraldehyde-treated tyrosine-absorbed grass pollen extract. Clin Allergy 76; 6 (5): 429-39. **It does not meet ALL the inclusion criteria**

Francis, J. N., Lloyd, C. M., Sabroe, I., Durham, S. R., and Till, S. J. T lymphocytes expressing CCR3 are increased in allergic rhinitis compared with non-allergic controls and following allergen immunotherapy. Allergy 2007; 62 (1): 59-65. **It does not meet ALL the inclusion criteria**

Francis, J. N., Till, S. J., and Durham, S. R. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. J Allergy Clin Immunol 2003; 111 (6): 1255-61. **It does not meet ALL the inclusion criteria**

Franco, C., Barbadori, S., Freshwater, L. L., and Kordash, T. R. A double-blind, placebo controlled study of Alpare mite D. pteronyssinus immunotherapy in asthmatic patients. Allergol Immunopathol (Madr) 95; 23 (2): 58-66. **It does not meet ALL the inclusion criteria**

Frank, A. Perennial coseasonal hyposensitisation (author's transl). Wien Med Wochenschr 80; 130 (8): 270-4. **It does not meet ALL the inclusion criteria**

Frank, M. O. Skin testing and immunotherapy in children. J Allergy Clin Immunol 95; 96 (1): 138. **No original data**

Frank, M. O. Skin testing and immunotherapy in children. J Allergy Clin Immunol 95; 96 (1): 138. **No original data**

Frankland, A. W. Preseasonal injection treatment in hay fever using aqueous extracts. Int Arch Allergy Appl Immunol 65; 28 (1): 1-11. **It does not meet ALL the inclusion criteria**

Freedman, S. S. and Boyd, G. K. Pollen hyposensitization: interval between maintenance injections. J Asthma Res 67; 5 (2): 133-8. **It does not meet ALL the inclusion criteria**

Freedman, S. S. and Pelletier, G. A. Asthma in childhood: treatment of 1070 cases. Ann Allergy 70; 28 (4): 133-41. **Does not apply to any of the key questions**

Frew A, Dubuske L, Amersdorffer J, and and Holdich T Significant benefits of combined symptom and medication scores for ultra short course subcutaneous immunotherapy compared with placebo in patients with grass pollen allergic rhinoconjunctivitis. Allergy ; **Other reason for exclusion (specify):**poster

Frostad, A. B. Immunotherapy with major allergens of timothy grass pollen. Allergy 81; 36 (5): 345-7. **No original data**

Frostad, A. B., Grimmer, O., Sandvik, L., and Aas, K. Hyposensitization. Comparing a purified (refined) allergen preparation and a crude aqueous extract from timothy pollen. Allergy 80; 35 (2): 81-95. **It does not meet ALL the inclusion criteria**

Frostad, A. B., Grimmer, O., Sandvik, L., and Aas, K. Hyposensitization. Comparing a purified (refined) allergen preparation and a crude aqueous extract from timothy pollen. Allergy 80; 35 (2): 81-95. **obs case series**

Fu, C. L., Ye, Y. L., Lee, Y. L., and Chiang, B. L. Both allergen-specific CD4 and CD8 Type 2 T cells decreased in asthmatic children with immunotherapy.

Pediatr Allergy Immunol 2003; 14 (4): 284-91. **It does not meet ALL the inclusion criteria**
Fuchs, E. Allergic bronchial asthma; diagnosis and desensitization (author's transl). Prax Pneumol 74; 28 (2): 78-84. **No original data**
Fuchs, E. Specific desensitization with inhalation antigens. Dtsch Med Wochenschr 66; 91 (19): 904-6. **No original data**
Fujimura, T., Yonekura, S., Taniguchi, Y., Horiguchi, S., Saito, A., Yasueda, H., Nakayama, T., Takemori, T., Taniguchi, M., Sakaguchi, M., and Okamoto, Y. The Induced Regulatory T Cell Level, Defined as the Proportion of IL-10Foxp3(+) Cells among CD25(+)CD4(+) Leukocytes, Is a Potential Therapeutic Biomarker for Sublingual Immunotherapy: A Preliminary Report. Int Arch Allergy Immunol 2010; 153 (4): 378-387. **Does not apply to any of the key questions**
Fujimura, T., Yonekura, S., Taniguchi, Y., Horiguchi, S., Saito, A., Yasueda, H., Nakayama, T., Takemori, T., Taniguchi, M., Sakaguchi, M., and Okamoto, Y. The Induced Regulatory T Cell Level, Defined as the Proportion of IL-10Foxp3(+) Cells among CD25(+)CD4(+) Leukocytes, Is a Potential Therapeutic Biomarker for Sublingual Immunotherapy: A Preliminary Report. Int Arch Allergy Immunol 2010; 153 (4): 378-387. **It does not meet ALL the inclusion criteria**
Furin, M. J., Norman, P. S., Creticos, P. S., Proud, D., Kagey-Sobotka, A., Lichtenstein, L. M., and Naclerio, R. M. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. J Allergy Clin Immunol 91; 88 (1): 27-32. **It does not meet ALL the inclusion criteria**
Furin, M. J., Norman, P. S., Creticos, P. S., Proud, D., Kagey-Sobotka, A., Lichtenstein, L. M., and Naclerio, R. M. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. J Allergy Clin Immunol 91; 88 (1): 27-32. **It does not meet ALL the inclusion criteria**
Furin, M. J., Norman, P. S., Creticos, P. S., Proud, D., Kagey-Sobotka, A., Lichtenstein, L. M., and Naclerio, R. M. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. J Allergy Clin Immunol 91; 88 (1): 27-32. **Not an RCT**
G. Blumberga, L. Groes and R. Dahl SQ-standardized house dust mite immunotherapy as an immunomodulatory treatment in patients with asthma. 2011 (2): 178-85. **Does not apply to any of the key questions**
G. Ciprandi, F. Morandi, R. Olcese, M. Silvestri and M. A. Tosca Subcutaneous and sublingual immunotherapy and T regulatory cells: There is clinical relevance. Clinical and Experimental Allergy 2010 40 (10): 1578-1579. **No original dataOther reason for exclusion (specify):**correspondence**Not an RCT**
G. Senti, S. Von Moos, F. Tay, N. Graf, T. Sonderegger, P. Johansen and T. M. Kundig Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: A double-blind, placebo-controlled dose escalation study. Journal of Allergy and Clinical Immunology 2012 129 (1): 128-135. **Therapy NOT AVAILABLE in the U.S**
G. Xu and H. B. Li Evaluation of therapeutic effect of allergen specific immunological treatment. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011 46 (1): 19-20. **No original data**
Gadermaier, E., Flicker, S., Aberer, W., Egger, C., Reider, N., Focke, M., Vrtala, S., Kundi, M., and Valenta, R. Analysis of the antibody responses induced by subcutaneous injection immunotherapy with birch and Fagales pollen extracts adsorbed onto aluminum hydroxide. Int Arch Allergy Immunol 2010; 151 (1): 17-27. **It does not meet ALL the inclusion criteria**
Gagro, A., Rabatic, S., Trescec, A., Dekaris, D., and Medar-Lasic, M. Expression of lymphocytes Fc epsilon RII/CD23 in allergic children undergoing hyposensitization. Int Arch Allergy Immunol 93; 101 (2): 203-8. **Does not apply to any of the key questions**
Gallesio, M. T. and Furno, F. Specific hyposensitizing therapy. Considerations on its effectiveness and validity. Minerva Med 79; 70 (18): 1299-303. **It does not meet ALL the inclusion criteria**
Galli, E., Chini, L., Nardi, S., Benincori, N., Panei, P., Fraioli, G., Moschese, V., and Rossi, P. Use of a specific oral hyposensitization therapy to Dermatophagoides pteronyssinus in children with atopic dermatitis. Allergol Immunopathol (Madr) 94; 22 (1): 18-22. **Does not apply to any of the key questions**
Gamboa, P. M., Castillo, J. G., Wong, E., de la Cuesta, C. G., and Oehling, A. Variations of histamine release in an atopic population. II. Clinical situation according to age and duration of immunotherapy. Allergol Immunopathol (Madr) 89; 17 (6): 279-83. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**
Gamboa, P., Gonzalez, G., Jauregui, I., Jorro, G., Molero, I., Eseverri, J. L., Gonzalez, R., Luna, I., Marcos, C., Miro, J., Pulido, Z., Gracia, T., Iriarte, P., Carreno, A., Navarro, J. A., Rocafort, S., Garcia-Robaina, J. C., Souto, I., Casas, R., Lleonart, R., Nevot, S., Asensio, O., Bosque, M., Blasco, A., and de la Torre, F. A prospective and multicenter safety-monitoring study of a short up-dosing schedule of immunotherapy with a mass-units-standardized extract of mites. Allergol Immunopathol (Madr) 2004; 32 (1): 13-7. **It does not meet ALL the inclusion criteria no comparator group**
Gammeri, E., Arena, A., D'Anneo, R., and La Grutta, S. Safety and tolerability of ultra-rush (20 minutes) sublingual immunotherapy in patients with allergic rhinitis and/or asthma. Allergol Immunopathol (Madr) 2005; 33 (4): 221-3. **Therapy NOT AVAILABLE in the U.S**
Gamzatova, A. A. and Gadzhimirzaev, G. A. The treatment of atopic rhinitis in children with an accelerated variant of specific immunotherapy. Vestn Otorinolaringol 94; (5-6): 33-7. **Not an RCT**

Gamzatova, A. A. and Gadzhimirzaev, G. A. The treatment of atopic rhinitis in children with an accelerated variant of specific immunotherapy. Vestn Otorinolaringol 94; (5-6): 33-7. **Not an RCT**
Gandarias, B., Alonso, M. D., Fernandez Rivas, M., Fernandez-Tavora, L., Miranda, P., Munoz Lejarazu, D., Sotillo, M., Tejero, J., and Rico, P. Retrospective study of tolerance to short initiation schedules in subcutaneous immunotherapy. J Investig Allergol Clin Immunol 2005; 15 (4): 242-8. **It does not meet ALL the inclusion criteria**
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Hejjaoui, A., Dhivert, H., Michel, F. B., and Bousquet, J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. IV. Systemic reactions according to the immunotherapy schedule. J Allergy Clin Immunol 90; 85 (2): 473-9. **obs case series**

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Horak, F., Jager, S., and Turk, R. Assessment of therapeutic success of a specific immunotherapy of grass pollen allergy. Laryngol Rhinol Otol (Stuttg) 83; 62 (9): 416-8. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**

House dust mite specific sublingual immunotherapy in children with asthma and rhinitis; A long term follow-up after cessation of treatment **Meeting abstract**

Hurst, D. S., Gordon, B. R., Fornadley, J. A., and Hunsaker, D. H. Safety of home-based and office allergy immunotherapy: A multicenter prospective study. Otolaryngol Head Neck Surg 99; 121 (5): 553-61. **It does not meet ALL the inclusion criteria**

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Hyposensitization in childhood asthma. Br Med J 68; 2 (5603): 478-9. **No original data**

Hyposensitization in childhood hay fever. A comparison of refined and whole timothy extracts **Excluded at data abstraction**

Hyposensitization with Dermatophagoides pteronyssinus antigen: trial in asthma induced by house dust **Excluded at data abstraction**

Hyposensitization with Dermatophagoides pteronyssinus in house dust allergy: a controlled study of clinical and immunological effects **Excluded at data abstraction**

Hyposensitization with extracts of Dermatophagoides pteronyssinus and house dust **Excluded at data abstraction**

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Immunotherapy as a method of causal treatment of atopic bronchial asthma **Library unable to locate**

Immunotherapy in allergy to dog: a double-blind clinical study **Part of** 5737

Immunotherapy in bronchial asthma sensitive to pollens. Study of its efficacy **Library unable to locate**

Immunotherapy in hay fever with two major allergens 19, 25 and partially purified extract of timothy grass pollen. A controlled double blind study. In vivo variables, season I **Part of** 4181

Immunotherapy is allergen-specific: A double-blind trial of mite or timothy extract in mite and grass dual-allergic patients **Library unable to locate**

Immunotherapy of hay fever with ragweed antigen E: comparisons with whole pollen extract and placebos **Excluded at data abstraction**

Immunotherapy vs inhaled budesonide in bronchial asthma: an open, parallel, comparative trial **Excluded at data abstraction**

Immunotherapy with a fast updosed hypoallergenic SCIT formulation: A retrospective study on tolerability in children and adolescents **Meeting abstract**

Immunotherapy with cat- and dog-dander extracts. IV. Effects of 2 years of treatment **Excluded at abstract level**

Immunotherapy with partially purified and standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma **Duplicate**

Immunotherapy with partially purified ansd standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma **Excluded at data abstraction**

Immunotherapy with sublingual birch pollen extract. A short-term double-blind placebo study **Excluded at data abstraction**

Immunotherapy. CMAJ 2005; 173 (6 Suppl): S46-50. **No original data**

Immunotherapy: new guidelines suggest a 'window' for prevention. Dis Manag Advis 2003; 9 (4): 59-61, 50. **No original data**

Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate **Duplicate**

Imperial College London Randomized double blind placebo controlled trial of grass pollen immunotherapy using a cluster regime completed. ClinicalTrials.gov accessed 31 Jul 2008 ; **Does not apply to any of the key questions No original data**

Imunoterapia com extrato de "Dermatophagoides pteronyssinus" em pacientes asmbticos **Library unable to locate**

Imuunotherapy administered under the tongue to treat dust mite allergy **Library unable to locate**

In 't Veen, J. C., Sterk, P. J., and Bel, E. H. Alternative strategies in the treatment of bronchial asthma. Clin Exp Allergy 2000; 30 (1): 16-33. **No original data**

Inal, A., Altintas, D. U., Yilmaz, M., Karakoc, G. B., Kendirli, S. G., and Sertdemir, Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. J Investig Allergol Clin Immunol 2007; 17 (2): 85-91. **It does not meet ALL the inclusion criteria**

Inci, D., Altintas, D. U., Kendirli, S. G., Yilmaz, M., and Karakoc, G. B. The effect of specific immunotherapy on exhaled breath condensate nitrite levels. Allergy 2006; 61 (7): 899-900. **It does not meet ALL the inclusion criteria**

Increasing long-term safety of seasonal grass pollen sublingual immunotherapy: The ECRIT study **Library unable to locate**

Influence of early specific immunotherapy by house dust mite allergens on development of asthma in children with atopic dermatitis **Library unable to locate**

Initial results of specific desensitization of seasonal allergic rhinitis in the Otolaryngologic Clinic of the I.P. Pavlov Medical Institute in Plovdiv, Bulgaria **Library unable to locate**

Injection of low-dose antigen attenuates the response to subsequent bronchoprovocative challenge **Excluded at data abstraction**

Inmunoterapia alergqnica en asma bronquial **Library unable to locate**

Intraseasonal short-time updosing with SQ-standardised subcutaneous immunotherapy in patients with intermittent allergic rhinitis: a new therapeutic option **Meeting abstract**

Investigation of asthma prevention by specific immunotherapy in children **Library unable to locate**

Investigation of the immunologic basis of clinical improvement by immunotherapy (IT) with grass pollen and dermatophagoides pteronyssinus (Der p) extracts in asthma abstract **Abstract only**

Ishimova, L. M., Sokolova, T. S., and Khutueva, S. K. h. Clinical aspects, specific diagnosis and hyposensitization in pollinosis in children. Pediatriia 70; 49 (4): 27-31. **RussianNon-English article**

Ishizaki, T. and Kawakami, Y. Effect of Broncasma Berna on bronchial asthma. A double blind study. Schweiz Med Wochenschr 73; 103 (12): 455-9. **No SIT**

Isotypic and antigenic restriction of the blocking antibody response to ryegrass pollen: correlation of rye group I antigen-specific IgG1 with clinical response **Part of** 4861

Ito, H., Nishimura, J., Mamiya, S., Suzuki, M., Yokota, A., and Baba, S. A study of the changes in the level of serum IgG4 antibody and soluble CD23 (s-CD23) in nasal allergy patients with immunotherapy. Auris Nasus Larynx 93; 20 (3): 185-96. **Therapy NOT AVAILABLE in the U.S**

Ito, K. Clinical study on hyposensitization therapy of bronchial asthma. Arerugi 68; 17 (3): 164-78. **Other reason for exclusion (specify):chinese**

Ito, K. Clinical study on pollenosis. Nippon Naika Gakkai Zasshi 92; 81 (9): 1502-8. **Therapy NOT AVAILABLE in the U.S**

Ito, K. Clinical study on pollenosis. Nippon Naika Gakkai Zasshi 92; 81 (9): 1502-8. **Therapy NOT AVAILABLE in the U.S**

Ito, Y., Takahashi, Y., Fujita, T., and Fukuyama, S. Clinical effects of immunotherapy on Japanese cedar pollinosis in the season of cedar and cypress pollination. Auris Nasus Larynx 97; 24 (2): 163-70. **It does not meet ALL the inclusion criteria**

Ito, Y., Takahashi, Y., Fujita, T., and Fukuyama, S. Clinical effects of immunotherapy on Japanese cedar pollinosis in the season of cedar and cypress pollination. Auris Nasus Larynx 97; 24 (2): 163-70. **It does not meet ALL the inclusion criteria**

Iusuf-zade, L. I. Effect of specific hyposensitization on the general and antigen-specific IgE content in the atopic form of bronchial asthma in children. Vopr Okhr Materin Det 80; 25 (3): 11-3. **Not an RCT**

Iusuf-zade, L. I. Effect of specific hyposensitization on the general and antigen-specific IgE content in the atopic form of bronchial asthma in children. Vopr Okhr Materin Det 80; 25 (3): 11-3. **Not an RCT**

J. A. Bird and S. Abramson Pediatric asthma and allergy. Journal of Asthma and Allergy Educators 2011 2 (5): 253-254. **It does not meet ALL the inclusion criteria**

J. Bucur, S. Dreborg, R. Einarsson, I. Ljungstedt-Pahlman, J. E. Nilsson and G. Persson Immunotherapy with dog and cat allergen preparations in dog-sensitive and cat-sensitive asthmatics. Ann Allergy 1989 62 (4): 355-61. **Not an RCT**

J. E. Lee, Y. S. Choi, M. S. Kim, D. H. Han, C. S. Rhee, C. H. Lee and D. Y. Kim Efficacy of sublingual immunotherapy with house dust mite extract in polyallergen sensitized patients with allergic rhinitis. 2011 (1): 79-84. **Not an RCT**

J. O. Warner Immunotherapy in asthma. Paediatrics and Child Health 2011 21 (7): 329-330. **Not an RCT**

J. Panasoff Slit vs. Slipt. Pediatric Allergy and Immunology 2011 22 (8): 876. **It does not meet ALL the inclusion criteria**

Jablonski, K. and Tronnier, H. Tinnitus as a side effect of hyposensitization treatment. Case report. Derm Beruf Umwelt 86; 34 (2): 39-41. **It does not meet ALL the inclusion criteria**d**Other reason for exclusion (specify):case report**

Jacobsen, L. Immunotherapy for the prevention of allergic diseases. Clin Allergy Immunol 2004; 18 529-40. **No original data**

Jacquemin, M. G. and Saint-Remy, J. M. Epitope-specific down-regulation of anti-allergen antibodies following injection of allergen-antibody complexes in hypersensitive patients. Int Arch Allergy Immunol 95; 107 (1-3): 313-5. **It does not meet ALL the inclusion criteria**

JAGGI, O. P. and VISWANATHAN, R. EVALUATION OF HYPOSENSITISATION IN CASES OF SEASONAL ASTHMA. J Indian Med Assoc 64; 43 107-11. **It does not meet ALL the inclusion criteria**dose unclear

Jahnz-Rozyk, K., Glodzinska-Wyszogrodzka, E., Rozynska-Polanska, R., Paluchowska, E., and Zabielski, L. S. The effect of specific immunotherapy on serum eotaxin level in patients with pollinosis: preliminary studies. Pol Merkur Lekarski 2001; 11 (63): 244-6. **Other reason for exclusion (specify):**

Jahnz-Rozyk, K., Kuna, P., Pojda, Z., and Pirozynska, E. The effect of specific immunotherapy on the concentration of some chemokines in BALF in patients with atopic bronchial asthma. Pol Merkur Lekarski 96; 1 (4): 223-6. **Other reason for exclusion (specify):**

Jahnz-Rozyk, K., Targowski, T., Glodzinska-Wyszogrodzka, E., and Plusa, T. Cc-chemokine eotaxin as a marker of efficacy of specific immunotherapy in patients with intermittent IgE-mediated allergic rhinoconjunctivitis. Allergy 2003; 58 (7): 595-601. **Therapy NOT AVAILABLE in the U.S**

Jarisch, R. Specific immune therapy. Padiatr Padol 90; 25 (6): 405-7. **It does not meet ALL the inclusion criteria**

Jarisch, R. Specific immune therapy. Padiatr Padol 90; 25 (6): 405-7. **It does not meet ALL the inclusion criteria**

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Jarisch, R., Sandor, I., Gotz, M., and Popow, C. Specific immunotherapy of allergic diseases: application, effect and side-effects (author's transl). Wien Klin Wochenschr Suppl 80; 117 15-8. **No original data**

Jarisch, R., Sandor, I., Gotz, M., and Popow, C. Specific immunotherapy of allergic diseases: application, effect and side-effects (author's transl). Wien Klin Wochenschr Suppl 80; 117 15-8. **No original dataOther reason for exclusion (specify):**venom

Jerzynska, J., Stelmach, W., Majak, P., Brzozowska, A., Sobocinska, A., and Stelmach, I. Effect of specific immunotherapy on serum levels of tumor necrosis factor alpha in asthmatic children. Allergy Asthma Proc 2008; 29 (3): 274-9. **It does not meet ALL the inclusion criteria**

Jo, T., Kikuchi, H., Hamaguchi, Y., Orita, R., and Komoto, K. Relationship between the specificity of the antigen used and its therapeutic effect in the hyposensitization therapy. Arerugi 70; 19 (9): 718-22. **Non-English article**

Johnson, K. H. and Millard, P. S. Desensitization therapy for asthma in allergic children. J Fam Pract 97; 44 (5): 439-40. **No original data**

Johnstone, D. E. Immunotherapy in children: past, present, and future. (Part I). Ann Allergy 81; 46 (1): 1-7. **No original data**

Johnstone, D. E. Immunotherapy in children: past, present, and future. (Part II). Ann Allergy 81; 46 (2): 59-66. **No original data**

Johnstone, D. E. Uses and abuses of hyposensitization in children. Am J Dis Child 72; 123 (1): 78-83. **Other reason for exclusion (specify): review**

Jones, S. K., Lovell, C. R., and Peachey, R. D. Delayed onset of inflammatory nodules following hay fever desensitization injections. Clin Exp Dermatol 88; 13 (6): 376-8. **Therapy NOT AVAILABLE in the U.S**

Jorde, W. and Kersten, W. Allergic pulmonary diseases in childhood. Diagnostic and therapeutic results. Med Klin 73; 68 (29): 961-5. **No original data**

Joshi, S. V., Tripathi, D. M., and Dhar, H. L. Allergen specific immunotherapy in nasobronchial allergy. Indian J Med Sci 2003; 57 (12): 527-34. **It does not meet ALL the inclusion criteria**no controls

Jung, C. M., Prinz, J. C., Rieber, E. P., and Ring, J. A reduction in allergen-induced Fc epsilon R2/CD23 expression on peripheral B cells correlates with successful hyposensitization in grass pollinosis. J Allergy Clin Immunol 95; 95 (1 Pt 1): 77-87. **It does not meet ALL the inclusion criteria**

Jung, C. M., Prinz, J. C., Rieber, E. P., and Ring, J. A reduction in allergen-induced Fc epsilon R2/CD23 expression on peripheral B cells correlates with successful hyposensitization in grass pollinosis. J Allergy Clin Immunol 95; 95 (1 Pt 1): 77-87. **It does not meet ALL the inclusion criteriaTherapy NOT AVAILABLE in the U.S**

Juniper, E. F., Kline, P. A., Ramsdale, E. H., and Hargreave, F. E. Comparison of the efficacy and side effects of aqueous steroid nasal spray (budesonide) and allergen-injection therapy (Pollinex-R) in the treatment of seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 90; 85 (3): 606-11. **No SIT**

Juniper, E. In re: Van Bever HP, Stevens WJ. (JACI 1990;86: 141-6). J Allergy Clin Immunol 91; 88 (2): 283-4. **No original data**

Juniper, E. In re: Van Bever HP, Stevens WJ. (JACI 1990;86: 141-6). J Allergy Clin Immunol 91; 88 (2): 283-4. **No original data**

Just, J., Bodart, E., Pothel, E., Boule, M., Grimfeld, A., and Tournier, G. Value of accelerated hyposensitization with mixed allergens in severe childhood asthma. Ann Pediatr (Paris) 92; 39 (4): 236-40. **It does not meet ALL the inclusion criteria**no controls

Justicia, J. L. and Mullol, J. Higher evidence for specific immunotherapy than reported in the ARIA update. J Allergy Clin Immunol 2008; 121 (2): 536; author reply 536. **No original data**

Jutel, M., Akdis, M., Budak, F., Aebischer-Casaulta, C., Wrzyszcz, M., Blaser, K., and Akdis, C. A. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol 2003; 33 (5): 1205-14. **It does not meet ALL the inclusion criteria**

Jutel, M., Akdis, M., Budak, F., Aebischer-Casaulta, C., Wrzyszcz, M., Blaser, K., and Akdis, C. A. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol 2003; 33 (5): 1205-14. **It does not meet ALL the inclusion criteria**

K. Aas Hyposensitization in house dust allergy asthma. A double-blind controlled study with evaluation of the effect on bronchial sensitivity to house dust. Acta Paediatr Scand 1971 60 (3): 264-8. **Other reason for exclusion (specify):**house dust

K. Nieminen, E. Valovirta and J. Savolainen Clinical outcome and IL-17, IL-23, IL-27 and FOXP3 expression in peripheral blood mononuclear cells of pollen-allergic children during sublingual immunotherapy. 2010 (1 Pt 2): e174-84. **Does not apply to any of the key questions Not an RCT**

Kaad, P. H. and Ostergaard, P. A. The hazard of mould hyposensitization in children with asthma. Clin Allergy 82; 12 (3): 317-20. **Other reason for exclusion (specify):ALUTARD--? depot prep**

Kaita, T. Studies on bronchial asthma in children. 3. Hyposensitization therapy of bronchial asthma in children. Hiroshima J Med Sci 67; 16 (3): 177-84. **It does not meet ALL the inclusion criteria**house dust IT

Kakinoki, Y., Ohashi, Y., Nakai, Y., Tanaka, A., and Washio, Y. Pollen immunotherapy inhibits T helper 1 and 2 cell responses, but suppression of T helper 2 cell response is a more important mechanism related to the clinical efficacy. Arch Otolaryngol Head Neck Surg 2000; 126 (1): 63-70. **It does not meet ALL the inclusion criteria no controls**

Kakinoki, Y., Ohashi, Y., Nakai, Y., Washio, Y., Nasako, Y., Tanaka, A., and Nakai, Y. Allergen induced mRNA expression of interleukin-5, but not of interleukin-4 and interferon-gamma, in peripheral blood mononuclear cells obtained before the pollen season predicts the clinical efficacy of immunotherapy for seasonal allergic rhinitis. Scand J Immunol 2000; 51 (2): 202-8. **It does not meet ALL the inclusion criteria no controls**

Kaliner, M. and Lemanske, R. Rhinitis and asthma. JAMA 92; 268 (20): 2807-29. **No original data**

Kalla, M., Rozniecki, J., Polanska, Z., and Swatko, A. Evaluation of the effectiveness of desensitization in bronchial asthma caused by house dust mites or grass pollen in the light of clinical results and the histamine and polymyxin inhalation test. Pol Tyg Lek 79; 34 (22): 865-8. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**

Kamin, W., Kopp, M. V., Erdnuess, F., Schauer, U., Zielen, S., and Wahn, U. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. Pediatr Allergy Immunol 2009; **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**

Kammoun, R., Yousfi, H., and Najah, S. 200 cases of allergic asthma treated with specific desensitization. Tunis Med 84; 62 (3): 217-20. **It does not meet ALL the inclusion criteria**no controls**Therapy NOT AVAILABLE in the U.S**

Kandil, A. A., Hasan, A., Taha, O., and El-Mesallamy, H. Eosinophil cationic protein as a diagnostic marker for asthmatic children treated by immunotherapy. Egypt J Immunol 2003; 10 (1): 67-76. **It does not meet ALL the inclusion criteria**homemade extracts**Does not apply to any of the key questions**

Kane, P. A., Ayad, M., Hane, A., and Wane, S. Specific desensitization, basic treatment of asthma. Our experience in Dakar apropos of 56 cases. Dakar Med 80; 25 (1): 51-8. **It does not meet ALL the inclusion criteria**no controls

Kang, B. C., Johnson, J., Morgan, C., and Chang, J. L. The role of immunotherapy in cockroach asthma. J Asthma 88; 25 (4): 205-18. **It does not meet ALL the inclusion criteria**

KAPLAN, M. A., SPITZER, R. H., GUTMAN, A. A., and KALAYIL, P. K. HYPOSENSITIZATION STUDIES WITH A PURIFIED DWARF RAGWEED FRACTION. Ann Allergy 63; 21 494-504. **It does not meet ALL the inclusion criteria**no controls**Therapy NOT AVAILABLE in the U.S**

Karaayvaz, M. and Ozanguc, N. Recall urticaria: a case report. J Allergy Clin Immunol 96; 97 (6): 1419-20. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**

Karaayvaz, M., Erel, F., Caliskaner, Z., and Ozanguc, N. Systemic reactions due to allergen immunotherapy. J Investig Allergol Clin Immunol 99; 9 (1): 39-44. **It does not meet ALL the inclusion criteria**

Karakaya, G., Sahin, S., and Fuat Kalyoncu, A. Erythema multiforme: As a complication of allergen-specific immunotherapy. Allergol Immunopathol (Madr) 2001; 29 (6): 276-8. **Other reason for exclusion (specify):case report**

Karl, S. and Rakoski, J. Hyposensitization with cross-reacting pollen allergens. Z Hautkr 88; 63 Suppl 4 55-7. **Non-English article**

Karlsson, R., Agrell, B., Dreborg, S., Foucard, T., Kjellman, N. I., Koivikko, A., and Einarsson, R. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized Cladosporium herbarum preparation. II. In vitro results. Allergy 86; 41 (2): 141-50. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**

Katelaris, C. H. Modern management of allergic rhinitis. Adv Otorhinolaryngol 97; 51 68-71. **No original dataOther reason for exclusion (specify): review**

Kato, S., Nakai, Y., Ohashi, Y., and Kato, M. RAST in diagnosis and therapy of allergic rhinitis. Acta Otolaryngol Suppl 91; 486 209-16. **It does not meet ALL the inclusion criteria**no controls**Does not apply to any of the key questions**

Kats, P. D., Ostroumov, A. I., Ametov, A. S., Iusuf-Zade, L. I., and Toritsina, L. K. Clinico-immunological characteristics of peroral specific hyposensitization in hay fevers in children. Pediatriia 85; (8): 18-21.

Other reason for exclusion (specify): Oral IT not SLIT

Kawakami, A., Koketsu, R., Suzukawa, M., Nagao, M., Hiraguchi, Y., Tokuda, R., Fujisawa, T., Nagase, H., Ohta, K., Yamamoto, K., and Yamaguchi, M. Blocking antibody is generated in allergic rhinitis patients during specific immunotherapy using standardized Japanese cedar pollen extract. Int Arch Allergy Immunol 2008; 146 Suppl 1 54-60. **It does not meet ALL the inclusion criteria**no controls

Kawakami, A., Koketsu, R., Suzukawa, M., Nagao, M., Hiraguchi, Y., Tokuda, R., Fujisawa, T., Nagase, H., Ohta, K., Yamamoto, K., and Yamaguchi, M. Blocking antibody is generated in allergic rhinitis patients during specific immunotherapy using standardized Japanese cedar pollen extract. Int Arch Allergy Immunol 2008; 146 Suppl 1 54-60. **It does not meet ALL the inclusion criteria**

Kelso, J. M., Jones, R. T., Tellez, R., and Yunginger, J. W. Oral allergy syndrome successfully treated with pollen immunotherapy. Ann Allergy Asthma Immunol 95; 74 (5): 391-6. **It does not meet ALL the inclusion criteria Number of subjects in study is 6 or fewer on active treatment (Unless it reports harms)**

KERR, J. W. and MURCHISON, L. E. A CONTROLLED TRIAL OF POLLEN ADSORBATE IN THE TREATMENT OF HAY FEVER. Scott Med J 63; 8 484-8. **Therapy NOT AVAILABLE in the U.S**

Kerr, J. W. Does immunotherapy have a role in the treatment of asthma?. Clin Allergy 86; 16 (2): 179-80. **No original dataOther reason for exclusion (specify): letter**

Kersten, W. How and when is immunotherapy for pollen allergy carried out?. Med Klin 80; 75 (21): 751-4. **It does not meet ALL the inclusion criteria**no controls

Keskin, O., Tuncer, A., Yildirim, S., Bursali, B., Adalioglu, G., and Sekerel, B. E. Does specific immunotherapy injection cause an increase in bronchial reactivity?. J Asthma 2005; 42 (9): 765-8. **It does not meet ALL the inclusion criteria**no rel outcomes**Does not apply to any of the key questions**

Kim, H. B., Jin, H. S., Lee, S. Y., Kim, J. H., Kim, B. S., Park, S. J., and Hong, S. J. The effect of rush immunotherapy with house dust mite in the production of IL-5 and IFN-gamma from the peripheral blood T cells of asthmatic children. J Korean Med Sci 2009; 24 (3): 392-7. **It does not meet ALL the inclusion criteria**

Kim, S. T., Han, D. H., Moon, I. J., Lee, C. H., Min, Y. G., and Rhee, C. S. Clinical and immunologic effects of sublingual immunotherapy on patients with allergic rhinitis to house-dust mites: 1-year follow-up results. Am J Rhinol Allergy 2010; 24 (4): 271-5. **It does not meet ALL the inclusion criteria**no controls

Kim, S. T., Han, D. H., Moon, I. J., Lee, C. H., Min, Y. G., and Rhee, C. S. Clinical and immunologic effects of sublingual immunotherapy on patients with allergic rhinitis to house-dust mites: 1-year follow-up results. Am J Rhinol Allergy 2010; 24 (4): 271-5. **It does not meet ALL the inclusion criteria**

Kimura, I., Tanizaki, Y., Goda, Y., Komagoe, H., and Kitani, H. Decrease in reactivity of basophils by immunotherapy with housedust extract. Clin Allergy 85; 15 (1): 1-7. **It does not meet ALL the inclusion criteria**

King, T. P. and Norman, P. S. Standardized extracts, weeds. Clin Rev Allergy 86; 4 (4): 425-33. **No original data**

Kitao, Y. Investigation of specific immunotherapy in patients with nasal allergy to housedust and mite: histamine release assay from their peripheral leukocytes. Nippon Jibiinkoka Gakkai Kaiho 87; 90 (6): 896-902. **Does not apply to any of the key questions**

Klein, G. L. and Ziering, R. W. Diagnosis and treatment of allergic rhinitis and asthma in infancy and childhood. Compr Ther 84; 10 (3): 26-30. **No original data**

Klein, G. L. and Ziering, R. W. Diagnosis and treatment of allergic rhinitis and asthma in infancy and childhood. Compr Ther 84; 10 (3): 26-30. **No original data**

Klein, J. S. Ragweed immunotherapy in adult asthma. N Engl J Med 96; 335 (3): 204; author reply 205-6. **No original data**

Klein-Tebbe, J. and Kunkel, G. Current status of specific hyposensitization in the treatment of bronchial asthma. Pneumologie 91; 45 (8): 630-2. **No original data**

Kljaic-Turkalj, M., Cvoriscec, B., Tudoric, N., Stipic-Markovic, A., Rabatic, S., Trescec, A., Gagro, A., and Dekaris, D. Decrease in CD23+ B lymphocytes and clinical outcome in asthmatic patients receiving specific rush immunotherapy. Int Arch Allergy Immunol 96; 111 (2): 188-94. **It does not meet ALL the inclusion criteria**

Koker, O., Guneser, S., Altintas, D., and Kozanoglu, M. Effect of specific immunotherapy in Dermatophagoides pteronyssinus allergic children. Acta Paediatr Jpn 94; 36 (2): 150-2. **It does not meet ALL the inclusion criteria**

Komagoe, H., Sudo, M., Tanizaki, Y., Kitani, H., Goda, Y., Sasaki, Y., Tada, S., Takahashi, K., and Kimura, I. Changes in basophil reactivity during immunotherapy with house dust. Arerugi 84; 33 (3): 131-4 **Non-English article: japanese**

Kopitowski, Karin Inmunoterapia con alergenos para el asma. Evid. actual. prbct. ambul 2004; 7 (1): 26-27. **Other reason for exclusion (specify):case report**

Kopp, M. V., Hamelmann, E., Zielen, S., Kamin, W., Bergmann, K. C., Sieder, C., Stenglein, S., Seyfried, S., and Wahn, U. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. Clin Exp Allergy 2009; 39 (2): 271-9. **Therapy NOT AVAILABLE in the U.S**

Kopp, M. V., Stenglein, S., Kamin, W., Friedrichs, F., von Berg, A., Zielen, S., Hamelmann, E., Wahn, U.,

and Kuehr, J. Omalizumab (Xolair) in children with seasonal allergic rhinitis: leukotriene release as a potential in vitro parameter to monitor therapeutic effects. Pediatr Allergy Immunol 2007; 18 (6): 523-7. **It does not meet ALL the inclusion criteria**

Korzeniowska-Zuk, E. and Romanski, B. Studies on the possibility of desensitizing patients sensitive to plant pollens and house dust by an oral route. Pneumonol Alergol Pol 92; 60 (7-8): 32-8. **Other reason for exclusion (specify): oral IT**

Kossowski, S., Gieldanowski, J., Greczek-Harkawy, J., and Ziemski, Z. L. Clinical and immunologic studies on fetid atrophic rhinitis (ozena) of the nasopharyngeal cavity treated with a specific vaccine. Arch Immunol Ther Exp (Warsz) 73; 21 (5): 715-20. **It does not meet ALL the inclusion criteria**

Kossowski, S., Gieldanowski, J., Greczek-Harkawy, J., and Ziemski, Z. L. Clinical and immunologic studies on fetid atrophic rhinitis (ozena) of the nasopharyngeal cavity treated with a specific vaccine. Arch Immunol Ther Exp (Warsz) 73; 21 (5): 715-20. **It does not meet ALL the inclusion criteriaNo SIT**

Kowal, K., Nolte, H., Skov, P. S., and DuBuske, L. M. Effect of allergen-specific immunotherapy on recombinant human interleukin 3-mediated amplification of allergen-induced basophil histamine release. Allergy Asthma Proc 2005; 26 (6): 456-62. **It does not meet ALL the inclusion criteria**

Kowal, K., Nolte, H., Skov, P. S., and DuBuske, L. M. Effect of allergen-specific immunotherapy on recombinant human interleukin 3-mediated amplification of allergen-induced basophil histamine release. Allergy Asthma Proc 2005; 26 (6): 456-62. **It does not meet ALL the inclusion criteria**

Kowal, K., Osada, J., Zukowski, S., Dabrowska, M., Dubuske, L., and Bodzenta-Lukaszyk, A. Expression of interleukin 4 receptors in bronchial asthma patients who underwent specific immunotherapy. Ann Allergy Asthma Immunol 2004; 93 (1): 68-75. **It does not meet ALL the inclusion criteria**

Kowal, K., Osada, J., Zukowski, S., Dabrowska, M., Dubuske, L., and Bodzenta-Lukaszyk, A. Expression of interleukin 4 receptors in bronchial asthma patients who underwent specific immunotherapy. Ann Allergy Asthma Immunol 2004; 93 (1): 68-75. **patient preference**

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MAKINO, S. STUDIES ON INHALATION TESTS IN BRONCHIAL ASTHMA. (III). INFLUENCE OF HYPOSENSITIZATION THERAPY ON THE SENSITIVITY OF THE RESPIRATORY TRACT TO ALLERGENS AND ACETYLCHOLINE.. Arerugi 64; 13 83-7. **Does not apply to any of the key questions**

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Mohapatra, S. S., Lockey, R. F., and Polo, F. Weed pollen allergens. Clin Allergy Immunol 2008; 21 127-39. **No original data**
Moller, C. Effect of pollen immunotherapy on food hypersensitivity in children with birch pollinosis. Ann Allergy 89; 62 (4): 343-5. **It does not meet ALL the inclusion criteria**
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39 (4): 291-6. **It does not meet ALL the inclusion criteria**
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Monzon S, Venturini M, Colas C, Lezaun A, Casanovas M, Reichelt C, and Lara S Specific immunotherapy with modified Salsola kali extract: Preliminary results. Alergologia e Inmunologia Clinica ; **It does not meet ALL the inclusion criteria**
Monzon S, Venturini M, Colas C, Lezaun A, Casanovas M, Reichelt C, and Lara S Specific immunotherapy with modified Salsola kali extract: Preliminary results. Alergologia e Inmunologia Clinica ; **It does not meet ALL the inclusion criteria**
Moreno, C., Cuesta-Herranz, J., Fernandez-Tavora, L., and Alvarez-Cuesta, E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy 2004; 34 (4): 527-31. **Not an RCT**
Moreno, C., Cuesta-Herranz, J., Fernandez-Tavora, L., and Alvarez-Cuesta, E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy 2004; 34 (4): 527-31. **It does not meet ALL the inclusion criteria no** comparrator group
Moreno, C., Fernandez-Tavora, L., Acero, S., Alonso, M. D., Barahona, M. J., Blanco, R., Cistero, A., Conde, J., Fernandez, J., Fernandez, S., Fernandez-Rivas, M., Garcia, B. E., Garcia-Rodriguez, R., Camacho, E., Gonzalez-Quevedo, T., Gonzalo, A., Guardia, P., Sanchez-Cano, M., Tabar, A. I., and de la Torre, F. Tolerance of a cluster schedule on the treatment of seasonal allergic respiratory disease with pollen extracts quantified in mass units. J Investig Allergol Clin Immunol 2003; 13 (4): 221-7. **It does not meet ALL the inclusion criteria no controls**
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Mosbech H, Dirkson A, Drebotrg S, Frolund L, Heinig JH, Svenden UG, Soborg M, Taudorf E, and Weeke B Hyposensitization in asthmatics with mPEG-modified and unmodiefied house dust mite extract. IV. Occurrence and prediction of side effects.. Allergy: European Journal of Allergy and Clinical Immunology ; **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**same paper as 3726
Mosbech, H. and Osterballe, O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. Allergy 88; 43 (7): 523-9. **It does not meet ALL the inclusion criteria no** controls **No original data**
Mosbech, H. House dust mite allergy. Allergy 85; 40 (2): 81-91. **No original data**
Mosbech, H., Dirksen, A., Dreborg, S., Frolund, L., Heinig, J. H., Svendsen, U. G., Soborg, M., Taudorf, E., and Weeke, B. Hyposensitization in asthmatics with mPEG-modified and unmodified house dust mite

extract. IV. Occurrence and prediction of side effects. Allergy 90; 45 (2): 142-50. **Therapy NOT AVAILABLE in the U.S**

Mosbech, H., Dreborg, S., Frolund, L., Ljungstedt-Pahlman, I., Svendsen, U. G., Soborg, M., Taudorf, E., and Weeke, B. Hyposensitization in asthmatics with mPEG modified and unmodified house dust mite extract. I. Clinical effect evaluated by diary cards and a retrospective assessment. Allergy 89; 44 (7): 487-98. **Therapy NOT AVAILABLE in the U.S**

Mosbech, H., Dreborg, S., Frolund, L., Ljungstedt-Pahlman, I., Svendsen, U. G., Soborg, M., Taudorf, E., and Weeke, B. Hyposensitization in asthmatics with mPEG modified and unmodified house dust mite extract. II. Effect evaluated by challenges with allergen and histamine. Allergy 89; 44 (7): 499-509. **Therapy NOT AVAILABLE in the U.S**

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Moverare, R., Vesterinen, E., Metso, T., Sorva, R., Elfman, L., and Haahtela, T. Pollen-specific rush immunotherapy: clinical efficacy and effects on antibody concentrations. Ann Allergy Asthma Immunol 2001; 86 (3): 337-42. **It does not meet ALL the inclusion criteria**

MUITTARI, A. A SPECIFIC HYPOSENSITIZATION IN BRONCHIAL ASTHMA.. Duodecim 64; 80 1141-8. finnish **Non-English article**

Munoz, D., Sanz, M. L., Tabar, A., Oehling, A., and Fernandez de Corres, L. Circulating immune complexes in pollinosis and chronic bronchopathies. Effect of immunotherapy. Allergol Immunopathol (Madr) 83; 11 (5): 379-84. **Does not apply to any of the key questions Other reason for exclusion (specify):**includes arms not allergic disease**Not an RCT**

Munoz-Lopez, F. Betting on immunotherapy. Allergol Immunopathol (Madr) 98; 26 (1): 3-4. **No original data**

Munoz-Lopez, F. Betting on immunotherapy. Allergol Immunopathol (Madr) 98; 26 (1): 3-4. **No original data**

Munoz-Lopez, F. Immunotherapy--methods of treatment and results in children. Allergol Immunopathol (Madr) 81; Suppl 9 171-3. **It does not meet ALL the inclusion criteria**

Munoz-Lopez, F. Is immunotherapy justified in the treatment of respiratory allergy?. Allergol Immunopathol (Madr) 2007; 35 (3): 79-82. **It does not meet ALL the inclusion criteria**

Munoz-Lopez, F. New administration routes in immunotherapy. Allergol Immunopathol (Madr) 2000; 28 (6): 295-300. **It does not meet ALL the inclusion criteria no original data**

Munro-Ashman, D. and Frankland, A. W. Treatment of allergy to house dust with pyridine-extracted alum-precipitated extracts of the house dust mite. Ann Allergy 76; 36 (2): 95-8. **Therapy NOT AVAILABLE in the U.S**

Munro-Ashman, D., McEwen, H., and Feinberg, J. G. The patient self (P-S) test. Demonstration of a rise in blocking antibodies after treatment with Allpyral. Int Arch Allergy Appl Immunol 71; 40 (3): 448-53. **Therapy NOT AVAILABLE in the U.S**

Murray, A. B., Ferguson, A. C., and Morrison, B. J. Non-allergic bronchial hyperreactivity in asthmatic children decreases with age and increases with mite immunotherapy. Ann Allergy 85; 54 (6): 541-4. **It does not meet ALL the inclusion criteria**

N. E. Eriksson, S. Ahlstedt and O. Lovhagen Immunotherapy in spring-time hay fever. A clinical and immunological study comparing two different treatment extract compositions. ALLERGY 1979 34 (4): 233-47. **It does not meet ALL the inclusion criteria**

Nagao, M., Hiraguchi, Y., Hosoki, K., Tokuda, R., Usui, T., Masuda, S., Yamaguchi, M., and Fujisawa, T. Allergen-induced basophil CD203c expression as a biomarker for rush immunotherapy in patients with Japanese cedar pollinosis. Int Arch Allergy Immunol 2008; 146 Suppl 1 47-53. **It does not meet ALL the inclusion criteria no** comparator

Nagata, M. Allergen-immunotherapy in asthma. Arerugi 2008; 57 (1): 9-14. **No original data - (specify): Non-English article: japanese**

Nagata, M. Rush immunotherapy in bronchial asthma. Kokyu To Junkan 92; 40 (8): 775-81. **Non-English article: japanese**

Nagata, M., Saito, K., Kikuchi, I., Tabe, K., Hagiwara, K., Kanazawa, M., and Sakamoto, Y. Immunotherapy attenuates eosinophil transendothelial migration induced by the supernatants of antigen-stimulated mononuclear cells from atopic asthmatics. Int Arch Allergy Immunol 2004; 134 Suppl 1 21-4. **It does not meet ALL the inclusion criteria**

Nagata, M., Shibasaki, M., Sakamoto, Y., Fukuda, T., Makino, S., Yamamoto, K., and Dohi, Y. Specific immunotherapy reduces the antigen-dependent production of eosinophil chemotactic activity from mononuclear cells in patients with atopic asthma. J Allergy Clin Immunol 94; 94 (2 Pt 1): 160-6. **It does not meet ALL the inclusion criteria**iomkr**Does not apply to any of the key questions**

Nagata, M., Shibasaki, M., Sakamoto, Y., Yamamoto, K., and Dohi, Y. The influence of rush immunotherapy on the production of interleukin-5 from mononuclear cells. Arerugi 93; 42 (2): 158-61. **It does not meet ALL the inclusion criteria no** c ontrols

Nagata, M., Shibasaki, M., Sakamoto, Y., Yamamoto, K., and Dohi, Y. The influence of rush immunotherapy on the production of interleukin-5 from mononuclear cells. Arerugi 93; 42 (2): 158-61. **It does not meet ALL the inclusion criteria**

Nagata, M., Tabe, K., Yamamoto, H., Maruo, H., Kiuch, H., Sakamoto, Y., Yamamoto, K., and Dohi, Y. The analysis of factors contributing to the safety and efficacy of rush immunotherapy in bronchial asthma. Arerugi 93; 42 (5): 628-34. **It does not meet ALL the inclusion criteriaOther reason for exclusion (specify): japanese**

Nagata, M., Tabe, K., Yamamoto, H., Sakamoto, Y., and Matsuo, H. Clinical significance of allergen specific immunotherapy in adult house-dust-mite-sensitive bronchial asthma: impact on disease severity and medical cost. Arerugi 99; 48 (12): 1316-21. **It does not meet ALL the inclusion Non-English article: japanese**

Nagata, M., Yamamoto, H., Tabe, K., Kimura, I., Houya, I., Kuramitsu, K., Kiuchi, H., Yanagihara, Y., Sakamoto, Y., Yamamoto, K., and et, a. l. Effect of rush immunotherapy in house-dust-mite (HDM)-sensitive adult bronchial asthma: changes in in vivo and in vitro responses to HDM. Intern Med 93; 32 (9): 702-9. **It does not meet ALL the inclusion criteria**. no controls

Nagata, M., Yamamoto, H., Tabe, K., Tanaka, K., Kimura, I., Sakamoto, K., Sakamoto, Y., Yamamoto, K., and Dohi, Y. A clinical evaluation of rush immunotherapy in adult patients with severe bronchial asthma. Arerugi 89; 38 (12): 1319-26. **It does not meet ALL the inclusion criteria Non-English article: japanese**

Nagaya, H. Induction of antigen-specific suppressor cells in patients with hay fever receiving immunotherapy. J Allergy Clin Immunol 85; 75 (3): 388-94. **Does not apply to any of the key questionsStudy evaluates outcomes in animals only or in vitro**

Nagaya, H. Long-term effects of conventional immunotherapy in southern California. Ann Allergy 80; 44 (4): 193-9. **It does not meet ALL the inclusion criteria**

Nagaya, H., Lee, S. K., Reddy, P. M., Pascual, H., Jerome, D., Sadai, J., Gupta, S., and Lauridsen, J. Lymphocyte response to grass pollen antigens: a correlation with radioallergosorbent test and effect of immunotherapy. Ann Allergy 77; 39 (4): 246-52. **It does not meet ALL the inclusion criteria**

Nagaya, H., Maren, S., and Nagaya, N. Allergy immunotherapy as an early intervention in patients with child-onset atopic asthma. Int Arch Allergy Immunol 2006; 139 (1): 9-15. **It does not meet ALL the inclusion criteria**

Nagore, E., Martinez-Escribano, J. A., Tato, A., Sabater, V., and Vilata, J. J. Subcutaneous nodules following treatment with aluminium-containing allergen extracts. Eur J Dermatol 2001; 11 (2): 138-40. **It does not meet ALL the inclusion criteria**

Nakagawa, T. IgG subclass changes in response to desensitisation. Monogr Allergy 86; 19 253-61. **Does not apply to any of the key questions**

Nakagawa, T. The role of IgG subclass antibodies in the clinical response to immunotherapy in allergic disease. Clin Exp Allergy 91; 21 (3): 289-96. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

Nakagawa, T., Kozeki, H., Katagiri, J., Fujita, Y., Yamashita, N., Miyamoto, T., and Skvaril, F. Changes of house dust mite-specific IgE, IgG and IgG subclass antibodies during immunotherapy in patients with perennial rhinitis. Int Arch Allergy Appl Immunol 87; 82 (1): 95-9. **It does not meet ALL the inclusion criteria**

Nakagawa, T., Takaishi, T., Sakamoto, Y., Ito, K., Miyamoto, T., and Skvaril, F. IgG4 antibodies in patients with house-dust-mite-sensitive bronchial asthma: relationship with antigen-specific immunotherapy. Int Arch Allergy Appl Immunol 83; 71 (2): 122-5. **It does not meet ALL the inclusion criteriaNot an RCT**

Nakagawa, T., Yoshinoya, S., Sakamoto, Y., Ito, K., and Miyamoto, T. Circulating immune complexes in patients with house-dust-mite-sensitive bronchial asthma. Clin Allergy 84; 14 (2): 129-38. **It does not meet ALL the inclusion criteria**

Nakai, Y., Ohashi, Y., Tanaka, A., Kakinoki, Y., Washio, Y., Masamoto, T., Yamada, K., Nakai, Y., and Ohmoto, Y. Cry j 1-induced synthesis of interleukin-5 and interferon-gamma by peripheral blood mononuclear cells of patients with seasonal allergic rhinitis due to Japanese cedar pollens. Acta Otolaryngol Suppl 98; 538 143-51. **It does not meet ALL the inclusion criteria**

Nakajima, H., Ohtsuka, S., Nishina, T., Sugino, M., Kimura, F., Hanafusa, T., Ikemoto, T., and Shimizu, A. Multiple sclerosis after allergen-specific

immunotherapy and influenza vaccination. Eur Neurol 2003; 50 (4): 248-9. **Other reason for exclusion (specify):case report**
Nakamura, S. Clinical effects of hyposensitization treatment on bronchial asthma. Arerugi 68; 17 (5): 348-56. **Other reason for exclusion (specify): japanese**
Nakamura, S. Results of the skin test and the desensitization therapy for bronchial asthma at the Allergy Center. Iryo 71; 25 (5): 351-2. **Other reason for exclusion (specify): japanese**
Nakano, A., Nakano, K., Okawa, T., Yamakoshi, T., Terada, N., Numata, T., and Konno, A. The effect of Japanese cedar-specific immunotherapy on cytokine production in peripheral blood mononuclear cells. Acta Otolaryngol 2002; 122 (1): 54-60. **Therapy NOT AVAILABLE in the U.S**
Nakayama, Y., Shimanuki, K., Uehara, S., and Hirakata, A. Analysis of 80 cases of childhood asthma provoked by mold allergens. Acta Paediatr Jpn 71; 13 (2): 36-43. **No SITNot an RCT**
Nalebuff, D. J. Modified RAST to determine initial immunotherapy doses. Otolaryngol Head Neck Surg 85; 93 (5): 691-2. **No original data**
Nalebuff, D. J., Fadal, R. G., and Ali, M. Determination of initial immunotherapy dose for ragweed hypersensitivity with the modified RAST test. Otolaryngol Head Neck Surg 81; 89 (2): 271-4. **It does not meet ALL the inclusion criteria**
Nalebuff, D. J., Fadal, R. G., and King, W. Allergic rhinosinusitis: the total rhinologic disease. Ear Nose Throat J 93; 72 (6): 430-1. **Other reason for exclusion (specify): letter**
Narasaki, N. and Suematsu, T. Therapy of bronchial asthma. Iryo 71; 25 (5): 345-9. **Non-English article: Japanese. No original data**
Nash, D. B., Sullivan, S. D., and Mackowiak, J. Optimizing quality of care and cost effectiveness in treating allergic rhinitis in a managed care setting. Am J Manag Care 2000; 6 (1 Suppl): S3-15; quiz S19-20. **No original data**
NATERMAN, H. L. FORMALINIZED POLLEN PROTEIN PRECIPITATES WITH TANNIC ACID OR UREA IN DESENSITIZATION TREATMENT. J Allergy Clin Immunol 65; 36 226-33. **Does not apply to any of the key questions**
Nathan, R. A., Santilli, J., Rockwell, W., and Glassheim, J. Effectiveness of immunotherapy for recurring sinusitis associated with allergic rhinitis as assessed by the Sinusitis Outcomes Questionnaire. Ann Allergy Asthma Immunol 2004; 92 (6): 668-72. **It does not meet ALL the inclusion criteria**
Negrini, A. C., Troise, C., Voltolini, S., Siccardi, M., and Grassia, L. Long-term hyposensitization and adverse immunologic responses. A laboratory evaluation. Ann Allergy 85; 54 (6): 534-7. **It does not meet ALL the inclusion criteria**
Negro Alvarez, J. M. Costs of specific immunotherapy. J Investig Allergol Clin Immunol 97; 7 (5): 362-3. **No original data**
Nelson, H. S., Areson, J., and Reisman, R. A prospective assessment of the remote practice of allergy: comparison of the diagnosis of allergic disease and the recommendations for allergen immunotherapy by board-certified allergists and a laboratory performing in vitro assays. J Allergy Clin Immunol 93; 92 (3): 380-6. **Other reason for exclusion (specify): review** of practice methods
Nelson, H. S., Brown, G., O'Barr, T. P., Branch, L. B., Spaulding, H., and Black, J. W. Clinical and immunological studies of timothy antigen D immunotherapy. J Allergy Clin Immunol 76; 57 (5): 463-72. **It does not meet ALL the inclusion criteria**
Nenasheva, N. M., Dotsenko, V. L., Goriachkina, L. A., and Iarovaia, G. A. Activity of the prekallikrein-kallikrein system and characteristics of its regulation in various allergies. Vopr Med Khim 86; 32 (5): 106-11. **No SIT**
Nesterenko, V. N. Specific hyposensitization in bronchial asthma in children. Med Sestra 84; 43 (2): 31-2. **RussianNon-English article**
Netterlid, E., Hindsen, M., Bjork, J., Ekqvist, S., Guner, N., Henricson, K. A., and Bruze, M. There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. Contact Dermatitis 2009; 60 (1): 41-9. **Does not apply to any of the key questions**
Nettis, E., Giordano, D., Pannofino, A., Ferrannini, A., and Tursi, A. Safety of inhalant allergen immunotherapy with mass units-standardized extracts. Clin Exp Allergy 2002; 32 (12): 1745-9. **It does not meet ALL the inclusion criteria**
Nichani, J. R. and de Carpentier, J. Safety of sublingual grass pollen immunotherapy after anaphylaxis. J Laryngol Otol 2009; 123 (6): 683-4. **It does not meet ALL the inclusion criteria**
Nielsen, L., Johnsen, C. R., Mosbech, H., Poulsen, L. K., and Malling, H. J. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 96; 97 (6): 1207-13. **Does not apply to any of the key questions**
Nieminen, K., Laaksonen, K., and Savolainen, J. Three-year follow-up study of allergen-induced in vitro cytokine and signalling lymphocytic activation molecule mRNA responses in peripheral blood mononuclear cells of allergic rhinitis patients undergoing specific immunotherapy. Int Arch Allergy Immunol 2009; 150 (4): 370-6. **It does not meet ALL the inclusion criteria**
Nikolaus, J. and Wettengel, R. Immunotherapy of bronchial asthma. Retrospective study on its practicability and results. Prax Klin Pneumol 82; 36 (9): 398-403. **It does not meet ALL the inclusion criteria**
Nikolaus, J. and Wettengel, R. Immunotherapy of bronchial asthma. Retrospective study on its practicability and results. Prax Klin Pneumol 82; 36 (9): 398-403. **It does not meet ALL the inclusion criteria**
Nilzen, A. Phagocytic activity of leucocytes in rhinitis allergica. Allerg Immunol (Leipz) 74-75; 20-21 (1): 29-32. **It does not meet ALL the inclusion criteria**

Nilzen, A. Phagocytic activity of leucocytes in rhinitis allergica. Allerg Immunol (Leipz) 74-75; 20-21 (1): 29-32. **It does not meet ALL the inclusion criteria**
Nish, W. A., Charlesworth, E. N., Davis, T. L., Whisman, B. A., Valtier, S., Charlesworth, M. G., and Leiferman, K. M. The effect of immunotherapy on the cutaneous late phase response to antigen. J Allergy Clin Immunol 94; 93 (2): 484-93. **It does not meet ALL the inclusion criteria**
Nishioka, G. J., Cook, P. R., Davis, W. E., and McKinsey, J. P. Immunotherapy in patients undergoing functional endoscopic sinus surgery. Otolaryngol Head Neck Surg 94; 110 (4): 406-12. **It does not meet ALL the inclusion criteria no** dose
Nizami, R. M. and Collins-Williams, C. Hyposensitization therapy in allergic disease. Ann Allergy 75; 35 (5): 296-304. **Other reason for exclusion (specify): review**
Noferi, A., Volpari, A. L., and Mancuso, A. Specific skin reaction of an immediate type in patients with allergic syndromes caused by inhalants after prolonged specific desensitization. Folia Allergol (Roma) 69; 16 (5): 498-503. **It does not meet ALL the inclusion criteria**
Nogami, H., Iwanaga, T., Kishikawa, R., Odajima, H., Tsurutani, H., Hirose, T., Inoue, T., and Nishima, S. Prognosis of intractable asthma. Arerugi 92; 41 (11): 1591-6. **Does not apply to any of the key questions**
Nolte, D. Hyposensitization in asthma--between belief and certainty. Med Klin (Munich) 89; 84 (9): 459-60. **No original data**
Nolte, D. Hyposensitization in asthma--between belief and certainty. Med Klin (Munich) 89; 84 (9): 459-60. **No original data**
Nolte, H. Optimal maintenance dose immunotherapy based on major allergen content or potency labeling. Allergy 98; 53 (1): 99-100. **Other reason for exclusion (specify): letter**
Nopp, A., Cardell, L. O., Johansson, S. G., and Oman, H. CD-sens: a biological measure of immunological changes stimulated by ASIT. Allergy 2009; 64 (5): 811-4. **It does not meet ALL the inclusion criteria**
Nordvall, S. L., Berg, T., Johansson, S. G., and Lanner, A. Clinical studies of a purified timothy pollen extract: desensitization therapy with a purified timothy pollen preparation compared to a crude timothy pollen extract. II. Results of the tests in vitro and their relation to symptoms and tests in vivo. Int Arch Allergy Appl Immunol 82; 67 (2): 132-8. **It does not meet ALL the inclusion criteria**
Nordvall, S. L., Renck, B., and Einarsson, R. Specific IgE and IgG antibody responses in children to timothy pollen components during immunotherapy. Allergy 89; 44 (6): 380-4. **Does not apply to any of the key questions**
Nordvall, S. L., Renck, B., and Einarsson, R. Specific IgE and IgG antibody responses in children to timothy pollen components during immunotherapy. Allergy 89; 44 (6): 380-4. **It does not meet ALL the inclusion criteria**
Norman, P. S. A rational approach to desensitization. J Allergy 69; 44 (3): 129-45. **Other reason for exclusion (specify):**course
Norman, P. S. Newer developments in immunotherapy for hay fever. Int Arch Allergy Appl Immunol 81; 66 Suppl 1 43-7. **Other reason for exclusion (specify): review**
Norman, P. S. Specific therapy in allergy. Pro (with reservations). Med Clin North Am 74; 58 (1): 111-25. **No original data**
Norman, P. S. Specific therapy in allergy. Pro (with reservations). Med Clin North Am 74; 58 (1): 111-25. **Other reason for exclusion (specify): review**
Norman, P. S. Sublingual swallow immunotherapy in the new world. Ann Allergy Asthma Immunol 2004; 93 (5): 405-6. **Other reason for exclusion (specify): review**
Norman, P. S. The rationale for immunotherapy in respiratory allergies. Trans Am Clin Climatol Assoc 78; 89 119-29. **No original data**
Norman, P. S., Winkenwerder, W. L., and Lichtenstein, L. M. Maintenance immunotherapy in ragweed hay fever. Booster injections at six week intervals. J Allergy 71; 47 (5): 273-82. **It does not meet ALL the inclusion criteria**
Norman, P. S., Winkenwerder, W. L., and Lichtenstein, L. M. Trials of alum-precipitated pollen extracts in the treatment of hay fever. J Allergy Clin Immunol 72; 50 (1): 31-44. **It does not meet ALL the inclusion criteria**
Norman, P. S., Winkenwerder, W. L., D'Lugoff, B. C., and Tignall, J. Controlled evaluations of repository therapy in ragweed hay fever. J Allergy 67; 39 (2): 82-92. **It does not meet ALL the inclusion criteria**
Norman, P. S., Winkenwerder, W. L., D'Lugoff, B. C., and Tignall, J. Controlled evaluations of repository therapy in ragweed hay fever. J Allergy 67; 39 (2): 82-92. **Therapy NOT AVAILABLE in the U.S**
Nouri-Aria, K. T., Pilette, C., Jacobson, M. R., Watanabe, H., and Durham, S. R. IL-9 and c-Kit+ mast cells in allergic rhinitis during seasonal allergen exposure: effect of immunotherapy. J Allergy Clin Immunol 2005; 116 (1): 73-9. **Other reason for exclusion (specify):**IL-9 biomarker as 1st endpt; but cx correls
Nugent, J. S. and Napoli, D. C. Immunotherapy triggering acute VCD. Allergy 2002; 57 (11): 1089-90. **Other reason for exclusion (specify):case report**
Nuhoglu, Y., Ozumut, S. S., Ozdemir, C., Ozdemir, M., Nuhoglu, C., and Erguven, M. Sublingual immunotherapy to house dust mite in pediatric patients with allergic rhinitis and asthma: a retrospective analysis of clinical course over a 3-year follow-up period. J Investig Allergol Clin Immunol 2007; 17 (6): 375-8. **It does not meet ALL the inclusion criteria**
Nusslein, H. G., Kleinlein, M., Hemmerlein, B., and Kalden, J. R. Different patterns of antigen-induced histamine release during immunotherapy in insect venom and pollen allergy. Agents Actions 86; 18 (1-2): 248-50. **It does not meet ALL the inclusion**

criteriatyrosine**Therapy NOT AVAILABLE in the U.S**
O'Brien, R. M., Byron, K. A., Varigos, G. A., and Thomas, W. R. House dust mite immunotherapy results in a decrease in Der p 2-specific IFN-gamma and IL-4 expression by circulating T lymphocytes. Clin Exp Allergy 97; 27 (1): 46-51. **Therapy NOT AVAILABLE in the U.S**
O'Brien, R. M., Xu, H., Rolland, J. M., Byron, K. A., and Thomas, W. R. Allergen-specific production of interferon-gamma by peripheral blood mononuclear cells and CD8 T cells in allergic disease and following immunotherapy. Clin Exp Allergy 2000; 30 (3): 333-40. **It does not meet ALL the inclusion criteria**
Obtulowicz, K. Pollen-induced allergy. Programming and monitoring of specific immunotherapy. Folia Med Cracov 88; 29 (1-2): 21-48. **Does not apply to any of the key questions**
Obtulowicz, K. Specific immunotherapy in the treatment of hay fever. Pol Tyg Lek 88; 43 (3-4): 97-101. **polishNon-English article**
Obtulowicz, K., Sanokowska, E., and Radwan, J. Specific immunotherapy in hay fever. Allerg Immunol (Paris) 87; 19 (3): 93-6. **It does not meet ALL the inclusion criteria**
Obtulowicz, K., Sanokowska, E., and Radwan, J. Specific immunotherapy in hay fever. Allerg Immunol (Paris) 87; 19 (3): 93-6. **It does not meet ALL the inclusion criteria Dose not specified**
Oda, N., Yamashita, N., Minoguchi, K., Takeno, M., Kaneko, S., Sakane, T., and Adachi, M. Long-term analysis of allergen-specific T cell clones from patients with asthma treated with allergen rush immunotherapy. Cell Immunol 98; 190 (1): 43-50. **It does not meet ALL the inclusion criteria**iomkr**Does not apply to any of the key questions**
Oehling, A. Hyposensitivity treatment of bronchial asthma. Prensa Med Argent 66; 53 (9): 776-84. **No original data**
Oehling, A., Sanz, M. L., and Resano, A. The real value of IgG4 determination in immunotherapy follow-up. Int Arch Allergy Immunol 99; 118 (2-4): 366-7. **Does not apply to any of the key questions**
Oehling, A., Sanz, M. L., and Resano, A. The real value of IgG4 determination in immunotherapy follow-up. Int Arch Allergy Immunol 99; 118 (2-4): 366-7. **It does not meet ALL the inclusion criteria Dose not specified**
Ohashi, Y. Immunotherapy for allergic rhinitis induced by Japanese cedar pollens. Arerugi 2008; 57 (5): 519-23. **Non-English article: japanese**
Ohashi, Y. Immunotherapy for allergic rhinitis induced by Japanese cedar pollens. Arerugi 2008; 57 (5): 519-23. **Non-English article: Japanese**
Ohashi, Y., Nakai, Y., Kakinoki, Y., Ohno, Y., Okamoto, H., Sakamoto, H., Kato, A., and Tanaka, A. The effect of immunotherapy on the serum levels of eosinophil cationic protein in seasonal allergic rhinitis. Clin Otolaryngol Allied Sci 97; 22 (2): 100-5. **It does not meet ALL the inclusion criteria**
Ohashi, Y., Nakai, Y., Kakinoki, Y., Ohno, Y., Tanaka, A., Masamoto, T., Sakamoto, H., Washio, Y., and Kato, A. Immunotherapy affects the seasonal increase in specific IgE and interleukin-4 in serum of patients with seasonal allergic rhinitis. Scand J Immunol 97; 46 (1): 67-77. **It does not meet ALL the inclusion criteria**
Ohashi, Y., Nakai, Y., Kihara, S., Nakagawa, T., and Miyamoto, T. House dust mite-specific IgE, IgG1, and IgG4 antibodies in patients with perennial rhinitis. Ann Otol Rhinol Laryngol 87; 96 (4): 434-7. **It does not meet ALL the inclusion criteria**

Ohashi, Y., Nakai, Y., Okamoto, H., Ohno, Y., Sakamoto, H., Sugiura, Y., Kakinoki, Y., Tanaka, A., Kishimoto, K., Washio, Y., and Hayashi, M. Serum level of interleukin-4 in patients with perennial allergic rhinitis during allergen-specific immunotherapy. Scand J Immunol 96; 43 (6): 680-6. **It does not meet ALL the inclusion criteria**
Ohashi, Y., Nakai, Y., Okamoto, H., Ohno, Y., Sakamoto, H., Tanaka, A., and Kakinoki, Y. Significant correlation between symptom score and IgG4 antibody titer following long-term immunotherapy for perennial allergic rhinitis. Ann Otol Rhinol Laryngol 97; 106 (6): 483-9. **Does not apply to any of the key questions**
Ohashi, Y., Nakai, Y., Sakamoto, H., Ohno, Y., Sugiura, Y., Okamoto, H., Tanaka, A., Kakinoki, Y., Kishimoto, K., and Hayashi, M. Serum levels of soluble interleukin-2 receptor in patients with perennial allergic rhinitis before and after immunotherapy. Ann Allergy Asthma Immunol 96; 77 (3): 203-8. **It does not meet ALL the inclusion criteria**
Ohashi, Y., Nakai, Y., Tanaka, A., Kakinoki, Y., Masamoto, T., Kato, A., and Sakamoto, H. The clinical role of specific IgE and IgG4 antibodies in patients having immunotherapy for seasonal allergic rhinitis. Clin Otolaryngol Allied Sci 98; 23 (2): 128-35. **It does not meet ALL the inclusion criteria**
Ohashi, Y., Nakai, Y., Tanaka, A., Kakinoki, Y., Ohno, Y., Masamoto, T., Sakamoto, H., Kato, A., Washio, Y., and Hayashi, M. Immunotherapy decreases seasonal rise in serum-soluble CD23 in seasonal allergic rhinitis. Laryngoscope 98; 108 (5): 706-11. **It does not meet ALL the inclusion criteria**
Ohashi, Y., Nakai, Y., Tanaka, A., Kakinoki, Y., Ohno, Y., Masamoto, T., Sakamoto, H., Kato, A., Washio, Y., and Hayashi, M. Serum levels of specific IgE, soluble interleukin-2 receptor, and soluble intercellular adhesion molecule-1 in seasonal allergic rhinitis. Ann Allergy Asthma Immunol 97; 79 (3): 213-20. **It does not meet ALL the inclusion criteria**
Ohashi, Y., Nakai, Y., Tanaka, A., Kakinoki, Y., Ohno, Y., Masamoto, T., Sakamoto, H., Kato, A., Washio, Y., and Hayashi, M. Soluble intercellular adhesion molecule-1 level in sera is elevated in perennial allergic rhinitis. Laryngoscope 97; 107 (7): 932-5. **It does not meet ALL the inclusion criteria**
Ohashi, Y., Nakai, Y., Tanaka, A., Kakinoki, Y., Washio, Y., Kato, A., Masamoto, T., Sakamoto, H., and Yamada, K. Ten-year follow-up study of allergen-specific immunoglobulin E and immunoglobulin G4,

soluble interleukin-2 receptor, interleukin-4, soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1 in serum of patients on immunotherapy for perennial allergic rhinitis. Scand J Immunol 98; 47 (2): 167-78. **It does not meet ALL the inclusion criteria**

Ohashi, Y., Nakai, Y., Tanaka, A., Kakinoki, Y., Washio, Y., Kato, A., Masamoto, T., Yamada, K., and Hayashi, M. Serologic study of the working mechanisms of immunotherapy for children with perennial allergic rhinitis. Arch Otolaryngol Head Neck Surg 98; 124 (12): 1337-46. **It does not meet ALL the inclusion criteria**

Ohashi, Y., Nakai, Y., Tanaka, A., Kakinoki, Y., Washio, Y., Yamada, K., Sakamoto, H., Nasako, Y., Hayashi, M., and Nakai, Y. A comparative study of the clinical efficacy of immunotherapy and conventional pharmacological treatment for patients with perennial allergic rhinitis. Acta Otolaryngol Suppl 98; 538 102-12. **It does not meet ALL the inclusion criteria Not an RCT**

Ohashi, Y., Tanaka, A., Kakinoki, Y., Ohno, Y., Sakamoto, H., Kato, A., Masamoto, T., Washio, Y., and Nakai, Y. Effect of immunotherapy on seasonal changes in serum-specific IgE and IgG4 in patients with pollen allergic rhinitis. Laryngoscope 97; 107 (9): 1270-5. **It does not meet ALL the inclusion criteria Dose not specified**

Ohkubo, K. Significance and methods of allergen immunotherapy for pollinosis. Arerugi 2008; 57 (2): 73-8. **No original data**

Ohkubo, K., Takizawa, R., Gotoh, M., and Okuda, M. Experience of specific immunotherapy with standardized Japanese cedar pollen extract. Arerugi 2001; 50 (6): 520-7. **Non-English article:** Japanese **Not an RCT**

Ohman, J. L. Jr Allergen immunotherapy in asthma: evidence for efficacy. J Allergy Clin Immunol 89; 84 (2): 133-40. **No original data**

Ohman, J. L. Jr Allergen immunotherapy in asthma: evidence for efficacy. J Allergy Clin Immunol 89; 84 (2): 133-40. **Other reason for exclusion (specify):**CME

Okano, M., Otsuki, N., Azuma, M., Fujiwara, T., Kariya, S., Sugata, Y., Higaki, T., Kino, K., Tanimoto, Y., Okubo, K., and Nishizaki, K. Allergen-specific immunotherapy alters the expression of B and T lymphocyte attenuator, a co-inhibitory molecule, in allergic rhinitis. Clin Exp Allergy 2008; 38 (12): 1891-900. **It does not meet ALL the inclusion criteria**

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Olaguibel, J. M. Long-term benefits of specific immunotherapy (SIT). Drugs Today (Barc) 2008; 44 Suppl B 39-41. **No original data**

Olaguibel, J. M., Tabar, A. I., Garcia Figueroa, B. E., and Cortes, C. Immunotherapy with standardized extract of Dermatophagoides pteronyssinus in bronchial asthma: a dose-titration study. Allergy 97; 52 (2): 168-78. **It does not meet ALL the inclusion criteria**

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Ornatskaia, M. M. and Mizernitskaia, O. N. Clinical aspects of specific hyporsensitization in bronchial asthma in children during the 1st year of life. Vopr Okhr Materin Det 77; 22 (7): 21-4. **Other reason for exclusion (specify):**

Ortolani, C., Pastorello, E., Moss, R. B., Hsu, Y. P., Restuccia, M., Joppolo, G., Miadonna, A., Cornelli, U., Halpern, G., and Zanussi, C. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. J Allergy Clin Immunol 84; 73 (2): 283-90. **It does not meet ALL the inclusion criteria**

Ortolani, C., Pastorello, E., Moss, R. B., Hsu, Y. P., Restuccia, M., Joppolo, G., Miadonna, A., Cornelli, U., Halpern, G., and Zanussi, C. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. J Allergy Clin Immunol 84; 73 (2): 283-90. **non random trial**

Oryshkevich, B. A. Allergic rhinitis. N Engl J Med 92; 326 (8): 576. **No original data**

OSHIMA, Y. SPECIFIC HYPOSENSITIZATION TREATMENT OF BRONCHIAL ASTHMA.. Arerugi 65; 14 165-86. **Other reason for exclusion (specify): japanese**

Osterballe O Immunotherapy with grass pollen major allergens. Clinical results from a prospective 3-year double blind study.. Allergy: European Journal of Allergy and Clinical Immunology ; **Does not apply to any of the key questions**

Osterballe, O. Nasal and skin sensitivity during immunotherapy with two major allergens 19, 25 and partially purified extract of timothy grass pollen. Allergy 82; 37 (3): 169-77. **It does not meet ALL the inclusion criteria**

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Osterballe, O., Lowenstein, H., Prahl, P., Skov, P., and Weeke, B. Immunotherapy in hay fever with two major allergens 19, 25 and partially purified extract of timothy grass pollen. A controlled double blind study. In vitro variables, season i. Allergy 81; 36 (3): 183-99. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

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Ostroumov, A. I. and Shliaposhnikov, E. D. Specific hyposensitization of pollinosis provoked by ambrosia pollen. Sov Med 68; 31 (9): 37-41. **Other reason for exclusion (specify):**

Ostroumov, A. I. and Shliaposhnikov, E. D. Specific hyposensitization of pollinosis provoked by ambrosia pollen. Sov Med 68; 31 (9): 37-41. **Non-English article: Russian**

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Ozdemir, C., Yazi, D., Gocmen, I., Yesil, O., Aydogan, M., Semic-Jusufagic, A., Bahceciler, N. N., and Barlan, I. B. Efficacy of long-term sublingual immunotherapy as an adjunct to pharmacotherapy in house dust mite-allergic children with asthma. Pediatr Allergy Immunol 2007; 18 (6): 508-15. **It does not meet ALL the inclusion criteria**

Ozden, M. G., Kefeli, M., Aydin, F., Senturk, N., Canturk, T., and Turanli, A. Y. Persistent subcutaneous nodules after immunotherapy injections for allergic asthma. J Cutan Pathol 2009; 36 (7): 812-4. **Other reason for exclusion (specify):case reportNot an RCT**

Ozden, M. G., Kefeli, M., Aydin, F., Senturk, N., Canturk, T., and Turanli, A. Y. Persistent subcutaneous nodules after immunotherapy injections for allergic asthma. J Cutan Pathol 2009; 36 (7): 812-4. **Other reason for exclusion (specify):case report**

P. Kuna, B. Samolinski, M. Worm, O. Pfaar and L. Klimek Sustained clinical efficacy of sublingual

immunotherapy with a high-dose grass pollen extract. European Annals of Allergy and Clinical Immunology 2011 43 (4): 117-121. **Other reason for exclusion (specify):**3rd year of 4440 (Kuna) BUT does not include data for placebo arm **Not an RCT**
P. Majak, J. Kaczmarek-Wozniak, A. Brzozowska, M. Bobrowska-Korzeniowska, J. Jerzynska and I. Stelmach One-year follow-up of clinical and inflammatory parameters in children allergic to grass pollen receiving high-dose ultrarush sublingual immunotherapy. 2010 (7): 602-6. **Not an RCT**
Pacor, M. L., Biasi, D., Carletto, A., and Lunardi, C. Effectiveness of oral immunotherapy in bronchial asthma caused by Dermatophagoides pternyssinus. Recenti Prog Med 95; 86 (12): 489-91. **Other reason for exclusion (specify): oral IT**
Pacor, M. L., Biasi, D., Carletto, A., Maleknia, T., and Lunardi, C. Oral immunotherapy in oculorhinitis from Gramineae. Recenti Prog Med 96; 87 (1): 4-6. **Other reason for exclusion (specify): oral IT**
Pajno, G. B., Barberio, G., De Luca, F., Morabito, L., and Parmiani, S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001; 31 (9): 1392-7. **It does not meet ALL the inclusion criteria**
Pajno, G. B., Caminiti, L., Vita, D., Barberio, G., Salzano, G., Lombardo, F., Canonica, G. W., and Passalacqua, G. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. J Allergy Clin Immunol 2007; 120 (1): 164-70. **It does not meet ALL the inclusion criteria**topic dermatatis
Pajno, G. B., Peroni, D. G., Vita, D., Pietrobelli, A., Parmiani, S., and Boner, A. L. Safety of sublingual immunotherapy in children with asthma. Paediatr Drugs 2003; 5 (11): 777-81. **Not an RCT**
Palma-Carlos, A. G. and Palma-Carlos, M. L. Trichophyton allergy: review of 89 cases. Eur Ann Allergy Clin Immunol 2006; 38 (6): 177-81. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**
Palma-Carlos, A. G., Palma-Carlos, M. L., Branco-Ferreira, M., Spinola, A., Santos, M. C., and Lopes-Pregral, A. Nasal allergen challenge and immunotherapy control. Allerg Immunol (Paris) 98; 30 (5): 153-6. **Does not apply to any of the key questions**
Palma-Carlos, A. G., Spinola-Santos, A., Ferreira, M. B., Santos, M. C., and Palma-Carlos, M. L. Immunotherapy in allergic rhinitis. Allerg Immunol (Paris) 2001; 33 (8): 323-6. **It does not meet ALL the inclusion criteria - No original data**
Paniagua, M. J., Bosque, M., Asensio, O., Larramona, H., and Marco, M. T. Immunotherapy with acarus extract in children under the age of 5 years. Allergol Immunopathol (Madr) 2002; 30 (1): 20-4. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**
Panzani, R. C., Ariano, R., and Augeri, G. Monitoring of specific IgG4 antibodies in respiratory allergy due to the pollen of Parietaria judaica. Evidence for a protective role. Allergol Immunopathol (Madr) 96; 24 (6): 263-8. **Not an RCT**
Paranos, S., Petrovic, S., and Vojovic, I. Specific skin reactions induced by individual pollen preparations in hypersensitivity persons. Srp Arh Celok Lek 98; 126 (9-10): 362-7. yugoslavia**Non-English article**
Park, H. S., Nahm, D. H., Kim, H. Y., Suh, Y. J., Cho, J. W., Kim, S. S., Lee, S. K., and Jung, K. S. Clinical and immunologic changes after allergen immunotherapy with Hop Japanese pollen. Ann Allergy Asthma Immunol 2001; 86 (4): 444-8. **It does not meet ALL the inclusion criteriaNot an RCT and doesnt include any harms**
Parkash, D., Garg, O. P., and Shivpuri, D. N. Hyposensitization in children with bronchial asthma. Indian J Pediatr 70; 37 (271): 366-72. **It does not meet ALL the inclusion criteria**
Parker, W. A. Jr, Whisman, B. A., Apaliski, S. J., and Reid, M. J. The relationships between late cutaneous responses and specific antibody responses with outcome of immunotherapy for seasonal allergic rhinitis. J Allergy Clin Immunol 89; 84 (5 Pt 1): 667-77. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**
Passalacqua, G. and Canonica, G. W. Sublingual or injection immunotherapy: the final answer?. Allergy 2004; 59 (1): 37-8. **No original data**
Passalacqua, G. Preventive effects of sublingual immunotherapy. Drugs Today (Barc) 2008; 44 Suppl B 83-6. **No original data**
Passalacqua, G. Sublingual immunotherapy: accumulated experience. J Investig Allergol Clin Immunol 97; 7 (5): 364-6. **No original data**
Passalacqua, G., Albano, M., Fregonese, L., Riccio, A., Pronzato, C., Mela, G. S., and Canonica, G. W. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. Lancet 98; 351 (9103): 629-32. **Therapy NOT AVAILABLE in the U.S**
Passalacqua, G., Bagnasco, M., Mariani, G., Falagiani, P., and Canonica, G. W. Local immunotherapy: pharmacokinetics and efficacy. Allergy 98; 53 (5): 477-84. **No original data**
Passalacqua, G., Musarra, A., Pecora, S., Amoroso, S., Antonicelli, L., Cadario, G., Di Gioacchino, M., Lombardi, C., Ridolo, E., Sacerdoti, G., Schiavino, D., and Senna, G. Quantitative assessment of the compliance with once-daily sublingual immunotherapy in children (EASY project: evaluation of a novel SLIT formulation during a year). Pediatr Allergy Immunol 2007; 18 (1): 58-62. **Does not apply to any of the key questions**
Passalacqua, G., Pasquali, M., Ariano, R., Lombardi, C., Giardini, A., Baiardini, I., Majani, G., Falagiani, P., Bruno, M., and Canonica, G. W. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. Allergy 2006; 61 (7): 849-54. **Therapy NOT AVAILABLE in the U.S**
Passali, D., De Seta, E., Masieri, S., and Bellussi, L. Specific local immunotherapy in young allergic

subjects. Acta Otorhinolaryngol Ital 83; 3 (4): 403-8. **It does not meet ALL the inclusion criteria**

Passali, D., De Seta, E., Masieri, S., and Bellussi, L. Specific local immunotherapy in young allergic subjects. Acta Otorhinolaryngol Ital 83; 3 (4): 403-8. **Does not apply to any of the key questionsOther reason for exclusion (specify):**nasal it

Pastorello, E. A., Incorvaia, C., Gerosa, A., Vassellatti, D., Italia, M., and Pravettoni, V. Allergen specific IgG subclass antibody response in hyposensitization with Dermatophagoides pteronyssinus extract. N Engl Reg Allergy Proc 87; 8 (6): 417-21. **It does not meet ALL the inclusion criteria**

Pastorello, E. A., Incorvaia, C., Gerosa, A., Vassellatti, D., Italia, M., and Pravettoni, V. Allergen specific IgG subclass antibody response in hyposensitization with Dermatophagoides pteronyssinus extract. N Engl Reg Allergy Proc 87; 8 (6): 417-21. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

Patriarca, G., Venuti, A., and Bonini, W. Identification of IgG-antibodies in subjects with hay fever before and after specific hyposensitizing treatment. Ann Allergy 73; 31 (5): 223-7. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

Patterson, R. Clinical efficacy of allergen immunotherapy. J Allergy Clin Immunol 79; 64 (3): 155-8. **No original data**

Paty, E., de Blic, J., Brunet, D., Le Bourgeois, M., Garcelon, M., Paupe, J., and Scheinmann, P. Accelerated desensitization with Dermatophagoides pteronyssinus in severe asthmatic children. Evaluation after one year of immunotherapy. Arch Fr Pediatr 90; 47 (3): 173-9. **It does not meet ALL the inclusion criteria**

Paul, K., Klettke, U., and Wahn, U. The combined influence of immunotherapy and mite allergen reduction on bronchial hyperresponsiveness in mite-sensitive asthmatic children. Eur J Pediatr 98; 157 (2): 109-13. **It does not meet ALL the inclusion criteria**

Pauli, G., Guisard, G., Bessot, J. C., and Oudet, P. Development of bronchial tolerance during therapeutic desensitization to dust. Rev Fr Allergol 72; 12 (3): 209-17. **It does not meet ALL the inclusion criteria**

Pegelow, K. O., Belin, L., Broman, P., Heilborn, H., Sundin, B., and Watson, K. Immunotherapy with alginate-conjugated and alum-precipitated grass pollen extracts in patients with allergic rhinoconjunctivitis. Allergy 84; 39 (4): 275-90. **Therapy NOT AVAILABLE in the U.S**

Pence, H. L. and Ward, G. W. Jr The role of injection therapy in allergic asthma. Postgrad Med 75; 57 (3): 137-41. **No original data**

Peng, Z. K. Immunologic changes during hyposensitization with the dust mite Dermatophagoides farinae extract in allergic asthma. Zhonghua Jie He He Hu Xi Xi Ji Bing Za Zhi 85; 8 (4): 207-10, 254-5. **Non-English article**

Peng, Z. K. Immunologic changes during hyposensitization with the dust mite Dermatophagoides farinae extract in allergic asthma. Zhonghua Jie He He Hu Xi Xi Ji Bing Za Zhi 85; 8 (4): 207-10, 254-5. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

Peng, Z. K., Naclerio, R. M., Norman, P. S., and Adkinson, N. F. Jr Quantitative IgE- and IgG-subclass responses during and after long-term ragweed immunotherapy. J Allergy Clin Immunol 92; 89 (2): 519-29. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

Pereira-Santos, M. C., Pregal, A. L., Spinola-Santos, A., Alonso, E., Palma-Carlos, M. L., and Palma-Carlos, A. G. Effect of allergen immunotherapy on soluble adhesion molecules. Allerg Immunol (Paris) 2001; 33 (6): 225-8. **Does not apply to any of the key questions**

Perennial versus preseasonal immunotherapy in the treatment of rhinoconjunctivitis in subjects allergic to grass pollen **Library unable to locate**

Perera, M. G., Bernstein, I. L., Michael, J. G., and Johansson, S. G. Predictability of the radioallergosorbent test (RAST) in ragweed pollenosis. Am Rev Respir Dis 75; 111 (5): 605-10. **Does not apply to any of the key questions**

Perez Martin, J, Moreno, M. A, Valdovinos Aviles, H, and Madariaga Marquez, J. B Inmunoterapia en pediatria con antigenos de allpyral (efectividad clinica).. Alergia Mqx 82; 29 (4): 111-21. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**allpyral

Peroni, D. G., Piacentini, G. L., Martinati, L. C., Warner, J. O., and Boner, A. L. Double-blind trial of house-dust mite immunotherapy in asthmatic children resident at high altitude. Allergy 95; 50 (11): 925-30. **It does not meet ALL the inclusion criteria**

Perrin, L. F., Sroussi, J., Cea-Gil, F., Deviller, P., and Lasne, Y. Serum IgE levels and specific IgE antibodies in house dust mite allergy: predictive value. J Asthma 83; 20 (2): 93-6. **Does not apply to any of the key questions**

Petersen, K. D., Gyrd-Hansen, D., and Dahl, R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. Allergol Immunopathol (Madr) 2005; 33 (6): 296-302. **Does not apply to any of the key questions**

Petersen, K. D., Gyrd-Hansen, D., and Dahl, R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. Allergol Immunopathol (Madr) 2005; 33 (6): 296-302. **It does not meet ALL the inclusion criteria no** controls

Petersen, K. D., Gyrd-Hansen, D., Linneberg, A., Dahl, R., Larsen, J. N., Lowenstein, H., and Kronborg, C. Willingness to pay for allergy-vaccination among Danish patients with respiratory allergy. Int J Technol Assess Health Care 2010; 26 (1): 20-9. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

Petersen, K. D., Kronborg, C., Gyrd-Hansen, D., Dahl, R., Larsen, J. N., and Linneberg, A. Characteristics of

patients receiving allergy vaccination: to which extent do socio-economic factors play a role?. Eur J Public Health 2010; **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

Petri, E., Austgen, M., and Trendelenburg, F. House dust mite allergy and allergic bronchial asthma (II). Clinical aspects of house dust mite allergy and specific therapy in sensitization against house dust mites. ZFA (Stuttgart) 81; 57 (13): 973-9. **No original data**

Petrovskaia, I. A., Bobkova, L. P., Evseeva, T. A., Kostiuk, A. G., and Glinskii, V. V. A clinical evaluation of different schedules for specific immunotherapy and a comparative analysis of the changes in immunity in pollinosis. Ter Arkh 89; 61 (12): 56-60. **Not an RCT**

Pfaar, O., Klimek, L., Fischer, I., Sieber, J., Amoroso, S., Moreno Aguilar, C., Shah, K., and Mosges, R. Safety of two cluster schedules for subcutaneous immunotherapy in allergic rhinitis or asthma patients sensitized to inhalant allergens. Int Arch Allergy Immunol 2009; 150 (1): 102-8. **It does not meet ALL the inclusion criteria no** controls

Pfaar, O., Mosges, R., Hormann, K., and Klimek, L. Cluster immunotherapy of persistent allergic rhinoconjunctivitis. Safety aspects of induction therapy with mite depot allergen preparations. HNO 2009; 57 (11): 1099-105. German **Non-English article**

Pfaar, O., Mosges, R., Hormann, K., and Klimek, L. Safety aspects of Cluster immunotherapy with semi-depot allergen extracts in seasonal allergic rhinoconjunctivitis. Eur Arch Otorhinolaryngol 2010; 267 (2): 245-50. **Not an RCT**

Pham-Thi, N., Scheinmann, P., Fadel, R., Combebias, A., and Andre, C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. Pediatr Allergy Immunol 2007; 18 (1): 47-57. **Therapy NOT AVAILABLE in the U.S**

Phelan, P. D. Dangers of immunotherapy for the treatment of asthma in children. Med J Aust 90; 153 (6): 367. **Other reason for exclusion (specify): letter**

PHILIPPE, J. ON CERTAIN ASPECTS WHICH A SENSITIZATION PROCESS MAY ASSUME.. Clinique (Paris) 63; 58 495-7. **No original data - Non-English article**

PHILIPPE, J. ON CERTAIN ASPECTS WHICH A SENSITIZATION PROCESS MAY ASSUME.. Clinique (Paris) 63; 58 495-7. **Non-English article**

Piazza I Comparison between immunotherapy and stemizole in the treatment of seasonal allergic rhinitis. Allergy ; **No original data**

Pichler, C. E., Helbling, A., and Pichler, W. J. Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. Allergy 2001; 56 (4): 301-6. **It does not meet ALL the inclusion criteria**pre-post data only

Pilette C, Nouri Aria KT, Jacobson MR, and and Durham SR Seasonal increases in interleukin-9 expression and in mast cell infiltration of the nasal mucosa in allergic rhinitis are inhibited by grass pollen immunotherapy. XXII Congress of the European Academy of Allergology and Clinical Immunology (EAACI) 2003; Paris, **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions**

Pilette C, Nouri Aria KT, Jacobson MR, and and Durham SR Seasonal increases in interleukin-9 expression and in mast cell infiltration of the nasal mucosa in allergic rhinitis are inhibited by grass pollen immunotherapy. XXII Congress of the European Academy of Allergology and Clinical Immunology (EAACI) 2003; Paris, **It does not meet ALL the inclusion criteria**

Pilette, C., Nouri-Aria, K. T., Jacobson, M. R., Wilcock, L. K., Detry, B., Walker, S. M., Francis, J. N., and Durham, S. R. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. J Immunol 2007; 178 (7): 4658-66. **Does not apply to any of the key questions**

Pilette, C., Nouri-Aria, K. T., Jacobson, M. R., Wilcock, L. K., Detry, B., Walker, S. M., Francis, J. N., and Durham, S. R. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. J Immunol 2007; 178 (7): 4658-66. **It does not meet ALL the**

Pinkawa, E. Effect of specific desensitization on serum concentration of protein fractions and immunoglobulins in children with asthma and pollinosis. Pol Tyg Lek 78; 33 (2): 61-3. **Does not apply to any of the key questions polishNon-English article**

Platts-Mills, T. A. Allergen-specific treatment for asthma: III. Am Rev Respir Dis 93; 148 (3): 553-5. **No original data (specify):Editorial**

Platts-Mills, T. A. Ragweed immunotherapy in adult asthma. N Engl J Med 96; 335 (3): 204; author reply 205-6. **No original data**

Plavsic, Z., Petrovic, M., and Popovac, D. Real effect of specific hyposensitisation in therapy of allergic respiratory diseases. Srp Arh Celok Lek 94; 122 (7-8): 210-1. **Russian Non-English article**

Plewako, H., Arvidsson, M., Oancea, I., Hasseus, B., Dahlgren, U., and Rak, S. The effect of specific immunotherapy on the expression of costimulatory molecules in late phase reaction of the skin in allergic patients. Clin Exp Allergy 2004; 34 (12): 1862-7. **It does not meet ALL the inclusion criteria**

Plewako, H., Arvidsson, M., Oancea, I., Hasseus, B., Dahlgren, U., and Rak, S. The effect of specific immunotherapy on the expression of costimulatory molecules in late phase reaction of the skin in allergic patients. Clin Exp Allergy 2004; 34 (12): 1862-7. **Other reason for exclusion (specify): mech**

Plewako, H., Holmberg, K., Oancea, I., Gotlib, T., Samolinski, B., and Rak, S. A follow-up study of immunotherapy-treated birch-allergic patients: effect on the expression of chemokines in the nasal mucosa. Clin Exp Allergy 2008; 38 (7): 1124-31. **It does not meet ALL the inclusion criteria**

Pokladnikova J, Krcmova I, and Vlcek J Economic evaluation of sublingual vs subcutaneous allergen immunotherapy (Brief record). Annals of Allergy, Asthma and Immunology ; **It does not meet ALL the inclusion criteria**

Pokladnikova J, Krcmova I, and Vlcek J Economic evaluation of sublingual vs subcutaneous allergen immunotherapy (Brief record). Annals of Allergy, Asthma and Immunology ; **It does not meet ALL the inclusion criteria**sthma not reportedly confirmed with PFTs; dose and units not specified (unsure if there is a parent article)

Polosa, R. Can immunotherapy prevent progression to asthma in allergic individuals?. J Allergy Clin Immunol 2002; 110 (4): 672-3; author reply 273. **Other reason for exclusion (specify):**Corresp **No original data**

Polosa, R., Al-Delaimy, W. K., Russo, C., Piccillo, G., and Sarva, M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective Cohort study. Respir Res 2005; 6 153. **Not an RCT**

Poncelet-Maton, E., Radermecker, M., and Salmon, J. Blood histamine levels in allergology: effect of specific desensitization and of animal immunization. Rev Med Liege 75; 30 (17): 563-6. **Does not apply to any of the key questions - No SIT**

Portnoy, J. M. and Finegold, I. Ragweed immunotherapy in adult asthma. N Engl J Med 96; 335 (3): 203-4; author reply 205-6. **Other reason for exclusion (specify): letter**

Portnoy, J., King, K., Kanarek, H., and Horner, S. Incidence of systemic reactions during rush immunotherapy. Ann Allergy 92; 68 (6): 493-8. **Not an RCT**

Pqrez Martin, Jes s Utilidad de la inmunoterapia en el asma. Alergia Mqx 98; 45 (5): 117-8. **No original data**

Pre-seasonal Specific Immunotherapy in rhino-conjunctivitis versus Placebo Abstract **Meeting Abstract**

Prigal, S. J. A ten-year study of repository injections of allergens: local reactions and their management. Ann Allergy 72; 30 (9): 529-35. **Not an RCT**

Prigal, S. J., Stern, A., Avedon, A. B., Franklin, H. L., Hilton, D. W., and Furman, M. L. The treatment of pollinosis with small doses of emulsions of ironated ragweed extract. Ann Allergy 65; 23 (9): 414-21. **It does not meet ALL the inclusion criteria**

Pronk-Admiraal, C. J., Schilte, P. P., and Bartels, P. C. Effect of immunotherapy on eosinophil activation in pollen sensitive children. Clin Lab 2001; 47 (5-6): 231-8. **Does not apply to any of the key questions**

Pumhirun, P., Tuchinda, S., Nondavanich, A., Jarujinda, S., and Poommark, C. Immunological and clinical evaluation during a 12 month period of immunotherapy. Asian Pac J Allergy Immunol 94; 12 (2): 111-5. **Not an RCT**

Purello-D'Ambrosio, F., Gangemi, S., Merendino, R. A., Isola, S., Puccinelli, P., Parmiani, S., and Ricciardi, L. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 2001; 31 (8): 1295-302. **Not an RCT**

Purohit, A., Niederberger, V., Kronqvist, M., Horak, F., Gronneberg, R., Suck, R., Weber, B., Fiebig, H., van Hage, M., Pauli, G., Valenta, R., and Cromwell, O. Clinical effects of immunotherapy with genetically modified recombinant birch pollen Bet v 1 derivatives. Clin Exp Allergy 2008; 38 (9): 1514-25. **Therapy NOT AVAILABLE in the U.S**

Purser, J. R. Treatment of hay fever in general practice by hyposensitization, using 'Pollinex'. Curr Med Res Opin 76; 4 (2): 124-7. **Therapy NOT AVAILABLE in the U.S**

Quality of Life and Symptoms assessment in sublingual immunotherapy for patients with house-dust mite related perennial rhinitis: definition of a responder profile **Library unable to locate**

R. A. Rahman Mahdy, W. M. Nada and A. A. Marei Subcutaneous allergen-specific immunotherapy versus topical treatment in vernal keratoconjunctivitis. Cornea 2012 31 (5): 525-528. **Does not apply to any of the key questions Other reason for exclusion (specify):vernal keratoconjunctivitis, which is not a condition that we have included in our study. The only types of conjunctivitis included in our study are seasonal and perennial allergic conjunctivitis.**

R. Mösges, V. Graute, H. Christ, H. J. Sieber, U. Wahn and B. Niggemann Safety of ultra-rush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy. 2010 (8): 1135-8. **It does not meet ALL the inclusion criteria no interval and no cumulative dose**

RACKEMANN, F. M. and LAMSA, T. THE NATURAL HISTORY OF RAGWEED HAY FEVER; A TWENTY-YEAR STUDY OF 120 PATIENTS. J Allergy Clin Immunol 65; 36 258-64. **Not an RCT**

RACKEMANN, F. M. PRINCIPLES OF SPECIFIC DESENSITIZATION TO POLLEN. Acta Allergol 64; 19 197-206. **Therapy NOT AVAILABLE in the U.S**

Radcliffe, M. J., Lewith, G. T., Turner, R. G., Prescott, P., Church, M. K., and Holgate, S. T. Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study. BMJ 2003; 327 (7409): 251-4. **Therapy NOT AVAILABLE in the U.S**

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Ragusa, F. V., Passalacqua, G., Gambardella, R., Campanari, S., Barbieri, M. M., Scordamaglia, A., and Canonica, G. W. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol 97; 7 (3): 151-4. **Other reason for exclusion (specify):**retrospective**Not an RCT**
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Railey, M. D., Adair, M. A., and Burks, A. W. Allergen immunotherapy for allergic rhinitis. Curr Allergy Asthma Rep 2008; 8 (1): 1-3. **No original data**
Rak, S. Effects of immunotherapy on the inflammation in pollen asthma. Allergy 93; 48 (17 Suppl): 125-8; discussion 143-4. **It does not meet ALL the inclusion criteria**
Rak, S. Quality of life (QoL): impact of specific immunotherapy (SIT) on social and physical ability. Drugs Today (Barc) 2008; 44 Suppl B 35-8. **No original data**
Rak, S., Bjornson, A., Hakanson, L., Sorenson, S., and Venge, P. The effect of immunotherapy on eosinophil accumulation and production of eosinophil chemotactic activity in the lung of subjects with asthma during natural pollen exposure. J Allergy Clin Immunol 91; 88 (6): 878-88. **It does not meet ALL the inclusion criteria**
Rak, S., Hakanson, L., and Venge, P. Immunotherapy abrogates the generation of eosinophil and neutrophil chemotactic activity during pollen season. J Allergy Clin Immunol 90; 86 (5): 706-13. **It does not meet ALL the inclusion criteria**
Rak, S., Hakansson, L., and Venge, P. Eosinophil chemotactic activity in allergic patients during the birch pollen season: the effect of immunotherapy. Int Arch Allergy Appl Immunol 87; 82 (3-4): 349-50. **Does not apply to any of the key questions**
Rak, S., Hallden, G., Sorenson, S., Margari, V., and Scheynius, A. The effect of immunotherapy on T-cell subsets in peripheral blood and bronchoalveolar lavage fluid in pollen-allergic patients. Allergy 93; 48 (6): 460-5. **Other reason for exclusion (specify): mech**
Rak, S., Lowhagen, O., and Venge, P. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. J Allergy Clin Immunol 88; 82 (3 Pt 1): 470-80. **It does not meet ALL the inclusion criteria**
Ramaiah, R. S., Gallagher, M. A., and Biagi, R. W. House dust mite allergy and hyposensitisation. A retrospective study. Br J Clin Pract 80; 34 (10): 282-3. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):**allpyral
Randhawa, I. S., Junaid, I., and Klaustermeyer, W. B. Allergen immunotherapy in a patient with human immunodeficiency virus: effect on T-cell activation and viral replication. Ann Allergy Asthma Immunol 2007; 98 (5): 495-7. **It does not meet ALL the inclusion criteria**
Randomized double-blind trial of a combination of cromoglycate disodium administration and specific desensitization treatment in adults with perennial extrinsic asthma and nonspecific bronchial hyperreactivity. **Library unable to locate**
Rank, M. A., Oslie, C. L., Krogman, J. L., Park, M. A., and Li, J. T. Allergen immunotherapy safety: characterizing systemic reactions and identifying risk factors. Allergy Asthma Proc 2008; 29 (4): 400-5. **It does not meet ALL the inclusion criteria**
Ransom, J. H. Clinical and laboratory evaluation of alum-precipitated ragweed extract. Ann Allergy 70; 28 (5): 221-6. **Does not apply to any of the key questions**. **It does not meet ALL the inclusion criteria**
RAPAPORT, H. G. THE VALUE OF HYPOSENSITIZATION IN THE TREATMENT OF POLLEN ALLERGY IN CHILDREN. J Asthma Res 64; 15 257-60. **No original data**
RAPAPORT, H. G. THE VALUE OF HYPOSENSITIZATION IN THE TREATMENT OF POLLEN ALLERGY IN CHILDREN. J Asthma Res 64; 15 257-60. **Other reason for exclusion (specify): review**
Razzouk, H. and Fay, A. A case of generalized accident caused by pollen sensitization. Mars Med 72; 109 (6): 445-8. **Not an RCT**
Rebien, W., Puttonen, E., Maasch, H. J., Stix, E., and Wahn, U. Clinical and immunological response to oral and subcutaneous immunotherapy with grass pollen extracts. A prospective study. Eur J Pediatr 82; 138 (4): 341-4. **It does not meet ALL the inclusion criteria**
Reha, C. M. and Ebru, A. Specific immunotherapy is effective in the prevention of new sensitivities. Allergol Immunopathol (Madr) 2007; 35 (2): 44-51. **Not an RCT**
Reich, M., Zwacka, G., and Markert, U. R. Nonspecific plasma proteins during sublingual immunotherapy. Chem Immunol Allergy 2003; 82 99-108. **Does not apply to any of the key questions**
Reid, M. J., Schwietz, L. A., Whisman, B. A., and Moss, R. B. Mountain cedar pollinosis: can it occur in non-atopics?. N Engl Reg Allergy Proc 88; 9 (3): 225-32. **Does not apply to any of the key questions**
Reisman, R. E. and Arbesman, C. E. Clinical and immunological studies following immunotherapy with aqueous and alum precipitated reagweed fraction A. Int Arch Allergy Appl Immunol 73; 44 (2): 161-70. **Therapy NOT AVAILABLE in the U.S**
Reisman, R. E., Wypych, J. I., and Arbesman, C. E. Relationship of immunotherapy, seasonal pollen exposure and clinical response to serum concentrations of total IgE and ragweed-specific IgE. Int Arch Allergy Appl Immunol 75; 48 (6): 721-30. **It does not meet ALL the inclusion criteria**
Relyveld, E. H., Henocq, E., Philippe, J., Meaume, J. E., Cousin, J., Fanet, G., and Raynaud, M. Purified and on aluminum hydroxide adsorbed dust in specific

desensitization treatments. Rev Fr Allergol 68; 8 (2): 81-90. **Therapy NOT AVAILABLE in the U.S**
Rennie, A. G., Cant, J. S., Foulds, W. S., Pennington, T. H., and Timbury, M. C. Ocular vaccinia. Lancet 74; 2 (7875): 273-5. **No SIT**
Rennie, A. G., Cant, J. S., Foulds, W. S., Pennington, T. H., and Timbury, M. C. Ocular vaccinia. Lancet 74; 2 (7875): 273-5. **Does not apply to any of the key questions No SIT**
Renovanz, B. H. Allergic bronchopneumopathies and immunotherapy. Med Monatsschr 76; 30 (3): 121-2. **Other reason for exclusion (specify): review**
Renz, H. Immunotherapy in broad allergy spectrum. Dtsch Med Wochenschr 2002; 127 (23): 1274-5. **No original data**
Report by the Federal Society of Pneumologists. Allergic bronchial asthma: chances for hyposensitization. MMW Fortschr Med 99; 141 (27): 43-4. **No original data**
Reyes Moreno, A., Castrejon Vazquez, M. I., and Miranda Feria, A. J. Failure of allergen-based immunotherapy in adults with allergic asthma. Rev Alerg Mex 2003; 50 (1): 8-12. **Not an RCT**
Rhinitis allergica due to house dust mite in children: long lasting effect of sublingual immunotherapy **Library unable to locate**
Rhinitis. Journal of Investigational Allergology and Clinical Immunology 2010 20 (SUPPL. 1): 37-42. **No original data**
Ricca, V., Ciprandi, G., Pesce, G., Riccio, A., Varese, P., Pecora, S., and Canonica, G. W. Preseasonal specific immunotherapy with modified Phleum pratense allergenic extracts: tolerability and effects. Allergol Immunopathol (Madr) 97; 25 (4): 167-75. **Therapy NOT AVAILABLE in the U.S**
Richter, I. and Kriebel, I. Allergic reactions to the house-dust mite in children with obstructive disease of the respiratory tract (author's transl). Med Klin 75; 70 (37): 1484-7. **It does not meet ALL the inclusion criteria**
Richter, I. and Oehme, J. Experiences with cutaneous allergy testing and specific hyposensitization in routine pediatric hospital practice. Monatsschr Kinderheilkd 72; 120 (10): 410-2. **It does not meet ALL the inclusion criteria**
Rieckenberg, M. R., Khan, R. H., and Day, J. H. Physician reported patient response to immunotherapy: a retrospective study of factors affecting the response. Ann Allergy 90; 64 (4): 364-7. **It does not meet ALL the inclusion criteria**
Rienzo, V. D., Minelli, M., Musarra, A., Sambugaro, R., Pecora, S., Canonica, W. G., and Passalacqua, G. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. Clin Exp Allergy 2005; 35 (5): 560-4. **Other reason for exclusion (specify):**Survey
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Rivlin, J., Kuperman, O., Freier, S., and Godfrey, S. Suppressor T-lymphocyte activity in wheezy children with and without treatment by hyposensitization. Clin Allergy 81; 11 (4): 353-6. **It does not meet ALL the inclusion criteria**
Robinson, J. and Brigden, W. Recurrent pericarditis. Br Med J 68; 2 (5600): 272-5. **No SIT**
Rocha, E. M. Effect of 2 therapeutic protocols in minor forms of respiratory allergy. Allerg Immunol (Paris) 86; 18 (2): 29-41. **It does not meet ALL the inclusion criteria**
Rocklin, R. E. Clinical and immunologic aspects of allergen-specific immunotherapy in patients with seasonal allergic rhinitis and/or allergic asthma. J Allergy Clin Immunol 83; 72 (4): 323-38. **No original data**
Rocklin, R. E., Sheffer, A. L., Greineder, D. K., and Melmon, K. L. Generation of antigen-specific suppressor cells during allergy desensitization. N Engl J Med 80; 302 (22): 1213-9. **Other reason for exclusion (specify): mech**
Roder, A., Darrelmann, N., Klingenberg, W., Krull, M., Suttorp, N., and Noga, O. Simultaneous SCIT with 2 separate allergen extracts demonstrates comparable safety compared to SCIT with a single allergen extract. J Investig Allergol Clin Immunol 2009; 19 (6): 512-3. **It does not meet ALL the inclusion criteria**
Roder, E., Berger, M. Y., de Groot, H., and Gerth van Wijk, R. Sublingual immunotherapy in youngsters: adherence in a randomized clinical trial. Clin Exp Allergy 2008; 38 (10): 1659-67. **Does not apply to any of the key questions**
Rodriguez Medina, R., Lopez Duran, J. L., Gasca Bauza, M. R., Cortez Gonzalez, E., and Zamora Limon, E. Effect of immunotherapy with allergens in asthmatic children with integral treatment. Rev Alerg Mex 2000; 47 (5): 162-5. **Not an RCT**
Rodriguez Perez, N. and Ambriz Moreno Mde, J. Safety of immunotherapy and skin tests with allergens in children younger than five years. Rev Alerg Mex 2006; 53 (2): 47-51. **It does not meet ALL the inclusion criteriaNot an RCT**
Rodriguez Santos, O. Sublingual immunotherapy with allergenic extract of Dermatophagoides pteronyssinus in asthmatic children. Rev Alerg Mex 2004; 51 (5): 177-80. **Other reason for exclusion (specify):**Spanish-rct **Non-English article**
Rodriguez-Perez, N., Ambriz-Moreno Mde, J., Canonica, G. W., and Penagos, M. Frequency of acute systemic reactions in patients with allergic rhinitis and asthma treated with sublingual immunotherapy. Ann Allergy Asthma Immunol 2008; 101 (3): 304-10. **Not an RCT**
Rogala, B. and Gluck, J. Allergen-specific IgE in circulating immune complexes in patients with inhalant allergy undergoing specific immunotherapy. J Investig Allergol Clin Immunol 99; 9 (3): 183-9. **Does not apply to any of the key questions**
Rogala, B., Gumprecht, J., Gawlik, R., and Strojek, K. Platelet aggregation in IgE-mediated allergy with elevated soluble Fc epsilon RII/CD23 level. J Investig Allergol Clin Immunol 95; 5 (3): 161-5. **Does not apply to any of the key questions- Therapy NOT AVAILABLE in the U.S**

Rogala, B., Jarzab, J., Karawajczyk, M., Jawor, B., and Rogala, E. Effect of specific immunotherapy on IgE immune complexes in seasonal allergic rhinitis. Pneumonol Alergol Pol 92; 60 Suppl 1 57-62. **Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):tyrosine-absorbed**

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Roger, A., Justicia, J. L., Navarro, L. A., Eseverri, J. L., Ferres, J., Malet, A., and Alva, V. Observational Study of the Safety of an Ultra-Rush Sublingual Immunotherapy Regimen to Treat Rhinitis due to House Dust Mites. Int Arch Allergy Immunol 2010; 154 (1): 69-75. **It does not meet ALL the inclusion criteria**

Rohatgi, N., Dunn, K., and Chai, H. Cat- or dog-induced immediate and late asthmatic responses before and after immunotherapy. J Allergy Clin Immunol 88; 82 (3 Pt 1): 389-97. **It does not meet ALL the inclusion criteria**

Rolinck-Werninghaus, C., Hamelmann, E., Keil, T., Kulig, M., Koetz, K., Gerstner, B., Kuehr, J., Zielen, S., Schauer, U., Kamin, W., Von Berg, A., Hammermann, J., Weinkauf, B., Weidinger, G., Stenglein, S., and Wahn, U. The co-seasonal application of anti-IgE after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. Allergy 2004; 59 (9): 973-9. **Does not apply to any of the key questions**

Rolinck-Werninghaus, C., Kopp, M., Liebke, C., Lange, J., Wahn, U., and Niggemann, B. Lack of detectable alterations in immune responses during sublingual immunotherapy in children with seasonal allergic rhinoconjunctivitis to grass pollen. Int Arch Allergy Immunol 2005; 136 (2): 134-41. **It does not meet ALL the inclusion criteria** . **Does not apply to any of the key questions**

Romanski, B., Pawlik, K., and Wilawska-Klubo, T. The advances of hyposensibilisation therapy in bronchial asthma patients allergic to house dust antigen. Allerg Immunol (Leipz) 77; 23 (3): 211-3. **Does not apply to any of the key questions**

Romo, A., Lorente, F., Romo, M. T., Garcia, M. J., and Lorenzo, C. Oral immunotherapy versus parenteral immunotherapy. Allergol Immunopathol (Madr) 96; 24 Suppl 1 92-103. **Other reason for exclusion (specify): oral IT**

Rose, G., Arlian, L., Bernstein, D., Grant, A., Lopez, M., Metzger, J., Wasserman, S., and Platts-Mills, T. A. Evaluation of household dust mite exposure and levels of specific IgE and IgG antibodies in asthmatic patients enrolled in a trial of immunotherapy. J Allergy Clin Immunol 96; 97 (5): 1071-8. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions Not an RCT**

Rose, G., Arlian, L., Bernstein, D., Grant, A., Lopez, M., Metzger, J., Wasserman, S., and Platts-Mills, T. A. Evaluation of household dust mite exposure and levels of specific IgE and IgG antibodies in asthmatic patients enrolled in a trial of immunotherapy. J Allergy Clin Immunol 96; 97 (5): 1071-8. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions Not an RCT**

Rossi, R. E. and Monasterolo, G. Evaluation of recombinant and native timothy pollen (rPhl p 1, 2, 5, 6, 7, 11, 12 and nPhl p 4)- specific IgG4 antibodies induced by subcutaneous immunotherapy with timothy pollen extract in allergic patients. Int Arch Allergy Immunol 2004; 135 (1): 44-53. **Does not apply to any of the key questions**

Rossi, R. E., Monasterolo, G., Coco, G., and Operti, D. Possible relationship between systemic side effects and sensitization to rPar j 2 in allergic patients submitted to an ultra-rush (20 min) sublingual immunotherapy and selected by component resolved diagnosis. Int Arch Allergy Immunol 2005; 138 (2): 105-10. **It does not meet ALL the inclusion criteria**

Rotne, H. Very late reactions to allergen-specific immunotherapy caused by physical exercise. Allergy 2000; 55 (2): 194. **It does not meet ALL the inclusion criteriaNot an RCT**

Ruiz de Leon Loriga, J., Lluch Perez, M., Valero Santiago, A., Zamorano Calderon, M., Huguet Casals, J., Malet Casajuana, A., and Garcia Calderon, P. A. Evaluation of immune parameters (including specific IgG4) during immunotherapy. Allergol Immunopathol (Madr) 89; 17 (3): 119-27. **Does not apply to any of the key questions**

Rumpold, H., Jarolim, E., Bonitz, W., Tejkl, M., Breitenbach, M., Scheiner, O., and Kraft, D. IgE and IgG antibody response in patients with type I allergy to birch pollen. Wien Klin Wochenschr 89; 101 (3): 107-10. **Does not apply to any of the key questions Other reason for exclusion (specify):**healthy controls

Rush allergen subcutaneous immunotherapy administered with infusion pump **Meeting abstract**

Rush sublingual immunotherapy in Parietaria allergic patients **Duplicate** of 1333

S. Barberi, M. P. Villa, G. B. Pajno, F. La Penna, M. Barreto, P. Cardelli, R. Amodeo, F. Tabacco, L. Caminiti and G. Ciprandi Immune response to sublingual immunotherapy in children allergic to mites. J Biol Regul Homeost Agents 2011 25 (4): 627-34. **Not an RCT**

S. G. Hendrix, R. Patterson, C. R. Zeiss, J. J. Pruzansky, I. M. Suszko, R. C. McQueen, R. G. Slavin, M. P. Miller, P. L. Lieberman and A. L. Sheffer A multi-institutional trial of polymerized whole ragweed for immunotherapy of ragweed allergy. J Allergy Clin Immunol 1980 66 (6): 486-94. **Not an RCT**

S. T. Shulman Allergies, allergies. Pediatric Annals 2011 40 (4): 177-178. **It does not meet ALL the inclusion criteria**

Sabbah, A., Bonnaud, F., Sonneville, A., Bonneau, J. C., and Pinon, H. Specific immunotherapy using Alpha-Fraction-Retard-D. pteronyssinus. Double-blind study in asthma. Allerg Immunol (Paris) 91; 23 (2): 58-60. french**Non-English article**

Sadan, N., Rhyne, M. B., Mellits, E. D., Goldstein, E. O., Levy, D. A., and Lichtenstein, L. M. Immunotherapy of pollinosis in children: investigation of the immunologic basis of clinical improvement. N Engl J Med 69; 280 (12): 623-7. **It does not meet ALL the inclusion criteria**

Sade, K., Berkun, Y., Dolev, Z., Shalit, M., and Kivity, S. Knowledge and expectations of patients receiving aeroallergen immunotherapy. Ann Allergy Asthma Immunol 2003; 91 (5): 444-8. **It does not meet ALL the inclusion criteria**

Sade, K., Kivity, S., Levy, A., and Fireman, E. The effect of specific immunotherapy on T-cell receptor repertoire in patients with allergy to house-dust mite. Allergy 2003; 58 (5): 430-4. **Does not apply to any of the key questions**

Safefy of cluster schedule for immunotherapy in allergic rinithis or asthma in children sensitised to grass pollen **Meeting abstract**

Safety and compliance of cluster-immunotherapy achieving the maintenance dose on the first treatment day with highly polymerised allergen extracts **Meeting abstract**

Safety and efficacy of Juniperus ashei sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis. A double-blind, placebo-controlled study **Duplicate** of 5825

Safety and efficacy of perennial immunotherapy with a depot vaccine in patients suffering from asthma and/or allergic rhinitis hypersensitive to alternaria tenius **Library unable to locate**

Salvaggio, J. E. Allergenic extract immunotherapy. Chest 86; 90 (5 Suppl): 53S-57S. **No original data**

SALVAGGIO, J. E. and LESKOWITZ, S. A COMPARISON OF THE IMMUNOLOGIC RESPONSES OF NORMAL AND ATOPIC INDIVIDUALS TO PARENTERALLY INJECTED, ALUM PRECIPITATED PROTEIN ANTIGEN. Int Arch Allergy Appl Immunol 65; 26 264-79. **Therapy NOT AVAILABLE in the U.S**

Salzano, F. A. Specific nasal provocation test with powder allergen. Allergy 97; 52 (33 Suppl): 32-5. **It does not meet ALL the inclusion criteria**

Salzano, F. A. Specific nasal provocation test with powder allergen. Allergy 97; 52 (33 Suppl): 32-5. **Therapy NOT AVAILABLE in the U.S**

Sanchez Palacios, A., Schamann Medina, F., Lamas Rua-Figueroa, A., Bosch Millares, C., Ramos Santos, S., and Garcia Marrero, J. A. Comparative clinical-immunological study of oral and subcutaneous immunotherapy in children with extrinsic bronchial asthma. Allergol Immunopathol (Madr) 89; 17 (6): 323-9. **It does not meet ALL the inclusion criteria**

Sanchez Palacios, A., Schamann, F., and Garcia, J. A. Sublingual immunotherapy with cat epithelial extract. Personal experience. Allergol Immunopathol (Madr) 2001; 29 (2): 60-5. **Not an RCT**

Sanchez-Morillas, L., Reano Martos, M., Iglesias Cadarso, A., Perez Pimiento, A., Rodriguez Mosquera, M., and Dominguez Lazaro, A. R. Vasculitis during immunotherapy treatment in a patient with allergy to Cupressus arizonica. Allergol Immunopathol (Madr) 2005; 33 (6): 333-4. **It does not meet ALL the inclusion criteria**

Sandberg, E. T. Immunotherapy for dust mite sensitivity. Hosp Pract (Minneap) 2000; 35 (3): 45. **No original data**

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Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and

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Side effects during immunotherapy with purified grass pollen extracts **Part of** 4181
Sieber J, Merk H, and and Ott H Seasonal sublingual immunotherapy is efficacious in allergic rhinitis from the first treatment season on also under high grass pollen exposure: the ECRIT study. XXVII EAACI Congress of the European Academy of Allergology and Clinical Immunology 2008; Barcelona, **Other reason for exclusion (specify):**mtg abst only
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Specific immunotherapy for rhinoconjunctivitis to grass pollens by the sub-lingual route: A double-blind study against placebo **Library unable to locate**

Specific immunotherapy improves the clinical response in patients with allergic rhinoconjunctivitis **Meeting abstract**

Specific immunotherapy in grass-pollen allergic asthma combination with inhaled steroid therapy vs specific immunotherapy alone. **Library unable to locate**

Specific immunotherapy with delayed release D. Pteronyssinus alpha fraction. A double blind study in asthma **Duplicate** of 4919

Specific immunotherapy with tablets. Krankenpfl J 2005; 43 (7-10): 260. **No original data**

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Spiegelman, J., Tuft, L., and Friedman, H. Hemagglutination titer changes of pollinosis patients treated with alum-precipitated pyridine ragweed extract. Int Arch Allergy Appl Immunol 67; 32 (1): 27-30. **Does not apply to any of the key questions**

Spinozzi, F., Cimignoli, E., Broccucci, L., Gerli, R., Cernetti, C., and Rambotti, P. Immunotherapy in allergic diseases. Evaluation of short-term efficacy of aluminum hydroxide-absorbed slow-release preparations. Clin Ter 91; 136 (4): 245-51. **Not an RCT**

Squillace, S. P. Immunotherapy in adult asthma. J Fam Pract 96; 42 (5): 455. **No original dataOther reason for exclusion (specify):journal club review of Peter's NEJM 1996 article**

Stammberger, H. The treatment of housedustmite-allergy-three years' experience with hyposensitization with D.pteronyssinus-Preparations (D.P.) (author's transl). Laryngol Rhinol Otol (Stuttg) 80; 59 (12): 820-8. **Therapy NOT AVAILABLE in the U.S**

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Stasiak-Barmuta, A., Dabrowska, I., Piotrowska, T., and Hofman, J. Study on specific immunotherapy with the aid of 3M Diagnostic Systems' tests. Pneumonol Alergol Pol 92; 60 Suppl 1 53-6. **Does not apply to any of the key questions- Other reason for exclusion (specify): mech**s

Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics **Excluded at data abstraction**

STEVENET, M. ASTHMA AND ASTHMA-LIKE CHRONIC BRONCHITIS IN THE ELDERLY SUBJECT. COMPARATIVE VALUE OF SPECIFIC DESENSITIZATION.. Toulouse Med 63; 64 773-80. **It does not meet ALL the inclusion criteria**

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Stevens, W. J., Verhelst, J. A., van den Bogaert, W., and Bridts, C. H. Clinical and biological evaluation of semi-rush and ordinary immunotherapy schemes in type I allergic respiratory diseases. Allergy 85; 40 (6): 447-52. **It does not meet ALL the inclusion criteria**

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Strimas, J. Asthma in children. N Engl J Med 92; 327 (16): 1174-5. **No original data**

Strimas, J. Asthma in children. N Engl J Med 92; 327 (16): 1174-5. **No original data**

Study of Desensitization Treatment on Bronchial Asthma **Library unable to locate**

Study of prolonged hyposensitization with D. pteronyssinus extract in allergic rhinitis **Excluded at data abstraction**

Sublingual allergoid immunotherapy with a 4-day updosing phase versus traditional initial scheme, or drugs alone. A controlled, randomised study in rhinitic patients with or without mild allergic asthma **Library unable to locate**

Sublingual immunotherapy (SLIT) with grass pollen allergen for grasspollen induced rhinoconjunctivitis in children **Meeting abstract**

Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial **Part of 4243**

Sublingual immunotherapy in allergic rhinitis and asthma in 2-5 year-old children sensitized to mites **Duplicate of 4990**

Sublingual immunotherapy in alternaria-induced rhinitis **Meeting abstract**

Sublingual immunotherapy in Parietaria pollen-induced rhinitis: a double-blind study **Excluded at data abstraction**

Sublingual immunotherapy in the treatment of allergic asthma in children: a controlled study **Library unable to locate**

Sublingual Immunotherapy with House Dust Extract for House Dust-Mite Allergic Rhinitis in Children **Excluded at data abstraction**

Sublingual immunotherapy: a double-blind, placebo-controlled trial with Parietaria judaica extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both **Duplicate** of 4573

Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study **Excluded at data abstraction**

Sullivan, C. J. Simultaneous aqueous ragweed extract and alum-precipitated pyridine ragweed extract used prophylactically. Ann Allergy 71; 29 (2): 71-5. **It does not meet ALL the inclusion criteria**

Sullivan, C. J., Phipatanakul, C. S., and Slavin, R. G. Combined use of aqueous and alum-precipitated pyridine ragweed extracts. Ann Allergy 72; 30 (4): 195-202. **It does not meet ALL the inclusion criteria**

Suppression of the late asthmatic reaction by hyposensitization in asthmatic children allergic to house dust mite (Dermatophagoides pteronyssinus) **Excluded at data abstraction**

Svanborg, N. Desensitization during Lomudal treatment. Acta Allergol 75; 30 suppl 12 106-12. **No SIT**

Symington, I. S., O'Neill, D., and Kerr, J. W. Comparision of a glutaraldehyde-modified pollen--tyrosine adsorbate with an alum-precipitated pollen vaccine in the treatment of hay fever. Clin Allergy 77; 7 (2): 189-94. **Therapy NOT AVAILABLE in the U.S**

Symposium B. II. Basic and clinical studies on the desensitization therapy **Meeting abstract**

T. Sykora, L. Tamele, M. Zemanova and M. Petras Efficacy and safety of specific allergen immunotherapy with standardized depod allergen H-Al depot. (pollens). Alergie 2004 6 (3): 170-178. **Therapy NOT AVAILABLE in the U.S**

Tabar, A. I., Fernandez-Tavora, L., Alonso, R., Castillo, R., Cistero-Bahima, A., de la Torre-Morin, F., Fernandez, J., Garcia-Figueroa, B. E., Fernandez, S., Garcia-Gonzalez, J. J., Garcia-Robaina, J. C., Moreno, F., Lobaton, P., Sanchez-Machin, I., and de la Torre-Martinez, F. Olerance of a cluster schedule with a house dust mite extract quantified in mass units: multicentre study. J Investig Allergol Clin Immunol 2004; 14 (3): 193-7. **It does not meet ALL the inclusion criteria**

Tabar, A. I., Garcia, B. E., Rodriguez, A., Olaguibel, J. M., Muro, M. D., and Quirce, S. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. Allergy 93; 48 (6): 450-3. **It does not meet ALL the inclusion criteria**

Tabar, A. I., Lizaso, M. T., Garcia, B. E., Echechipia, S., Olaguibel, J. M., and Rodriguez, A. Tolerance of immunotherapy with a standardized extract of Alternaria tenuis in patients with rhinitis and bronchial asthma. J Investig Allergol Clin Immunol 2000; 10 (6): 327-33. **It does not meet ALL the inclusion criteria**

Tabe, K., Mizukoshi, T., Nishi, Y., Noguchi, T., Shuh, S., Kobayashi, Y., Shibasaki, M., Yamamoto, H., Nagata, M., Sakamoto, Y., and Matsuo, H. A trial of new protocol of rush immunotherapy with standardized mite antigen. Arerugi 99; 48 (5): 526-32. **Not an RCT**

Tahamiler, R., Canakcioglu, S., Yilmaz, S., and Isildak, H. Long-term immunotherapy for perennial allergic rhinitis: relationship of specific IgG levels to skin-prick test results and clinical symptoms and signs. Ear Nose Throat J 2008; 87 (12): E29. **It does not meet ALL the inclusion criteriaoes not apply to any of the key questions**

Tahamiler, R., Yener, M., and Canakcioglu, S. The use of serum and nasal eosinophilic cationic protein in the evaluation of the effectiveness of immunotherapy in patients with allergic rhinitis. Kulak Burun Bogaz Ihtis Derg 2006; 16 (4): 155-9. **Does not apply to any of the key questions**

Takeuchi, H., Yamamoto, Y., Kitano, H., and Enomoto, T. Changes in thymus- and activation-regulated chemokine (TARC) associated with allergen immunotherapy in patients with perennial allergic rhinitis. J Investig Allergol Clin Immunol 2005; 15 (3): 172-6. **Does not apply to any of the key questions**

Takeuchi, K., Kishioka, C., Yuta, A., Sakakura, Y., Masuda, S., Ukai, K., and Majima, Y. Clinical efficacy of immunotherapy with house dust in the patients with perennial nasal allergy. Arerugi 2000; 49 (8): 627-33. **Not an RCT**

Taki, K. Relation between desensitization and skin reaction in allergic diseases. Kumamoto Med J 68; 21 (3): 95-107. **It does not meet ALL the inclusion criteriaDoes not apply to any of the key questions- Other reason for exclusion (specify):**strange extracts

Tamir, R., Castracane, J. M., and Rocklin, R. E. Generation of suppressor cells in atopic patients during immunotherapy that modulate IgE synthesis. J Allergy Clin Immunol 87; 79 (4): 591-8. **Does not apply to any of the key questions**

Tamir, R., Katz, Y., and Pick, A. I. Specific immunotherapy in allergic bronchial asthma. Harefuah 92; 123 (12): 536-40. Hebrew **Non-English article**

Tamir, R., Levy, I., Duer, S., and Pick, A. I. Immediate adverse reactions to immunotherapy in allergy. Allergy 92; 47 (3): 260-3. **It does not meet ALL the inclusion criteria**

Tanac, R., Demir, E., Aksu, G., Sari, G., and Kutukculer, N. Effect of immunotherapy on autoimmune parameters in children with atopic asthma. Turk J Pediatr 2002; 44 (4): 294-7. **Does not apply to any of the key questions**

Tanaka, A., Ohashi, Y., and Nakai, Y. Decrease of serum levels of soluble CD23 during immunotherapy in patients with perennial allergic rhinitis. Ann Otol Rhinol Laryngol 99; 108 (2): 193-200. **Does not apply to any of the key questions**

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Tari, M. G., Mancino, M., Madonna, F., Buzzoni, L., and Parmiani, S. Immunologic evaluation of 24 month course of sublingual immunotherapy. Allergol Immunopathol (Madr) 94; 22 (5): 209-16. **It does not meet ALL the inclusion criteria**linical outcomes reported elsewhere**Does not apply to any of the key questions**

Tari, M. G., Mancino, M., Pozzuoli, G., Mauro, B., Verga, A., and Monti, G. Immunotherapy with alginate-conjugated two grass pollen extract in patients with allergic rhinoconjunctivitis. Allergol Immunopathol (Madr) 90; 18 (1): 35-40. **Therapy NOT AVAILABLE in the U.S**

Taudorf, E. Oral immunotherapy of adults with allergic rhinoconjunctivitis. Clinical effects in birch and grass pollinosis. Dan Med Bull 92; 39 (6): 542-60. **No original data**

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Taylor, G. DSCG and hyposensitization. Acta Tuberc Pneumol Belg 74; 65 (3-4): 345-52. **No original data**

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Tebyrica, J. N and Tebyrica, C. N Imunoterapia com extrato de Dermatophagoides pteronyssinus em criancas asmaticas.. Arq. bras. med 83; 57 (5): 223-8. **portuguese Non-English article**

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The cities study: Conventional immunotherapy-investigating existing schedules **Meeting abstract**

The clinical and immunological efficacy of house dust mite specific sublingual and subcutaneous immunotherapy in children; randomised, 3 years follow-up **Meeting abstract**

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The results of specific immunotherapy for house dust mites in patients with allergic rhinitis **Library unable to locate**

The role of allergen specific immunotherapy (SIT) in the treatment of mild persistent allergic rhinitis (MPAR) without concomitanat asthma **Library unable to locate**

The role of ragweed pollen in autumnal asthma **Excluded at data abstraction**

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W. Kamin, M. V. Kopp, F. Erdnuess, U. Schauer, S. Zielen and U. Wahn Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. 2010 (1 Pt 2): e160-5. **Other reason for exclusion (specify):no clinical outcomes**, study of harms only

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