APPENDIX A. – SEARCH STRATEGY

PubMed

(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

('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

(allergen-specific immunotherapy OR allergen immunotherapy OR immunotherapy) AND (rhinitis OR hay fever 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.

1. **Include article for review (check box if *yes*)**

☐ Yes, applies to at least one of the key questions without an exclusion

2. **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

3. **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 data

☐ 9. Other reason for exclusion (specify)

4. **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

5. **Get article**

- ☐ Unclear or no abstract
- ☐ Meta-analysis or Systematic Review or just useful reference
- ☐ I do not read this language

6. **Comment**

Submit Form and go to or Skip to Next

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)

Exclude article because -

1.

☐ 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

Include article if -

2. **(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)

Submit Form and go to or Skip to Next

Study Design Triage Form

Please indicate the article's study design and comparators

Included study design

- Randomized controlled trial

Clear Response

Excluded study designs

- 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

What is being compared?

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

Comments:

Submit Form and go to or Skip to Next

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

Submit Form and go to _____ or Skip to Next

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

SECOND REVIEWER INITIALS

Submit Form and go to or Skip to Next

Intervention Characteristics Form

Answer the following for the ENTIRE study

To be included, studies must report either:

- *Maintenance dose with frequency and duration specified OR*
- *Cumulative dose*

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)	*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)	*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 ☐ 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	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 ☐ 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	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 ☐ 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

☐ 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)	☐ 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)	☐ 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

SECOND REVIEWER INITIALS

Submit Form and go to or Skip to Next

Patient Characteristics Form

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

SECOND REVIEWER INITIALS

Multiple Allergen Form

ONLY FILL THIS FORM IF MULTIPLE ALLERGENS WERE STUDIED IN A SINGLE ARTICLE

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 Clear Response		

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

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

COMMENTS

SECOND REVIEWER INITIALS

Submit Form and go to or Skip to Next

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

COMMENTS

SECOND REVIEWER INITIALS

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

Were any long term outcomes 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 ● Reported	Convenience ● Reported	Convenience ● Reported	Convenience ● Reported

● Not reported Clear Response	● Not reported Clear Response	● Not reported Clear Response	● 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	Serum antibody levels CD25	Serum antibody levels CD25	Serum antibody levels CD25

● Reported ● Not reported Clear Response	● Reported ● Not reported Clear Response	● Reported ● Not reported Clear Response	● 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	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	Missed days of work	Missed days of work	Missed days of work

● Reported ● Not reported Clear Response	● Reported ● Not reported Clear Response	● Reported ● Not reported Clear Response	● Reported ● Not reported Clear Response

COMMENTS

SECOND REVIEWER INITIALS

Submit Form and go to or Skip to Next

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

SECOND REVIEWER INITIALS

Submit Form and go to or Skip to Next

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

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*

4. ***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

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*

5. *outcome assessment between groups*

☐ Yes--low risk of bias

☐ No--high risk of bias OR unclear/unspecified

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*

6. ***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

COMMENTS

SECOND REVIEWER INITIALS

☐ 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

Submit Form and go to or Skip to Next

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: Grassex; 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 cx 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 patientt 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

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 (mcg 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% mcg 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 SUBCUTANEOUS IMMUNOTHERAPY

TABLE 1. - STUDY CHARACTERISTICS SCIT

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Asthma						
Adkinson 1997 USA [1] Limb 2006 USA[2]	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
Altintas 1999 Turkey [3]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive skin test	Not stated
Bousquet 1985 France [4]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Positive skin test	Unclear
Bousquet 1988 France [5]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Positive skin test	Not stated
Creticos 1996 USA [6]	Asthma	Seasonal	Single	Weeds: Short ragweed	No previous immunotherapy Positive skin test Monosensitized individuals only	Government Other
Garcia-Ortega 1993 Spain [7]	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
Hill 1982 Australia [8]	Asthma	Seasonal	Single	Grass: rye	Age: Children Positive skin test Minimum duration of disease: 3 years	Non-profit Industry
Kohno 1998	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides	Positive specific IgE test	Non-profit

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Japan [9]				pteronyssinus and farinae	Positive skin test	
Maestrelli 2004 Italy [10]	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
Malling 1986 Denmark-Sweden[11]	Asthma	Seasonal	Single	Mold: Cladosporium	No previous immunotherapy Positive skin test Excluded Pregnancy	Government Industry
Ohman 1984 USA [12]	Asthma	Perennial	Single	Animals: Cats	No previous immunotherapy Positive skin test	Government Non-profit
Olsen 1997 Denmark [13]	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Age: >18 years Positive specific IgE test Positive skin test Excluded Pregnancy	Not stated
Pifferi 2002 Italy [14]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Monosensitized individuals only	Not stated
Schubert 2009 Germany [15]	Asthma	Perennial	Single	Dust mites: Unspecified dust mites	Positive specific IgE test Positive skin test	Not stated
Valovirta 1986 Denmark-Finland [16]	Asthma	Perennial	Single	Animals: Dogs	Age: 5-18 years No previous immunotherapy Positive specific IgE test Positive skin test	Government Non-profit
Van Bever 1991 Belgium [17]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Positive specific IgE test Positive skin test	Not stated
Van Bever 1990 Belgium [18]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Positive specific IgE test Positive skin test	Not stated
Van Metre 1988 USA [19]	Asthma	Perennial	Single	Animals: Cats	Positive specific IgE test Positive skin test	Government Other
Wang 2006 China [20]	Asthma	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: 6-45 years Positive specific IgE test Positive skin test	Industry
Rhinitis						
Durham 1999 England and Canada [21]	Rhinitis	Seasonal	Single	Grass: Timothy grass	Positive skin test	Government Industry
Junqueira de Queiros 2008 Brasil[22]	Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive skin test Excluded Pregnancy	Government Non-profit
McHugh 1990	Rhinitis	Perennial	Single	Dust mites: Dermatophagoides	No previous immunotherapy	Government

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
United Kingdom[23]				pteronyssinus	Positive skin test	Non-Profit
Polosa 2004 Italy [24] Polosa 2003 Italy[25]	Rhinitis	Seasonal	Single	Weeds: Parietaria	Positive skin test Monosensitized individuals only	Industry
Van Metre 1980 USA [26]	Rhinitis	Seasonal	Single	Weeds: Ragweed	Positive specific IgE test Positive skin test	Government Non-profit
Van Metre 1981 USA [27]	Rhinitis	Seasonal	Single	Weeds: Ragweed	Positive specific IgE test Positive skin test Minimum duration of disease: 2 years	Government Non-profit
Rhinoconjunctivitis						
Bernstein 1976 USA[28]	Rhinoconjunctivitis	Seasonal	Single	Weeds: Ragweed	Positive skin test	Industry Not stated
Crimi 2004 Italy[29]	Rhinoconjunctivitis	Seasonal	Single	Weeds: Parietaria	Positive skin test	Industry
Dreborg, 2011 United Kingdom[30]	Rhinoconjunctivitis	Perennial	Multiple	Grass: Timothy Dust mite	Age: 17-55 years No previous immunotherapy Positive skin test pregnant women were excluded	Industry
Frew 2006 United Kingdom[31]	Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy grass	Age: 18 – 60 years No previous immunotherapy Positive specific IgE test Positive skin test	Industry
Frostad 1983 Norway[32]	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
James * 2011 United Kingdom[33]	Rhinoconjunctivitis	Seasonal	Single	Grass: grass mix	Positive skin test	Government
Klimek 1999 Germany[34]	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix Trees: trees mix	Age: 15-50 years No previous immunotherapy Positive skin test	Government Industry

APPENDIX

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Leynadier 2000 France[35]	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
Olsen 1995 Denmark[36]	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
Shamji , 2012 United Kingdom[37]	Rhinoconjunctivitis	Seasonal	Single	Grass: Unspecified grass	Age: 18-60 years No previous immunotherapy Positive skin test	Industry
The PAT study Möller 2002 Multiple European countries[38]	Rhinoconjunctivitis	Seasonal	Multiple	Trees: Birch Grass: Timothy grass	Age: Children No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Varney 1991 United Kingdom[39]	Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Walker, 2000 United Kingdom[40]	Rhinoconjunctivitis	Seasonal	Single	Grass: grass mix	No previous immunotherapy Monosensitized individuals only Positive skin test	Industry
Zenner. 1996 Germany[41]	Rhinoconjunctivitis	Seasonal	Multiple	Grass mix: Rye- Secale cereal and Grass mix	Age: 16-53 years Positive skin test	Industry
Asthma and Rhinitis						
Akmanlar 2000 Turkey[42]	Asthma and Rhinitis	Perennial	Multiple	Dust mites:Dermatophagoides pteronyssinus and farinae	Age: children No previous immunotherapy Positive skin test Monosensitized individuals only	Not stated
Ariano 2006 Italy[43]	Asthma and Rhinitis	Seasonal	Single	Weeds: Parietaria judaica	Age: 18-50 years No previous immunotherapy Minimum duration of disease: 2 years	Not stated
Arvidsson 2004 Sweden[44] Arvidsson 2002 Sweden[45]	Asthma and Rhinitis	Seasonal	Single	Trees: White birch	No previous immunotherapy Positive specific IgE test Positive skin test	Industry

APPENDIX

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Cantani 1997 Italy[46]	Asthma and Rhinitis	Seasonal and Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus Grass: Perennial ryegrass Weeds: Parietaria	No previous immunotherapy Positive skin test	Not stated
Ferrer 2005 Spain[47]	Asthma and Rhinitis	Seasonal	Single	Weeds: Parietaria judaica	Age: 15 – 55 years Positive specific IgE test Positive skin test Monosensitized individuals only	Industry
Hedlin 1999 Denmark-Sweden[48]	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
Horst 1989 France[49]	Asthma and Rhinitis	Seasonal	Single	Mold: Alternaria	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Not stated
Munoz Lejarazu, 1993 Spain[50]	Asthma and Rhinitis	Seasonal	Single	Grass: Timothy grass	No previous immunotherapy Positive skin test Positive specific IgE test Monosensitized individuals only	Government
Muro 1999 Spain[51]	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
Naclerio 1997 USA[52] Iliopoulos 1991 USA[53]	Asthma and Rhinitis	Seasonal	Single	Weeds: Ragweed	Positive skin test	Government
Newton 1978 United Kingdom[54]	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides farinae	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Nouri-Aria 2003 United Kingdom[55] Walker 2001 United Kingdom[40]	Asthma and Rhinitis	Seasonal	Single	Grass: Timothy grass	No previous immunotherapy Positive skin test	Government Non-profit

APPENDIX

Study Author, Year Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Petersen 1988 Denmark[56]	Asthma and Rhinitis	Perennial	Multiple	Trees: White birch and Tree mix	Positive skin test pregnant women were excluded	Industry
Pichler, 1996 Switzerland+ Denmark[57]	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Positive specific IgE test Positive skin test	Industry
Prieto 2010 Spain[58]	Asthma and Rhinitis	Seasonal	Single	Mold: Alternaria	Positive skin test	Industry
Tabar 2005 Spain[59]	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Positive specific IgE test Positive skin test	Industry Government
Tabar 2007 Spain[60]	Asthma and Rhinitis	Seasonal	Single	Mold: Alternaria	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Government Industry
Varney, 2003 United Kingdom[61]	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Asthma and Rhinoconjunctivitis						
Alvarez-Cuesta 1994 Spain[62]	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
Bousquet 1991 France-Germany[63] Bousquet 1991 France-Germany[64]	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 India[65]	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Trees: date sugar palm/wild date palm	No previous immunotherapy Positive skin test	Government Non-profit
Dolz 1996 Spain[66]	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
Dreborg 1986 Multiple European countries[67]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Mold: Cladosporium	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
Kuna 2011 Poland[68]	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
Mirone 2004 Italy[69]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Weeds: Short ragweed	No previous immunotherapy Positive skin test Positive specific IgE test Monosensitized individuals only	Industry
Osterballe 1982 Denmark[70] Osterballe 1981 Denmark[71] Osterballe 1980 Denmark[72] Osterballe 1982 Denmark[73]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy grass	Monosensitized individuals only	Government Industry
Pence 1975 USA[74]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Mountain cedar	No previous immunotherapy Positive skin test	Non-profit
Rak 2001 Denmark-Sweden[75] Rak 2005 Denmark-Sweden[76]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Birch	Positive specific IgE test Positive skin test	Government Industry
Tabar 2010 Spain[81]	Asthma and Rhinoconjunctivitis	Perennial	Single	Dust mite	Age: 5-45 years Positive skin test Positive specific IgE test	Government
Varnery. 1997 United Kingdom[77]	Asthma and Rhinoconjunctivitis	Perennial	Single	Animals: Cats	No previous immunotherapy Positive skin test	Not stated
Weyer, 1981 France[78]	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Positive skin test	Industry Non-profit

TABLE 2.- PATIENT CHARACTERISTICS SCIT

Study	Patients randomized	Comparators	Age (years) (mean+/- S.D)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
Asthma						
[6] Creticos 1996	90	SCIT Placebo	36 +/- 10 35 +/- 10	51/49 50/50	37/8 53/16	At least 1
[8]Hill 1982	20	SCIT Placebo	Range 9-14 Range 9-14	Entire study 65/35	11/NR 9/NR	3 3
[3]Altintas 1999	35	SCIT-Adsorbed aluminum SCIT-Adsorbed calcium SCIT-aqueous 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
[4]Bousquet 1985	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
[5]Bousquet 1988	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
[7]Garcia-Ortega 1993	36	SCIT Control (conventional therapy)	Range 13-45 Range 13-45	Entire study N 16/20	18/NR 18/NR	NR
[14]Pifferi2002	29	SCIT no treatment	11 +/- 3 10 +/- 2	Entire Study 55/45	15/0 14/4	NR
[17] Van Bever 1991	18	SCIT Placebo	9 (Range 7-11) 12 (Range 8-22)	NR	9/0 9/0	NR
[18] Van Bever 1990	19	SCIT Placebo (after 1 year of SCIT)	12.2 (Range 8- 16) 12 (Range 9-14)	NR	9/NR 10/NR	NR
[20] Wang 2006	132	SCIT Placebo	Range 6-45	56/44 61/39	64/2 65/1	7.1 +/- 0.81 7.3 +/- 0.79
[15] Schubert 2009	34	SCIT Cluster SCIT Classic	10 8.5	NR NR	20/2 14/2	NR
[9] Kohno1998	16	SCIT Placebo	25.8 26.3	75/25 66/34	8/0 6/2	NR

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- S.D)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
[10] Maestrelli 2004	95*	SCIT Placebo	20 +/- 8 23 +/- 10	61/39 71/29	41/8 31/15	1
[13] Olsen 1997	31	SCIT Placebo	32 (Range 18-56) 40.7 (Range 22-64)	NR	NR	NR
[12] Ohman 1984	17	SCIT Placebo	26 (Range 22-31) 30 (Range 24-48)	NR NR	9/0 8/0	NR
[19] Van Metre 1988	22	SCIT Placebo	Range 21-52 Range 21-52	N 5/6 N 5/6	11/1 11/0	NR
[16] Valovirta 1986	27	SCIT Placebo	11 (Range 5-18) 10.5 (Range 5-16)	60/40 58/42	15/0 12/0	NR
[11] Malling1986	23	SCIT Placebo	25 (Range 17-43) 31 (Range 16-54)	64/36 82/19	11/1 11/0	16 24
[1] Adkinson1997 [2] Limb2006	121	SCIT Placebo	9 +/- 2 9 +/- 2	80/20 76/24	61/8 60/3	greater than 1 greater than 1
Rhinitis						
[24] Polosa 2004 [25] Polosa 2003	30	SCIT Placebo	32 (Range 21-54) 34 (Range 20-53)	67/33 33/67	15/0 15/0	7.8 8.2
[26] Van Metre 1980	39*	SCIT Placebo	Range 18-50 Range 18-50	80/20 71/29	15/0 14/0	NR
[27] Van Metre 1981	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
[21] Durham 1999	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
[22] Junqueira de Queiros 2008	50*	SCIT Placebo	22 +/- 14 21 +/- 13	66/34 34/66	25/10 25/10	NR

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- S.D)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
[23] McHugh1990	80	SCIT- purified SCIT- crude Placebo	Range 17-52 Range 17-52 Range 17-52	NR	30/3 20/2 30/2	NR
Rhinoconjunctivitis						
[29]Crimi 2004	30	SCIT Placebo	32 (Range 21-54) 34 (Range 20-53)	67/33 33/67	15/1 15/0	7.8 8.2
[28]Bernstein 1976	148	SCIT Placebo	Entire study 30.0	Entire study 53/57	68/NR 60/NR	At least 3 At least 3
[31]Frew 2006	410	SCIT 100,000 SQ-U SCIT 10,000 SQ-U Placebo	38 +/- 9 (Range 18-60) 37 +/- 9.0 (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
[39]Varney 1991	40	SCIT Placebo	38(Range 32-48) 42(Range 33-50)	69/31 50/50	21/2 19/3	NR
[33]James 2011	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
[40] Walker 2000	44	SCIT Placebo	32 (Range 22-64) 32 (Range 23-59)	45/55 59/41	22/2 22/5	NR
[37]Shamji 2012	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)
[32] Frostad 1983	60	SCIT purified Timothy SCIT crude Timothy SCIT grass mix Control	Median age 25	NR	24/4 17/3 19/3 30/NR	NR
[34] Klimek 1999	48	SCIT Pharmacotherapy	30 (Range 21-49) 31 (Range 15-50)	63/37 66/34	24/0 24/0	Median: 13 Median: 12
[35] Leynadier 2000	29	SCIT Placebo	29 (Range 18-44) 31 (Range 20-42)	47/53 54/46	16/1 13/1	8 11

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- S.D)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
[38] Möller 2002	205	SCIT Placebo	Entire study 16 (Range 11-20)	Entire study 66/34	103/NR 102/NR	NR
[36] Olsen 1995	25*	SCIT-Artemisia SCIT- Betula /Phleum extract	Range 18-45	Entire study 40.0/60.0	9/3 11/2	NR
[41] Zenner 1996	86	SCIT Placebo	28 (Range 18-53) 29 (Range 16-49)	N 30/15 N 29/12	45/1 41/0	13 12
[30] Dreborg 2011	20	SCIT Timothy SCIT dust mite	29 (Range 17-55)	55/45	9/2 11/4	NR
Asthma and Rhinitis						
[43] Ariano 2006	30	SCIT Pharmacotherapy	35 +/- 10 32 +/- 11	55/45 60/40	20/NR 10/NR	2 2
[47] Ferrer 2005	57	SCIT Placebo	36 +/- 11 33 +/- 10	39/61 52/48	28/6 29/9	NR
[52] Naclerio 1997 [53] Iliopoulos 1991	20	SCIT Placebo	NR NR	NR NR	10/0 10/0	1 1
[44] Arvidsson 2004 [45] Arvidsson 2002	49*	SCIT placebo	33 (Range 21-45) 31 (Range 19-45)	38/62 44/56	22/1 22/1	NR
[50] Munoz Lejarazu, 1993	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
[55] Nouri-Aria 2003 [40] Walker 2001	44	SCIT Placebo	32 (Range 22-64) 32 (Range 23-59)	45/55 59/41	22/2 22/5	NR
[51] Muro 1999	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
[59] Tabar 2005	239	Cluster Conventional	19 +/- 10 18 +/- 9	63/37 60/40	120/23 119/20	4 4
[54] Newton 1978	16	SCIT Placebo	29 (Range 20-38) 30 (Range 18-44)	43/57 57/43	7/1 7/1	16 7.7

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- S.D)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
[58] Prieto 2010	40	SCIT Placebo	25 (Range 22-29) 22 (Range 18-26)	43/57 72/28	21/5 18/0	NR
[49] Horst 1989	24	SCIT Placebo	12 +/- 5 (Range 7-23) 13 +/- 15 (Range 5-56)	75/25 74/26	13/0 11/2	NR
[60] Tabar 2007	28	SCIT Placebo	13 SE 4 15 SE 6	86/14 93/7	14/1 14/4	NR
[42] Akmanlar 2000	18	SCIT Rush SCIT Conventional	7 +/- 2.6 9 +/- 4	NR NR	9/0 9/0	NR
[57] Pichler 1996	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; Asthma:5.1
[61] Varney 2003	36	SCIT Placebo	33 (Range 19-48) 37(Range 23-55)	N 6/9 N 7/6	15/4 13/4	NR
[56] Petersen. 1988	54	SCIT SCIT	30 (Range 15-72) 32 (Range 15-56)	48/52 41/59	27/4 27/5	8.3 6.8
[48] Hedlin 1999	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
[46] Cantani 1997	300	SCIT Pharmacotherapy	Entire study 4 (Range 3.-7)	Entire study 58/42	151/NR 149/NR	NR
Asthma and Rhinoconjunctivitis						
[69] Mirone 2004	32	SCIT Placebo	37 (Range 27-54) 36 (Range 23-60)	44/56 69/31	16/3 16/4	NR
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	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

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- S.D)	Sex % male/female	Patients enrolled/ dropouts	Duration of disease (Mean years affected)
[74] Pence 1975	40	SCIT Placebo	37 44	41/59 40/60	17/3 15/5	NR
[75]Rak 2001 [76]Rak 2005	41	SCIT Nasal steroid	30 (Range 18-41) 29 (Range 21-42)	43/57 65/35	21/0 20/0	NR
[67] Dreborg 1986	30	SCIT Placebo	11 (Range 5-17) 11 (Range 5-17)	NR	16/NR 14/NR	NR
[68] Kuna 2011	50	SCIT Placebo	12 +/-4 11 +/-4	50/50 50/50	30/NR 20/NR	2 years
[78] Weyer 1981	33	SCIT Placebo	26 (Range 9-42) 26 (Range 15-46)	N 7/10 N 9/7	17/NR 16/NR	5 6
[63] Bousquet 1991 [64] Bousquet 1991	70 4 dropouts in the entire study	SCIT grass Placebo grass SCIT multiple Placebo multiple	21 +/- 10 (Range 14-44) 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
[65] Chakraborty 2006	35	SCIT Placebo	32 33	NR	18/0 17/0	NR
[66] Dolz 1996	28	SCIT Placebo	18.3 21.5	NR	18/NR 10/NR	4.7 years 4.8 years
[62] Alvarez-Cuesta 1994	28	SCIT Placebo	23 (Range 15-65) 29 (Range 15-65)	21/79 22/78	14/0 14/0	NR
[77] Varnery 1997	28	SCIT Placebo	34 (Median) Range 22-46 32 (Median) Range 19-50	N 3/10 N 7/8	13/NR 15/NR	NR
[81] Tabar 2010	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 3. INTERVENTION CHARACTERISTICS -SCIT

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[6]Creticos 1996	SCIT Ragweed Placebo	ONLY rescue medication	0.5 mL of 1:10 dilution (actual mean dose in year = 4 mcg of Amb a1)	NR	Every 2 weeks for 3 months thereafter every 4 weeks	10 µg of Amb a1	2 years
[8]Hill 1982	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
[3]Altintas 1999	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
[4]Bousquet 1985	SCIT Rush Placebo	NR	3000 BU(=to 0.1 ml of 1/100 w/v)	NR	Weekly	NR	7 weeks (not clearly stated)
[5]Bousquet 1988	SCIT Dust mite No treatment	conventional therapy	3000 BU	NR	Weekly for 6 weeks; then every 2 weeks for 1 year	NR	1 year
[7]Garcia-Ortega 1993	SCIT Dust mite Cluster Pharmacotherapy	conventional therapy	100000 SQ	2000000 SQ	Every 15 days		7 months
[14]Pifferi 2002	SCIT Dust mite HDM No treatment	conventional therapy	800 U	24758.33 U (mean)	4 -6 weeks	NR	3 years
[17]Van Bever 1991	SCIT Dust mite Cluster Placebo	conventional therapy	1000 BU	16497 BU	Every 4 weeks	NR	1 year

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[18]Van Bever 1990	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
[20]Wang 2006	SCIT dust mite alum-precipitated Placebo	ONLY rescue medication	100000 SQ-U	NR	6 weeks	9.8 **µg** Der p1	1 year
[15]Schubert 2009	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
[9]Kohno 1998	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
[10]Maestrelli 2004	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
[13]Olsen 1997	SCIT dust mite HDM 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
[12]Ohman 1984	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 per ml or 300 mcg/ml of cat albumin)	16 weeks

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[19]Van Metre 1988	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
[16]Valovirta 1986	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
[11]Malling 1986	SCIT Cladosporidium Placebo	conventional therapy	18,000 BU mean "maintenance" dose 46,000 BU mean "top" dose 100000 BU (target "top" dose; achieved only by 1 patient)	444,000 BU	Every 4 weeks	NR	5-7 months
[1]Adkinson 1997 [2]Limb 2006	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 perennial ryegrass) 6 µg Alt a1 Not reported for Bermuda grass English plantain white oak Cladosporium herbarum Aspergillus fumigatus	27 months
[24]Polosa 2004 [25]Polosa 2003	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
[26]Van Metre 1980	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

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[27]Van Metre 1981	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
[21]Durham 1999	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
[22]Junqueira de Queiros 2008	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
[23]McHugh 1990 [79]Ewan 1988	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
[29]Crimi 2004	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
[28]Bernstein 1976	SCIT Ragweed alum-precipitated Placebo	conventional therapy	6000 PNU (target)	7287 to 23945 PNU (actual)	Weekly		pre-seasonal and during season

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[31]Frew 2006	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
[39]Varney 1991	SCIT Timothy aluminum-Alutard Placebo	conventional therapy	30000 BU/ml	BU/ml	Monthly	30000 BU = 100000 SQ phleum pratense	7 months
[33]James 2011	SCIT 4 years SCIT 2y + Placebo 2 y	NR	100,000 SQ units	NR	Monthly	20 µg Phl p5	4 years
[40]Walker 2000	SCIT Placebo	NR	100,000 SQ units			20 µg Phl p5 (P pratense)	3 years
[37]Shamji 2012	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
[32]Frostad 1983	SCIT pure SCIT crude SCIT grass mix Control	ONLY rescue medication		103000 BU 276000 BU 238000 BU			3 years
[34]Klimek 1999	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

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[35]Leynadier 2000	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
[38]Möller 2002	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
[36]Olsen 1995	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
[41]Zenner 1996	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
[81] Tabar 2010	SCIT 5 years SCIT 3 years Control		0.8 mL = 3.6 mcg Der p 1	NR	Monthly	3.6 mcg Der p 1	5 years
[43]Ariano 2006	SCIT Parietaria Pharmacotherapy	NR	4 IR (only during pollen season) to 8 IR	NR	Every 4 weeks		3 years
[47]Ferrer 2005	SCIT Parietaria alum-precipitated Placebo	ONLY rescue medication	20 BU	NR	Every 4 weeks	1.2 µg of Par j 1	20 months

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[52]Naclerio 1997 [53]Iliopoulos 1991	SCIT Ragweed Placebo after SCIT	NR	5000 AU	NR	every 2 weeks	12 µg of Amb a 1	4 years for SCIT group (Placebo patients had 3 years of SCIT before switching to Placebo.
[44]Arvidsson 2004 [45]Arvidsson 2002	SCIT White birch Cluster alum-precipitated Placebo	NR	100000 SQ-U	NR	every 6 weeks		2 years
[50]Munoz Lejarazu 1993	SCIT- Timothy Perennial SCIT- Timothy Seasonal	NR	20 BU	613 BU (perennial) 393 BU (seasonal)	Every 4 weeks	NR	3 years
[55] Nouri-Aria 2003 [40] Walker 2001	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
[51]Muro 1999	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
[59]Tabar 2005	SCIT Dust miteCluster 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

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[54]Newton 1978	SCIT Dust mite alum-precipitated Placebo	NR	0.7 ml at 4000 PNU/ml	57 640 PNU	Every 3 weeks		15 months
[58]Prieto 2010	SCIT Alternaria alum-precipitated Placebo	conventional therapy	0.8 ml		Every 4 weeks	0.2 µg /ml Alt a 1	1 year
[49]Horst 1989	SCIT Japanese Cedar Rush Placebo	conventional therapy	2000 BU	NR	Weekly for 6 weeks then every 2 weeks for 1 year		1 year
[60]Tabar 2007	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	15 months
[42]Akmanlar 2000	SCIT Dust mite Rush SCIT Dust mite Conventional	conventional therapy	100000 SQ-U 50000- 100000 SQ-U	NR	Biweekly Every 4 weeks		3 years
[57]Pichler 1996	SCIT Dust mite Cluster HDM alum-precipitated Placebo	conventional therapy		100000 SQ-U	Every 8 weeks		12 months
[61]Varney 2003	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
[56]Petersen. 1988	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

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[48]Hedlin 1999	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
[46]Cantani 1997	SCITDust mite Parietaria ryegrass alum-precipitated Pharmacotherapy	conventional therapy	500 BU per month	26000 BU	Every 4 weeks		3 years
[69]Mirone 2004	SCIT Ragweed alum-precipitated Placebo	ONLY rescue medication		11140 PNU		31.2 mcg of antigen E (for year 2)	preseasonal for 2 years (January to August)
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	SCIT Timothy partially purified alum-precipitated SCIT Ag 19 25 alum-precipitated	ONLY rescue medication	10000 BU	NR	Every 4 weeks		3 years
[74]Pence 1975	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
[75]Rak 2001 [76]Rak 2005	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

APPENDIX

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[67]Dreborg 1986	SCIT Cladosporium Placebo	conventional therapy	100000 BU (reached after 18 weeks	NR	Every 4 weeks		10 months
[68]Kuna 2011	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
[78]Weyer 1981	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
[63]Bousquet 1991 [64]Bousquet 1991	SCIT grass Placebo grass SCIT multiple Placebo multiple	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)
[65]Chakraborty 2006	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
[66]Dolz 1996	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
[62]Alvarez-Cuesta 1994	SCIT Cat Placebo	conventional therapy	40 BU	NR	Every 4 weeks	13.2 µg Fel d I antigen	1 year

Study	ARMS	Conventional/ Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[77]Varnery 1997	SCIT Cat alum-precipitated Placebo	ONLY rescue medication	100000 SQ U	NR	Every 4 weeks	15 µg Fel d 1 (maintenance)	treatment not specified
[81] Tabar 2010	SCIT 5 years SCIT 3 years Control		0.8 mL = 3.6 mcg Der p 1	NR	Monthly	3.6 mcg Der p 1	5 years

BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit mcg 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 4.- RISK OF BIAS SCIT

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
Asthma							
[6]Creticos 1996	Low risk	Low risk	High risk	High risk	High risk	No	Medium risk
[8]Hill 1982	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
[3]Altintas 1999	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
[4]Bousquet 1985	Low risk	Low risk	High risk	High risk	High risk	Yes or unclear	High risk
[5]Bousquet 1988	Low risk	High risk	High risk	High risk	Low risk	No	Medium risk
[7]Garcia-Ortega 1993	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
[14]Pifferi 2002	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
[17]Van Bever 1991	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
[18]Van Bever 1990	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[20]Wang 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[15]Schubert 2009	Low risk	High risk	High risk	High risk	High risk	No	High risk
[9]Kohno 1998	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
[10]Maestrelli 2004	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[13]Olsen 1997	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
[12]Ohman 1984	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[19]Van Metre 1988	Low risk	High risk	Low risk	High risk	High risk	No	Medium risk
[16]Valovirta 1986	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk

APPENDIX

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
[11]Malling 1986	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
[1]Adkinson 1997 [2]Limb 2006	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
Rhinitis							
[24]Polosa 2004 [25]Polosa 2003	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[26]Van Metre 1980	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
[27]Van Metre 1981	Low risk	High risk	High risk	High risk	High risk	No	High risk
[21]Durham 1999	Low risk	Low risk	High risk	High risk	High risk	Yes or unclear	High risk
[22]Junqueira de Queiros 2008	Low risk	Low risk	Low risk	High risk	Low risk	No	Medium risk
[23]McHugh 1990	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
Rhinoconjunctivitis							
[29]Crimi 2004	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
[28]Bernstein 1976	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
[31]Frew 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[39]Varney 1991	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
[33]James 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[40]Walker 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[37]Shamji 2012	Low risk	Low risk	Low risk	High risk	High risk	Yes or unclear	Medium risk
[32]Frostad 1983	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[34]Klimek 1999	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[35]Leynadier 2000	Low risk	Low risk	High risk	High risk	Low risk	No	Medium risk
[38]Möller 2002	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[36]Olsen 1995	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
[41]Zenner 1996	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[30]Dreborg 2011	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Asthma and Rhinitis							
[43]Ariano 2006	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
[47]Ferrer 2005	Low risk	Low risk	High risk	Low risk	High risk	Yes or unclear	Medium risk

APPENDIX

Study	Random allocation subjects	Allocation scheme concealed	Intervention group concealed	Incomplete data addressed	Other biases	Sponsor company involved in design	Overall Risk of Bias
[52]Naclerio 1997 [53]Iliopoulos 1991	Low risk	Low risk	Low risk	Low risk	High risk	No	Low risk
[44]Arvidsson 2004 [45]Arvidsson 2002	Low risk	Low risk	High risk	Low risk	High risk	Yes or unclear	Medium risk
[50]Munoz Lejarazu 1993	Low risk	High risk	High risk	High risk	Low risk	No	Medium risk
[55]Nouri-Aria 2003 [40]Walker 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[51]Muro 1999	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[59]Tabar 2005	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[54]Newton 1978	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[58]Prieto 2010	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[49]Horst 1989	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
[60]Tabar 2007	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
[42]Akmanlar 2000	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
[57]Pichler 1996	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[61]Varney 2003	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[56]Petersen 1988	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[48]Hedlin 1999	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[46]Cantani 1997	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
Asthma and Rhinoconjunctivitis							
[69]Mirone 2004	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[70]Osterballe 1982 [71]Osterballe 1981 [72]Osterballe 1980 [73]Osterballe 1982	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[74]Pence 1975	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[75]Rak 2001 [76]Rak 2005	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[67]Dreborg 1986	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
[68]Kuna 2011	Low risk	Low risk	Low risk	Low risk	High risk	Yes or unclear	Medium risk
[78]Weyer 1981	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High 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
[63]Bousquet 1991 [64]Bousquet 1991	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
[65]Chakraborty 2006	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
[66]Dolz 1996	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
[62]Alvarez-Cuesta 1994	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[77]Varnery 1997	Low risk	Low risk	Low risk	High risk	High risk	No	Medium risk
[81] Tabar 2010	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 5-ASTHMA SYMPTOM SCORES-SCIT

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[20] Wang 2006	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	Arm 1 vs Arm 2 pre p=0.543 Arm 1 vs Arm 2,post p=0.019
[10] Maestrelli 2004	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	Arm 1 vs Arm 1 p NS Arm 2 vs Arm 2 p NS Arm 1 vs Arm 2 p NS
[57] Pichler 1996	Dust mites	SCIT Placebo	12 months	asthma symptom scores		5.5 13	3.5 7	Arm 1 vs Arm 1 p=0.014 Arm 2 vs Arm 2 p=0.85 Arm 1 vs Arm 2 post p=0.09

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[9] Kohno 1998	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	Arm 1 vs Arm 1 p < .03 Arm 2 vs Arm 2 p NS
[13] Olsen 1997	Dust mite	SCIT Placebo	1 year	Mean asthma symptom score per week	NR	22 25	9.5 22	Arm 1 vs Arm 1 p<0.001 Arm 2 vs Arm 2 p NS
[14] Pifferi 2002	Dust mite	SCIT Pharmacotherapy	3 years	Numbers of asthma exacerbations per year		8 8.5	1 4.5	Arm 1 vs Arm 2 p < 0.01
[5] Bousquet 1988	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	Arm 1 vs Arm 1 p <0.0001 Arm 2 vs Arm 2 p NS Arm 1 vs Arm 2 p <0.0001
[59] Tabar 2005	Dust mite	SCIT Cluster SCIT Conventional	1 year	Asthma symptom score		2.1 1.8	0.6 0.7	Arm 1 vs Arm 1, p <0.001 Arm 2 vs Arm 2, p <0.001
[81] Tabar 2010	Dust mite	SCIT 3 years SCIT 5 years	5 years	Global asthma score	0-5		80.9% reduction 79.9% reduction	Arm 1 vs Arm 2, p=0.330
[55] Nouri-Aria, 2003 [40] Walker 2001	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	Arm 1 vs Arm 2 p < 0.05

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[6] Creticos 1996	Short ragweed	SCIT Placebo	Year 2	7 point scale	0-6	4.6 4.3	2.9 3.5	Arm 1 vs Arm 2 p=0.3
[8] Hill 1982	Rye grass	SCIT Placebo	Year 1 (preseasonal IT x >4 months)	Median asthma symptom score	Calculated score from 3 domains	3 (before season) 4 (before season)	7 (during season) 5 (during season)	Arm 1 vs Arm 1 p <0.05 Arm 2 vs Arm 2 p NS
[8] Hill 1982	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)	Arm 1 vs Arm 1 p NS Arm 2 vs Arm 2 p significant but value not reported (No report of statistical comparison between year 1 and year 2)
[67] Dreborg 1986	Cladosporium	SCIT – Cluster Placebo	6 months (during 2 weeks with highest spore counts)	Bronchial symptoms	0-3	210 240	170 260	Arm 1 vs Arm 2 p NS
[11] Malling 1986	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	Arm 1 vs. Arm 2 p = 0.07

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[12] Ohman 1984	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
[12] Ohman 1984	Cats	SCIT Placebo	17 weeks	Time to first increase in symptoms on exposure to cats		NR NR	NR NR	Arm 1 vs Arm 1 p <0.05 Arm 2 vs Arm 2 p NS Arm 1 vs Arm 2 p <0.05 (comparison of change scores from baseline)
[1] Adkinson 1997 [2] Limb 2006	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)	Arm 1 vs Arm 1 p= 0.02 Arm 2 vs Arm 2 p= 0.003 Arm 1 vs Arm 2 p = 0.5 (Mean difference pre = 0.003; post = -0.08)
[46] Cantani 1997	Dust mites ryegrass and parietaria	SCIT pharmacotherapy	Year 3	Mean percentage of NIGHTS with asthma		NR NR	40 66	Arm 1 vs Arm 2 p<0.0005
[46] Cantani 1997	Dust mites ryegrass and parietaria	SCIT control	Year 3	Mean percentage of DAYS with asthma		NR NR	32 56	Arm 1 vs Arm 2 p=0.0001

TABLE 6-COMBINED ASTHMA AND RHINOCONJUNCTIVITIS SYMPTOM SCORES- SCIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[49] Horst 1989	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)

[68] Kuna 2011	Alternaria	SCIT Placebo	Baseline-3yr			SCIT: 13.8 Placebo 11.2	SCIT: 2.3 placebo: 21.4	SCIT pre vs Post p<0.001 Placebo pre vs post p<0.001 Pre SCIT vs Placebo: p>0.05 Post: SCIT vs Placebo, p=0.001
[43] Ariano 2006	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
[55] Nouri-Aria 2003 [40] Walker 2001	Timothy	SCIT Placebo	2 years	Median total symptom score (chest, nose, eye, mouth, and throat)	Each domain using a scale of 0-3; totaled daily	2576 1962	1277 50% improvement 1386 29% improvement	SCIT vs Placebo p = 0.01
[44] Arvidsson 2004 [45] Arvidsson 2002	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)
[77] Varnery. 1997	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 7- ASTHMA MEDICATION SCORES-SCIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[20] Wang 2006	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[14] Pifferi 2002	Dust mite	SCIT Pharmacotherapy	3 years	Days of therapy/year (Salbutamol)		40 50	7 40	SCIT vs Pharmacotherapy p <0.01
[14] Pifferi 2002	Dust mite	SCIT Pharmacotherapy	3 years	Days of therapy/year (systemic steroids)		22 25	1 12	SCIT vs Pharmacotherapy p <0.01
[10] Maestrelli 2004	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 SCIT post p < 0.01 (difference = +6.4%) Placebo pre vs Placebo post p NS (difference = -1.1)
[57] Pichler 1996	Dust mites	SCIT Placebo	18 months	number of patients taking steroids		6 4	4 2	NR
[57] Pichler 1996	Dust mites	SCIT Placebo	18 months	number of patients taking beta-2 agonists		11 9	8 6	NR
[13] Olsen 1997	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 vs SCIT post p<0.05 Placebo pre vs Placebo post p NS
[13] Olsen 1997	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 vs SCIT post p<0.05 Placebo pre vs Placebo post p NS
[5] Bousquet 1988	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 SCIT post p <0.0001 Placebo pre vs Placebo post p NS SCIT vs Placebo (post) p <0.0001

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[11] Malling 1986	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
[68] Kuna 2011	Alternaria	SCIT 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 2 p=0.001
[8] Hill 1982	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 SCIT post p <0.05 Placebo pre vs Placebo post p NS
[8] Hill 1982	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
[6] Creticos 1996	Short ragweed	SCIT Placebo	Year 2	Medication score		33 +/- 7 28 +/- 4	29 +/- 8 33 +/- 8	SCIT vs Placebo p=0.7
[75] Rak 2001 [76] Rak 2005	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
[1] Adkinson 1997 [2] Limb 2006	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)

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[46] Cantani 1997	Dust mite-Parietaria-ryegrass	SCIT Placebo	3 year	Mean drug usage for asthma attacks		NR	52 180	SCIT vs Placebo p= 0.0003

TABLE 8- ASTHMA COMBINED SYMPTOM AND MEDICATION SCORES-SCIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[7] Garcia-Ortega 1993	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
[42] Akmanlar 2000	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
[3] Altintas 1999	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.
[11] Malling 1986	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)

[49] Horst 1989	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
[68] Kuna 2011	Alternaria	SIT Placebo	3 years	Combined symptom medication score		75 75	30 (65% reduction compared to placebo) 62	Arm 1 vs. Arm 2 p<0.001
[49] Horst 1989	Alternaria	SCIT Placebo	1 year	Global symptom and medication score			0.84 +/- 0.93 3.55 +/- 2.00	SCIT vs placebo p <0.005
[62] Alvarez-Cuesta 1994	Cat	SCIT Placebo	1 year	Combined symptom and medication score (for asthma and rhino-conjunctivitis)	NR	NR NR	0.14% 1.42%	SCIT vs placebo p<0.001 (favors SCIT)
[62] Alvarez-Cuesta 1994	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)
[31] Frew 2006	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	SCIT high vs SCIT low p =0. 34 CI -0.95 to 0.33 SCIT low vs Placebo p =0.13 CI -1.69 to -0.20 SCIT high v s placebo p =0.001 CI -1.89 to -0.62

TABLE 9.SCIT – ASTHMA STUDIES REPORTING COMBINED ASTHMA AND RHINOCONJUNCTIVITIS MEDICATION SCORES

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[55] Nouri-Aria 2003	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
[43] Ariano 2006	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
[44] Arvidsson 2004 [45] Arvidsson 2002	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
[67]Dreborg 1986	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

TABLE 10- ASTHMA PFT RESULTS-SCIT

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
[20] Wang 2006	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	Arm 1 vs Arm 1 p=0.02 Arm 2 vs Arm 2 p=0.01 Arm 1 vs Arm 2 pre p=0.26 Arm 1 vs Arm 2 post p=0.14
[20] Wang 2006	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	Arm 1 vs Arm 1 p=0.02 Arm 2 vs Arm 2 p=0.02 Arm 1 vs Arm 2 pre p=0.16 Arm 1 vs Arm 2,post p=0.11
[20] Wang 2006	Dust mite	SCIT Placebo	1 year	FEV1 (% predicted)	87.96 +/-1.43 87.97 +/-1.74	NR NR	Arm 1 vs Arm 1 p NS Arm 2 vs Arm 2 p NS
[20] Wang 2006	Dust mite	SCIT Placebo	1 year	FVC (% predicted)	94.15 +/-1.39 95.17 +/-1.71	NR NR	Arm 1 vs Arm 1 p NS Arm 2 vs Arm 2 p NS
[10] Maestrelli 2004	Dust mite	SCIT Placebo	3 years	Morning PEF scores (% predicted)	99 97	104 101	Arm 1 vs Arm 1 p<0.05
[54] Newton 1978	Dust mites	SCIT Placebo	15 months	Mean morning peak flow	245 288	232 257	Arm 1 vs Arm 2 p= NS
[59] Tabar 2005	Dust mite	SCIT Cluster SCIT conventional	1 year	PEF variability (%)	6.8 6.8	4.6 6.3	Arm 1 vs Arm 1, p <0.001 Arm 1 vs Arm 2, p = 0.02
[9] Kohno 1998	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	Arm 1 vs Arm 1 p < .03 Arm 2 vs Arm 2 p NS
[5] Bousquet 1988	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	Arm 1 vs Arm 1 p <0.0001 Arm 2 vs Arm 2 p NS Arm 1 vs Arm 2 (post) p<0.0001
[12] Ohman 1984	Cats	SCIT Placebo	17 weeks	Percentage drop peak flow after exposure to cats	9 3	1 4	Arm 1 vs Arm 1 p NS Arm 2 vs Arm 2 p NS Arm 1 vs Arm 2 p NS

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
[77] Varnery. 1997	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)	Arm 1 vs Arm 1 p=0.004 Arm 2 vs Arm 2 p= 0.002
[1] Adkinson 1997 [2] Limb 2006	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)	Arm 1 vs Arm 2 p = 0.05 (mean difference pre = 2.9; post = -3.8)
[75] Rak 2001 [76] Rak 2005	Birch	SCIT Nasal steroid	Peak of medication use (week 4)	Asthma medication usage (beta-2 agonist) Puff per week	NR	4.6 5.0	No significant differences were found between the groups with respect to medication for asthma
[75] Rak 2001 [76] Rak 2005	Birch	SCIT Nasal steroid	6 weeks	Peak expiratory flow% predicted	NR	104 97	No differences were found between the two groups
[44] Arvidsson 2004 [45] Arvidsson 2002	White birch	SCIT Placebo	2 years	Peak flow	NR NR	NR NR	Arm 1 vs Arm 2 p NS
[6] Creticos 1996	Short ragweed	SCIT Placebo	Year 2	Mean daily PEFR during peak season	454 444	480 461	Arm 1 vs Arm 2 p=0.03
[67] Dreborg 1986	Cladosporium	SCIT Placebo	6 months	Mean PEF	290 310	280 340	Arm 1 vs Arm 2 p NS

TABLE 11- SCIT-CHALLENGES SCORES

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[6] Creticos 1996	Short ragweed	SCIT Placebo	2 Year	Amount of allergen causing 20% drop in FEV1			-0.273 ± 0.045 -0.662 ±0.135	Arm 1 vs Arm 2, p=0.03
[20] Wang 2006	Dust mite	SCIT Placebo	1 year	Evening PEF (l/min)		293.1 +/- 10.5 316 +/- 12.1	312.2 +/- 9.27 335.1 +/- 10.7	Arm 1 vs Arm 2, pre p=0.16 Arm 1 vs Arm 2,post p=0.11 Arm 1 vs Arm 1 p<0.02
[20] Wang 2006	Dust mite	SCIT Placebo	1 year	PC20 Histamine		1.367 ± 0.172 1.489 ± 0.21	3.58 ± 0.393 3.42 ± 0.385	Arm 1 vs Arm 2, pre p=0.65 Arm 1 vs Arm 2,post p=0.77 Arm 1 vs Arm 1 p<0.001
[10] Maestrelli 2004	Dust mite	SCIT Placebo	3 years	Morning PEF scores		95 97	104 101	Arm 1 vs Arm 1 p<0.05
[10] Maestrelli 2004	Dust mite	SCIT Placebo	3 years	Methacholine challenge		158 95	183 175	Arm 1 vs Arm 1 = NS Arm2 vs Arm2 = NS
[12] Ohman 1984	Cats	SCIT Placebo	17 weeks	Allergen bronchial provocation, PD20 FEV1 (in BU)		4.27 8.8	20.7 12.3	Arm 1 vs Arm 1, p <0.05 Arm 1 vs Arm 2, p NS
[12] Ohman 1984	Cats	SCIT Placebo	17 weeks	PD FEV1 in BU (Methacholine)		3.0 1.7	4.7 3.8	Arm 1 vs Arm 1, p NS Arm 2 vs Arm 2, p NS
[12] Ohman 1984	Cats	SCIT Placebo	17 weeks	Percentage drop in peak flow rates on exposure to cats		9 3	1 4	Arm 1 vs Arm 1, p NS Arm 2 vs Arm 2, p NS Arm1 vs Arm2, p NS
[1]Adkinson 1997 [2]Limb 2006	Cats	SCIT Placebo	last follow up	PEFR		81.9 84.8	2.5 -1.4	Arm 1 vs Arm 1, p = 0.5
[1]Adkinson 1997 [2]Limb 2006	Cats	SCIT Placebo	last follow up	Bronchial provocation to methacholine		0.23 0.32	0.41 0.39	Arm 1 vs Arm 2, p = 0.99
[44]Arvidsson 2004 [45]Arvidsson 2002	White birch	SCIT Placebo	2 years	Allergen Bronchial provocation test PD20		120 600	800 450	Arm 1 vs Arm 2 p<0.01

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[44]Arvidsson 2004 [45]Arvidsson 2002	White birch	SCIT Placebo	2 years	Conjunctival provocation test		NR NR	NR NR	Arm vs Arm 2 = NS
[44]Arvidsson 2004 [45]Arvidsson 2002	White birch	SCIT Placebo	2 years	Methacholine provococation test		0.62 0.50	0.9 2.3	Arm 1 vs Arm 1= NS Arm 1 vs Arm 1= NS Arm 2 vs Arm 2<0.02
[44]Arvidsson 2004 [45]Arvidsson 2002	White birch	SCIT Placebo	2 years	Peak flow		NR NR	NR NR	Arm 1 vs Arm 2, p =NS
[54]Newton 1978	Dust mites	SCIT Placebo	15 months	Mean Peak flow		245 288	232 257	Arm 1 vs Arm 2, p= NS
[54]Newton 1978	Dust mites	SCIT Placebo	15 months	Mean dose of allergen in PNU to achieve 25% fall in PEF		234 298	408 215	Arm 1 vs Arm2, p<0.005 (ED50)
[57]Pichler 1996	Dust mites	SCIT Placebo	12 months	Conjunctival provocation test		100000 100000	100000 100000	Arm 1 vs Arm 1 p=0.469 Arm 2 vs Arm 2 p=0.4062 Arm 1 vs Arm 2 p=0.0196
[57]Pichler 1996	Dust mites	SCIT Placebo	12 months	Methacholine provocation test		46 NR	130 97.5	Arm 1 vs Arm 1 p<0.005 Arm 2 vs Arm 2 p=NS Arm 1 vs Arm 2 p=NS
[80]Tari 1990	Dust mites	SCIT Placebo	18 months	Nasal provocation test			5.2% improved	Arm 1 vs Arm 2, p<0.01
[80]Tari 1990	Dust mites	SCIT Placebo	18 months	Allergen bronchial provocation test PD-FEV1		170.8 ±18.4	300.3 ±28.4	
[80]Tari 1990	Dust mites	SCIT Placebo	18 months	Methacholine provocation test		280.8±16.4	502.3±26.6	Arm 1 vs Arm 1, p<0.05
[80]Tari 1990	Timothy grass	SCIT Placebo	3 months	Conjunctival provocation threshold		4025.6 2109.5	NR NR	Arm 1 vs Arm 2 p<0.001

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[67] Dreborg 1986	Cladosporium	SCIT Placebo	10 week period during peak season	Conjunctival provocation tets		NR NR	NR NR	Arm 1 vs Arm 2 p>0.05 Arm 1 vs Arm 1, p=0.01
[67] Dreborg 1986	Cladosporium	SCIT Placebo	10 week period during peak season	Bronchial provocation test		NR NR	NR NR	Arm 1 vs Arm 2 p<0.05 Arm 1 vs Arm 1, p<0.01
[42] Akmanlar 2000	Dust mites	SCIT-Rush SCIT-conventional	3 years	Allergen bronchial provocation test		20470 20470		Arm1 vs Arm2, p=0.41 (6 months)
[3] Altintas 1999	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
[62] Alvarez-Cuesta 1994	Cats	SCIT Placebo	1 year	Allergen bronchial provocation test			3.42 times improvement 1.08 times improvement	Arm1, pre vs post, p<0.05 Arm2, pre vs post,p=NS Arm1 vs Arm2, p<0.05
[62] Alvarez-Cuesta 1994	Cats	SCIT Placebo	1 year	Chemical bronchial provocation test		0.56 0.81	0.57 0.58	Arm1, pre vs post, p=NS Arm2, pre vs post,p=NS
[62] Alvarez-Cuesta 1994	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
[63] Bousquet 1991 [64] Bousquet 1991	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	Arm1 vs Arm2, p<0.01 Arm3 vs Arm4, p=NS Arm1 vs Arm3, p=NS

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[4] Bousquet 1985	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	Arm1, pre vs post, p<0.01 Arm2, pre vs post,p=NS Arm1 vs Arm2, p<0.01
[29] Crimi 2004	Parietaria	SCIT Placebo	3 years	Methacholine bronchial challenge PC-15		6.36 5.21	6.89 5.64	Arm1 vs Arm2, p=NS
[7] Garcia-Ortega 1993	Dust mite	SCIT-Cluster Conventional treatment	7 months	Allergen bronchial provocation, PD-20		47±52 70±93	425±303 106±196	Arm1, pre vs post, p=0.01 Arm1 vs Arm2, p=0.001
[7] Garcia-Ortega 1993	Dust mite	SCIT-Cluster Conventional treatment	7 months	Methacholine bronchial provocation		18±26 19±27		Arm1 vs Arm2, p=NS
[48] Hedlin 1999	Cat, dust mite, Birch, Timothy	SCIT Placebo	1 year	Allergen bronchial provocation, PC-20		1900 1400	100000 5600 (SQU/ml)	Arm1, pre vs post, p<0.001 Arm2, pre vs post, p<0.01 Arm1 vs Arm2, p=0.001
[48] Hedlin 1999	Cat, dust mite, Birch, Timothy	SCIT Placebo	1 year	Histamine bronchial provocation		0.18 0.28	1.68 0.54 (mg/ml)	Arm1, pre vs post, p=0.002 Arm2, pre vs post, p<0.05 Arm1 vs Arm2, p=NS
[49] Horst 1989	Alternaria	SCIT Placebo	1 year	Nasal challenge		2.8±0.6 2.8±1.0	1.6±1.2 2.5±1.1	Arm1, pre vs post, p<0.001 Arm2, pre vs post, p=NS Arm1 vs Arm2, p<0.05
[49] Horst 1989	Alternaria	SCIT Placebo	6 months	Airway responsiveness to allergen		1:303.7±123.7 1:230.0±154.5	1:65.0±13.2 1:291.7±158.9	Arm1, pre vs post, p<0.03 Arm2, pre vs post, p=NS
[49] Horst 1989	Alternaria	SCIT Placebo	6 months	Airway responsiveness to histamine		397.1±206.9 241.3±61.1	1391.3±283.3 252.3±45.0 (µg/ml)	Arm1, pre vs post, p<0.03 Arm2, pre vs post, p=NS
[68] Kuna	Alternaria	SCIT Control	3 years	Nasal Challenge		207 199	67 185	Arm 1 pre v. post p<0.05

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[30] Dreborg	Dust Mite Timothy	SCIT Timothy SCIT dust mite	3 years	Conjunctival Provocation Challenge		6166 724	100000 26915	Arm 1: 16.2 fold increase p<0.05 Arm 2: 32 fold increase, p<0.05

TABLE 12- SCIT- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[6] Creticos 1996	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
[21] Durham 1999	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
[55] Nouri-Aria 2003 [40] Walker 2001	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
[55] Nouri-Aria 2003 [40] Walker 2001	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)
[29] Crimi 2004	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
[28] Bernstein 1976	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[31] Frew 2006	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
[32] Frostad 1983	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
[22] Junqueira de Queiros 2008	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
[23] McHugh 1990	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
[34] Klimek 1999	Grass mix-Trees mix	SCIT Pharmacotherapy	44 weeks	median nasal symptoms score			106.5 264	SCIT vs Pharmacotherapy p= 0.02
[35] Leynadier 2000	Grass mix	SCIT Placebo	1 year	Unspecified nasal symptom scores			33.5 38.6	SCIT vs Placebo p NS
[12] Ohman 1984	Cat	SCIT Placebo	17 weeks	Time to increase in nasal symptoms on exposure to cats				SCIT pre vs post p NS Placebo pre vs post p NS SCIT 1 vs placebo p NS
[24] Polosa 2004 [25] Polosa 2003	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[38] Möller 2002	SCIT Grass and Birch	SCIT Placebo	5 years	VAS Nose symptom score		0 0	-21.5 -7.4	SCIT vs Placebo p <0.01
[36] Olsen 1995	Mugwort Birch Timothy	SCIT-Artemisia SCIT- Betula /Phleum extract	2 years	Nasal and ocular symptom score		20	21	SCIT pre vs post p NS
[39] Varney 1991	Timothy	SCIT Placebo	7 months	Total nasal symptom score			49 143	SCIT vs Placebo p=0.002 CI 38 to 111
[41] Zenner. 1996	Grass mix	SCIT Placebo	10 weeks	Unspecified nasal symptom scores			44.5 63.3	SCIT vs Placebo p =0.014
[60] Tabar 2007	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
[57] Pichler, 1996	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
[61] Varney, 2003	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
[69] Mirone 2004	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
[70]Osterballe 1982 [71]Osterballe 1981 [72]Osterballe 1980 [73]Osterballe 1982	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
[75] Rak 2001 [76] Rak 2005	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
[63] Bousquet 1991 [64] Bousquet 1991	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
[66] Dolz 1996	Timothy-Orchard-Ryegrass	SCIT Placebo	3 year	Unspecified nasal symptom scores		0 0	0 35	SCIT pre vs post <0.0001

TABLE 13- SCIT- OCULAR SYMPTOM SCORES

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[12] Ohman 1984	Cats	SCIT Placebo	17 weeks	Time to first increase in ocular symptoms on exposure				SCIT pre vs post p<0.05 SCIT vs Placebo NS
[21] Durham 1999	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
[55] Nouri-Aria 2003 [40] Walker 2001	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)
[31] Frew 2006	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 100,000 Vs Placebo p<0.001 CI (-0.72,-0.28) SCIT 10,000 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)
[34] Klimek 1999	Grass mix	SCIT Pharmacotherapy		Conjunctival symptoms			21 40	SCIT vs Placebo p=0.099

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[35] Leynadier 2000	Grass mix	SCIT Placebo	1 year	Unspecified ocular scale			16 17.3	SCIT vs Placebo p NS
[38] Möller 2002	Birch and Timothy grass	SCIT Placebo	5 year	VAS- Ocular symptoms	0-100mm		-29.4 mm -11.8 mm (Change from baseline)	SCIT vs Placebo p<0.01
[39] Varney 1991	Timothy	SCIT Placebo	7 months	Ocular symptom scores			37 87	SCIT pre vs post p=0.02 CI 10 to 82
[41] Zenner 1996	Rye- Secale cereal and Grass mix	SCIT Placebo	10 weeks	Ocular symptom scores			26.6 mean 28.3 mean	SCIT vs Placebo 0.256
[47] Ferrer 2005	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
[60] Tabar 2007	Alternaria	SCIT Placebo	12 months after maintenance dose began	median score of the weekly average of the active group	0-3	0.33±0.34 0.13±0.27	0.33±0.47 0.11±0.18	
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass	SCIT- partially purified extract SCIT- Ag 19 25	3 years	conjunctivitis symptom score		0 20	0 0	
[66] Dolz 1996	Mix grass	SCIT Placebo		Ocular symptom scores			0 34	SCIT pre vs post p<0.001
[67] Dreborg 1986	Cladosporium	SCIT Placebo	10 weeks	None	0-3			SCIT vs Placebo p>0.05

TABLE 14- SCIT- RHINITIS COMBINED SYMPTOM SCORES

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[31] Frew 2006	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	Arm 1 vs Arm 2 p =0. 34 CI -0.95 to 0.33 Arm 2 vs Arm 3 p =0.13 CI -1.69 to -0.20 Arm 1 vs Arm 3 p =0.001 CI -1.89 to -0.62
[60] Tabar 2007	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
[61] Varney, 2003	Dust mites	SCIT Placebo	12 months	total symptom score	1-3/7	171 +/- 23 195 +/- 42	72 +/- 26 132 +/- 48	Arm 1 vs Arm 1 p = 0.002 Arm 2 vs Arm 2 p NS Arm 1 vs Arm 2 p NS
[74] Pence 1975	Mountain cedar	SCIT Placebo	Peak of pollen season	Combined total symptoms score			5.46 8.83	Arm 1 vs Arm 2 p <0.01
[78] Weyer, 1981	Grass mix	SCIT Placebo	8 months	Total symptom scores	0-100		16 +/- 10 24 +/- 18	Arm 1 vs Arm 2 p≤ 0.09
[30] Dreborg	Dust Mite Timothy	SCIT Timothy SCIT dust mite	3 years	Combined Symptom Score				Arm 1 pre vs post p=0.041 Arm 2 pre vs post p=0.018 Arm 1 vs Arm2 NS
[40] Walker	Grass Mix	SCIT Placebo	2 years	Combined Symptoms (lung,nasal,eye)		2576 1962	1277 1386	Arm 1 v Arm 2 p=0.01
[50] Munoz	Timothy Grass	SCIT-Perennial SCIT-Seasonal	3 years	Combined Symptom Score			53.4+/-49 46.1+/-47.55	

TABLE 15- SCIT- RHINITIS MEDICATION SCORES

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[39] Varney 1991	Timothy	SCIT Placebo	7 months	Nasal drug score intake			78 232	Arm 1 vs Arm 2 p=0.001 CI 178 to 574
[21] Durham 1999	Timothy grass	SCIT Placebo	3 years (pollen season)	Rescue medication score			672 357	Arm 1 vs Arm 1 p = 0.88
[23] McHugh 1990	Dust mite	SCIT pure-pharmalgen SCITcrude-allpyral	3 months	Medication score for rhinitis		1.42 +/- 0.42 0.94 +/- 0.29	0.19 +/- 0.12 1.02 +/- 0.57	Arm 1 vs Arm 1 p< 0.05 Arm 1 vs Arm 3 p p< 0.05
[34] Klimek 1999	Grass mix-Trees mix	SCIT Pharmacotherapy	44 weeks	topical antihistamine doses			71 546	Arm 1 vs Arm 2 p= 0.02
[35] Leynadier 2000	Grass mix	SCIT Placebo	1 year	Medication score		11.1 5.0	40.8 -1.2	Arm 1 vs Arm 2 p=0.005
[24] Polosa 2004 [25] Polosa 2003	Parietaria	SCIT Placebo	3 years	Unspecified medication score		12 18	0 75	Arm 1 vs Arm 2 p =0.002
[28] Bernstein 1976	Ragweed	SCIT Placebo	1 month	days where drugs were required	0-1		0.41 0.58	Arm 1 vs Arm 2 p =0.01
[32] Frostad 1983	Timothy	SCIT pure SCIT crude SCIT grass mix Control	3 years	Percent of patients using antihistamines			14 48 56	Arm 1 vs Arm 2 p =0.02 Arm 1 vs Arm 3 p =0.01
[36] Olsen 1995	Timothy-Birch-Mugwort	SCIT Placebo	2 years	medication score		50	0	Arm 1 vs Arm 1 p =0.067
[47] Ferrer 2005	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	Arm 1 vs Arm 1 p= 0.007 Arm 2 v Arm 2: NS Arm 1 vs Arm 2 p =NS
[81] Tabar	Dust Mites	SCIT-5 Years SCIT-3 Years Control	5 Years	Rhinitis-Medication Score		5.5 5.5 4.5	2 3 4.2	Arm 1 vs Arm 3 p<0.01 Arm 2 vs Arm p<0.01

TABLE 16- SCIT RHINITIS AND ASTHMA COMBINED MEDICATION SCORE

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[39] Varney 1991	Timothy	SCIT Placebo	7 months	total drug score intake			129 627	Arm 1 vs Arm 2 p=0.002 CI 178 to 574
[31] Frew 2006	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	Arm 1 vs Arm 2 p= 0.79 Arm 1 vs Arm 3 p= 0.0007 Arm 2 vs Arm 3 p= 0.16
[24] Polosa 2004 [25] Polosa 2003	Parietaria	SCIT Placebo	3 years	Unspecified medication score		12 18	0 75	Arm 1 vs Arm 2 p =0.002
[29] Crimi 2004	Parietaria	SCIT Placebo	3 years	sum of scores		12 18	5 59% improvement 78 -263% improvement	Arm 1 vs Arm 2 p =0.001
[47] Ferrer 2005	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	Arm 1 vs Arm 1 p= 0.033 Arm 2 vs Arm 2 p NS Arm 1 vs Arm 2 p =0.039
[61] Varney, 2003	Dust mites	SCIT Placebo	12 months	Total Medication score		74 +/- 31 65 +/- 26	59 +/- 15 66+/- 35	Arm 1 vs Arm 2 p NS
[69] Mirone 2004	Short ragweed	SCIT Placebo	1 year	Rescue medication score		3 1.9	0.6 2.8	Arm 1 vs Arm 1 p=0.006 Arm 2 vs Arm 2 p NS
[78] Weyer, 1981	Grass mix	SCIT Placebo	8 months	Unspecified medication score			3 +/- 5 11 +/- 13	Arm 1 vs Arm 2 p≤ 0.007
[66] Dolz 1996	Timothy-Orchard-Ryegrass	SCIT Placebo	3 year	Medication score			20 65	Arm1 vs Arm1 <0.01

[60] Tabar 2007	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	Arm 1 vs Arm 2 p= 0.002
[40] Walker	Grass Mix	SCIT Placebo	2 years	Combined medications (lung,nasal,eye)		1815 2124	357 1851	Arm 1 v Arm 2 p=0.007
[50] Munoz	Timothy Grass	SCIT-Perennial SCIT-Seasonal	3 years	Combined Medication Score			15.7+/-25.30 8.7+/-11.61	

TABLE 17- SCIT- RHINITIS COMBINED SYMPTOMS AND MEDICATION SCORES

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[26] Van Metre 1980	Ragweed	SCIT Placebo	End of pollen season	Total symptom and medication scores	0-1		0.41 0.58	Arm 1 vs Arm 2 p =0.01
[27] Van Metre 1981	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	Arm 1 vs Arm 2 p <0.01 Arm 2 vs Arm 3 p <0.01 Arm 1 vs Arm 3 p NS
[59] Tabar 2005	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	Arm 1 vs Arm 1 p<0.001 Arm 2 vs Arm 2 p <0.001
[60] Tabar 2007	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	

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[68] Kuna 2011 (SMS)	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%
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy	SCIT partially purified SCIT Ag 19 25	3 years	Combined total symptoms and Medication score		113 197	1 130	Arm 1 vs Arm 2 psignificant
[78] Weyer, 1981	Grass mix	SCIT Placebo	8 months	Total symptom and medication scores	NR	8+/-6 12+/-10	10+/- 7 18 +/- 15	Arm 1 vs Arm 2 p≤ 0.03
[65] Chakraborty 2006	Date trees	SCIT Placebo	2 years	Combined symptom and medication score	0-3		57% improvement	Arm1 vs Arm1 p <0.001 Arm2 vs Arm2 p NS
[33] James	Grass	SCIT+2 yrs SCIT SCIT+Placebo	4 years	Combined rhinitis-medication score				Pre-Post Arm 1 p=0.03 Pre-post Arm 2 p=0.03
[37] Shamji	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	Arm 1 vs Arm 3 p=0.001
[56] Peterson	Birch Pollen	SCIT-Birch + Pollen mix alum-precipitated SCIT-Birch alone alum-precipitated	3 Years	Combined Symptom Medication Score				No difference between groups

TABLE 18.- SCIT- ASTHMA SECONDARY OUTCOMES

Study	ARMS	QOL	Prevention of asthma	Adherence
[68] Kuna 2011	SCIT Placebo	QOL SIT was associated with significant improvement in QOL with regard to asthma ($p<0.05$) and rhinoconjunctivitis ($p<0.05$)		
[81] Tabar 2010	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 19.- SCIT- RHINITIS SECONDARY OUTCOMES

RefId	ARMS	QOL	Prevention of asthma
[24] Polosa 2004 [25] Polosa 2003	SCIT Placebo		2 developed asthma 7 developed asthma (p=0.056)
[29] Crimi 2004	SCIT Placebo		Reported- NS
[31] Frew 2006	SCIT 100,000 SQU SCIT 10,000 SQU Placebo	RQLQ- 183* significant RQLQ-88 RQLQ-92	
The PAT study [82] Jacobsen, 2007 [83] Niggeman 2006 [38] Möller 2002	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 ($p<0.01$)
[47] Ferrer 2005	SCIT Placebo	Reported Reported	

[60] Tabar 2007	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	
[46] Cantani 1997	SCIT Control (drug-treated)	Reported - Not significant Difference	
[40] Walker	SCIT Placebo	Overall increase in QOL p=0.02	
[56] Peterson	SCIT SCIT	Reported subjective assessments- Improved but no statistical data	
[68] Kuna	SCIT Control	3 years : Improvement in RQLQ p<0.05	
[81] Tabar 2010	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 20. SCIT- BIOMARKERS

Study	ARMS	BIOMARKERS	BIOMARKER
[68] Kuna 2011	SCIT Placebo	Specific IgG4 : Significant increase in SIT arm (p<0.001). No significant change in placebo group (p=0.92). After 3 years Arm 1 vs. Arm 2 p<0.001.	

TABLE 21. SCIT- SAFETY

SCIT Local Reactions

Local reactions reported as patients

Study	Allergen	Number of patients in arm	Percent of patients with local reactions	Severity
[42] Akmanlar 2000	Other dust mites: Both Der P and F	18	17	Moderate
[3] Altintas 1999	Dermatophagoides pteronyssinus	34	18	Unspecified
[62] Alvarez-Cuesta 1994	Cats	28	25	Unspecified
[28] Bernstein 1976	Short ragweed	68	35	Unspecified
[65] Chakraborty 2006	Other tree date sugar palm/wild date palm	18	6	Unspecified
[66] Dolz 1996	Timothy grass Orchard grass Percentennial ryegrass	18	22	Moderate
[67] Dreborg 1986	Cladosporium	16	25	Unspecified
[54] Newton 1978	Dermatophagoides farinae	7	14	Unspecified
[60] Tabar 2007	Alternaria	14	7	Unspecified
[19] Van Metre 1988	Cats	11	55	Unspecified

Local reactions reported as events

Study	Allergen	Number of patients in arm	Number of events	Number of events per patient	Severity
[34] Klimek 1999	Grass mix	24	16	0.666667	Unspecified
[35] Leynadier 2000	Orchard grass meadow fescue perennial ryegrass sweet vernal grass timothy grass	16	6	0.375	Mild
[50] Munoz Lejarazu 1993	Timothy grass (perennial)	18	6	0.333333	Mild
[50] Munoz Lejarazu 1993	Timothy grass (seasonal)	26	8	0.307692	Mild
[12] Ohman 1984	Cats	9	3	0.333333	Severe
[58] Prieto 2010	Placebo	18	16	0.888889	Moderate
[58] Prieto 2010	Alternaria	21	17	0.809524	Moderate
[84] Reid 1986	Grass mix (grass extract included)	9	287	31.88889	Mild
[84] Reid 1986	Grass mix (grass extract included)	9	20	2.222222	Moderate

Study	Allergen	Number of patients in arm	Number of events	Number of events per patient	Severity
[84] Reid 1986	Grass mix (grass extract not included)	9	214	23.77778	Mild
[84] Reid 1986	Grass mix (grass extract not included)	9	7	0.777778	Moderate
[15] Schubert 2009	Unspecified dust mites (classic schedule)	10	80	8	Unspecified
[15] Schubert 2009	Unspecified dust mites (cluster schedule)	20	185	9.25	Unspecified
[85] Shaikh 1997	Dermatophagoides farinae	28	23	0.82	Unspecified
[16] Valovirta 1986	Placebo	12	251	20.91667	Mild
[16] Valovirta 1986	Dogs	15	309	20.6	Mild
[26] Van Metre 1980	Ragweed	15	5	0.333333	Unspecified
[27] Van Metre 1981	Ragweed (weekly)	15	33	2.2	Unspecified
[27] Van Metre 1981	Ragweed (clustered)	18	15	0.833333	Unspecified
[77] Varnery. 1997	Cats	13	6	0.461538	Unspecified
[77] Varnery. 1997	Placebo	15	6	0.4	Unspecified
[39] Varney 1991	Timothy grass	21	22	1.047619	Mild
[41] Zenner. 1996	Placebo	41	6	0.146341	Unspecified
[41] Zenner. 1996	Grass mix and Secale cereale	45	30	0.666667	Unspecified
[68] Kuna 2011	Alternaria placebo	30 (987 injections) 20 (702 injections)	4 SIT patients (11 injections)	1.1 %	Local edema

Cutaneous reactions reported as patients

Study	Allergen	Number of Patients in arm	Percent of patients with cutaneous reactions	Severity
[46] Cantani 1997	Dermatophagoides pteronyssinus Perennial Parietaria officinalis	151	2	Unspecified
[67] Dreborg 1986	Cladosporium	16	19	Unspecified
[31] Frew 2006	Timothy grass (100000 SQ-U)	203	14	Unspecified
[31] Frew 2006	Timothy grass (10000 SQ-U)	104	1	Unspecified
[31] Frew 2006	Placebo	103	1	Unspecified

SCIT Respiratory Reactions

Respiratory reactions reported as patients

Study	Allergen	Number of Patients in arm	Percent of patients with respiratory reactions	Severity
[42] Akmanlar 2000	Other dust mites: Both Der P and F (conventional schedule)	9	22	Severe
[42] Akmanlar 2000	Other dust mites: Both Der P and F (rush schedule)	9	33	Severe
[28] Bernstein 1976	Placebo	63	3	Moderate
[86] Blumberga 2006	Dermatophagoides pteronyssinus	26	4	Severe
[46] Cantani 1997	Dermatophagoides pteronyssinus Perennial ryegrass Parietaria officinalis	151	1	Unspecified
[66] Dolz 1996	Timothy grass Orchard grass Perennial ryegrass	18	39	Severe
[31] Frew 2006	Placebo	103	2	Unspecified
[31] Frew 2006	Timothy grass (100000 SQ-U)	203	12	Unspecified
[7] Garcia-Ortega 1993	Dermatophagoides pteronyssinus (cluster schedule)	18	11	Moderate
[9] Kohno 1998	Bronchodilators	8	25	Unspecified

Respiratory reactions reported as events

Study	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
[47] Ferrer 2005	Placebo	29	3	0.103448	Unspecified
[47] Ferrer 2005	Parietaria judaica	28	11	0.392857	Unspecified
[47] Ferrer 2005	Parietaria judaica	28	4	0.142857	Moderate
[10] Maestrelli 2004	Placebo	31	1	0.032258	Mild
[11] Malling 1986	Placebo	11	2	0.181818	Unspecified
[11] Malling 1986	Cladosporium	12	5	0.416667	Unspecified
[23] Malling 1986	Placebo	20	10	0.5	Mild
[55] Nouri-Aria 2003 [40] Walker 2001	Timothy grass	22	1	0.045455	Mild
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980	Timothy grass (partially purified)	20	3	0.15	Unspecified

Study	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
[73] Osterballe 1982					
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass (partially purified)	20	5	0.25	Moderate
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass (Ag 19 25)	20	4	0.2	Unspecified
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass (Ag 19 25)	20	8	0.4	Moderate
[87] Paranos 1997	Dermatophagoides pteronyssinus	7	4	0.571429	Unspecified
[87] Paranos 1997	Dermatophagoides pteronyssinus	7	2	0.285714	Moderate
[58] Prieto 2010	Alternaria	21	11	0.52381	Unspecified
[58] Prieto 2010	Alternaria	21	2	0.095238	Moderate
[58] Prieto 2010	Placebo	18	11	0.611111	Unspecified
[58] Prieto 2010	Placebo	18	3	0.166667	Moderate
[39] Varney 1991	Timothy grass	21	1	0.047619	Moderate
[39] Varney 1991	Placebo	19	2	0.105263	Unspecified
[41] Zenner. 1996	Grass mix Rye- Secale cereale	45	1	0.022222	Unspecified
[41] Zenner. 1996	Grass mix Rye- Secale cereale	45	1	0.022222	Severe
[81]Tabar 2010	Dust mite SCIT 5 years-SCIT 3 years	142 receiving SCIT	5	0.0352	3 patients had rhinoconjunctivitis 2 patients had asthma attacks Severity unspecified

SCIT Gastrointestional Reactions

Gastrointestional reactions reported as patients

Study	Allergen	Number of Patients in Arm	Percent of patients with gastrointestinal reactions	Severity
[42] Akmanlar 2000	Both Der P and F	18	17	Mild
[31] Frew 2006	Timothy grass (10000 SQ-U)	104	25	Mild

Gastrointestional reactions reported as events

Study	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
[44] Arvidsson 2004 [45] Arvidsson 2002	Placebo	24	19.8% of events	Unknown total number of events	Mild
[44] Arvidsson 2004 [45] Arvidsson 2002	White birch	22	27.6% of events	Unknown total number of events	Mild
[49] Horst 1989	Alternaria	13	2	0.153846	Moderate
[35] Leynadier 2000	Orchard grass meadow fescue perennial ryegrass sweet vernal grass timothy grass	16	2	0.125	Moderate
[10] Maestrelli 2004	Both der P and der F	41	2	0.04878	Mild
[11] Malling 1986	Cladosporium	12	32	2.666667	Moderate
[11] Malling 1986	Cladosporium	12	27	2.25	Severe
[23] Malling 1986	Dermatophagoides pteronyssinus (purified)	30	3	0.1	Mild
[23] Malling 1986	Dermatophagoides pteronyssinus (purified)	30	7	0.233333	Moderate
[55] Nouri-Aria 2003 [40] Walker 2001	Timothy grass	22	3	0.136364	Mild
[55] Nouri-Aria 2003 [40] Walker 2001	Placebo	22	4	0.181818	Mild
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass (Ag 19 25)	20	1	0.05	Unspecified
[15] Schubert 2009	Unspecified dust mites	20	10	0.5	Mild

Study	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
	(cluster schedule)				
[15] Schubert 2009	Unspecified dust mites (cluster schedule)	20	2	0.1	Moderate
[15] Schubert 2009	Unspecified dust mites (classic schedule)	10	6	0.6	Mild
[15] Schubert 2009	Unspecified dust mites (classic schedule)	10	1	0.1	Moderate
[77] Varnery. 1997	Placebo	15	2	0.133333	Mild
[77] Varnery. 1997	Cats	13	3	0.230769	Mild
[61] Varney, 2003	Dermatophagoides pteronyssinus	15	7	0.466667	Moderate

SCIT Unspecified Reactions

Unspecified reactions reported as patients

Study	Allergen	Number of Patients in Arm	Percent of patients with unspecified reactions	Severity
[6] Creticos 1996	Placebo	40	<1	Unspecified
[67] Dreborg 1986	Cladosporium	16	25	Unspecified
[8] Hill 1982	Ryegrass	11	9	Unspecified
[59] Tabar 2005	Dermatophagoides pteronyssinus (maintenance phase)	239	<1	Unspecified
[59] Tabar 2005	Dermatophagoides pteronyssinus (incremental-dose phase)	239	1	Unspecified

Unspecified reactions reported as events

Study	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
[44] Arvidsson 2004 [45] Arvidsson 2002	Placebo	24	20	0.833333	Unspecified
[44] Arvidsson 2004 [45] Arvidsson 2002	White birch	22	22	1	Unspecified
[47] Ferrer 2005	Parietaria judaica	28	1	0.035714	Unspecified
[47] Ferrer 2005	Placebo	29	1	0.034483	Unspecified

[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass (partially purified)	20	3	0.15	Unspecified

SCIT Unspecified Systemic Reactions
Systemic reactions reported as Patients

Study	Allergen	Number of Patients in Arm	Percent of patients with unspecified reactions	Severity
[62] Alvarez-Cuesta 1994	Cats	28	11	Unspecified
[28] Bernstein 1976	Short ragweed	68	25	Unspecified
[28] Bernstein 1976	Placebo	63	6	Unspecified
[86] Blumberga 2006	Dermatophagoides pteronyssinus	26	38	Unspecified
[86] Blumberga 2006	Placebo	28	29	Unspecified
[63] Bousquet 1991 [64] Bousquet 1991	Orchard grass London plane Olive Parietaria (grass pollen)	16	19	Unspecified
[63] Bousquet 1991 [64] Bousquet 1991	Orchard grass London plane Olive Parietaria (multiple pollen)	16	25	Unspecified
[4] Bousquet 1985	Dermatophagoides pteronyssinus	20	20	Unspecified
[6] Creticos 1996	Short ragweed	37	19	Unspecified
[19] Van Metre 1988	Cats	11	18	Unspecified

Systemic Reactions reported as Events

Study	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
[47] Ferrer 2005	Parietaria judaica	28	5	0.178571	Unspecified
[22] Junqueira de Queiros 2008	Dermatophagoides pteronyssinus	25	6	0.24	Unspecified
[48] Hedlin 1999	Cats Dermatophagoides pteronyssinus White birch Timothy grass (plus pollen extract)	15	5	0.333333	Unspecified
[34] Klimek 1999	Grass mix	24	7	0.291667	Unspecified
[35] Leynadier 2000	Placebo	13	2	0.153846	Unspecified
[35] Leynadier 2000	Orchard grass meadow fescue perennial ryegrass sweet vernal grass timothy grass	16	7	0.4375	Unspecified

Study	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
[23] McHugh 1990	Placebo	20	13	0.65	Unspecified
[23] McHugh 1990	Dermatophagoides pteronyssinus (purified)	30	31	1.033333	Unspecified
[55] Nouri-Aria 2003 [40] Walker 2001	Placebo	22	1	0.045455	Unspecified
[55] Nouri-Aria 2003 [40] Walker 2001	Timothy grass	22	3	0.136364	Unspecified
[12] Ohman 1984	Placebo	8	2	0.25	Unspecified
[12] Ohman 1984	Cats	9	10	1.111111	Unspecified
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass (Ag 19 25)	20	9	0.45	Unspecified
[87] Paranos 1997	Dermatophagoides pteronyssinus	7	2	0.285714	Unspecified
[84] Reid 1986	Grass mix (grass extract not included)	9	1	0.111111	Unspecified
[84] Reid 1986	Grass mix (grass extract included)	9	4	0.444444	Unspecified
[26] Van Metre 1980	Ragweed	15	19	1.266667	Unspecified
[27] Van Metre 1981	Ragweed (weekly)	15	13	0.866667	Unspecified
[27] Van Metre 1981	Ragweed (clustered schedule)	18	19	1.055556	Unspecified
[41] Zenner. 1996	Placebo	41	5	0.121951	Unspecified
[41] Zenner. 1996	Grass mix Rye- Secale cereale	45	9	0.2	Unspecified

Anaphylactic reactions reported as events

Study	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Definition of anaphylaxis
[11] Malling 1986	Cladosporium	12	1	0.083333	Involvement of the skin/mucosal tissue and reduced blood pressure or associated symptoms occurring rapidly after exposure to a likely allergen for that patient
[11] Malling 1986	Cladosporium	12	2	0.166667	Involvement of the skin/mucosal tissue and respiratory compromise occurring rapidly after exposure to a likely allergen for that patient
[23] Malling 1986	Dermatophagoides pteronyssinus	30	8	0.266667	The acute onset of a reaction (minutes to hours) with involvement of the skin mucosal tissue or both and respiratory compromise

	(purified)				
[50] Munoz Lejarazu 1993	Timothy grass (seasonal)	18	1	0.055556	The acute onset of a reaction (minutes to hours) with involvement of the skin mucosal tissue or both and respiratory compromise
[39] Varney 1991	Timothy grass	21	1	0.047619	The acute onset of a reaction (minutes to hours) with involvement of the skin mucosal tissue or both and respiratory compromise
[81] Tabar 2010	Dust mite SCIT 5 years-SCIT 3 years	142 receiving SCIT	1	0.007	

SCIT Comments on Adverse Reactions
Comments on adverse reactions reported as patients

Refid	Allergen	Number of patients in arm	Comments
[1] Adkinson 1997 [2] Limb 2006	White oak Dermatophagoides pteronyssinus Dermatophagoides farina Short ragweed Grass mix AlternariaBermuda grass English plantain Cladosporium As Percentgillus	61	Numbers were reported but adverse events were not specified. 21 AEs in 61 children
[1] Adkinson 1997 [2] Limb 2006	Placebo	60	Numbers were reported but adverse events were not specified. 4 AEs in 60 children
[42] Akmanlar 2000	Other dust mites: Both Der P and F (Conventional schedule)	9	bronchospasm
[42] Akmanlar 2000	Other dust mites: Both Der P and F (Rush schedule)	9	bronchospasm. 3 patients with local reactions were described as follows: local swelling larger than 3 cm making it necessary to adjust updosing in Conventional IT. These patients could not attain the optimum maintenance dose (100,00 SQ). One reached 20,000 SQ; others reached 60,000 and 80,000 SQ.
[62] Alvarez-Cuesta 1994	Cats	28	They report the different stage of the reaction building dose phase and maintenance dose phase)
[28] Bernstein 1976	Placebo	63	Total of 6 patients with systemic reactions in Placebo group.
[86] Blumberga 2006	Placebo	28	Subcutaneous nodules were observed in 26% more patients in the active group compared with placebo. placebo contained histamine.
[63] Bousquet 1991 [64] Bousquet 1991	Orchard grass London plane Olive Parietaria (multiple pollens)	16	None of the patients treated by placebo had a systemic reaction.
[4] Bousquet 1985	Dermatophagoides pteronyssinus	20	3 of the 4 required adrenalin!
[65] Chakraborty 2006	Date sugar palm/wild date palm	18	There was no systemic reaction in any of the 35 patients in the 2-year Percent rate of local adverse events of 0.024% for a total of 2095 injections administered

Refid	Allergen	Number of patients in arm	Comments
[6] Creticos 1996	Short ragweed	37	During treatment year 1 seven patients receiving ragweed extract reported systemic allergic symptoms after injections (on 14 occasions). Five of these reactions were mild and resolved spontaneously; nine consisted of rhinitis, generalized urticaria angioedema or some combination of these symptoms and were treated with antihistamines or epinephrine. Two patients receiving ragweed extract dropped out after having several systemic reactions.
[6] Creticos 1996	Placebo	40	One patient assigned to the placebo group received an injection of active extract by mistake and had a severe systemic reaction characterized by bronchospasm and hypotension. Recovery with treatment was rapid. Four other patients receiving placebo reported moderate reactions and received treatment. No evidence of treatment error was found in these cases.
[31] Frew 2006	Timothy grass (100000 SQ-U)	203	16 patients reported fatigue. 69 patients reported headache.
[31] Frew 2006	Timothy grass (10000 SQ-U)	104	19 patients reported headache. 10 patients reported fatigue.
[31] Frew 2006	Placebo	103	36 patients had headache. 4 patients had fatigue.
[69] Mirone 2004	Short ragweed	14	1 patient with generalized urticaria 2 patients with rhinoconjunctivitis
[20] Wang 2006	Dermatophagoides pteronyssinus	66	SIT GROUP: There were seven (0.4% of all injections) grade 1 71 (4.8%) grade 2 and seven (0.5%) grade 3 reactions in the SIT group.
[20] Wang 2006	Placebo	66	There were two (0.1%) grade 1 and 25 (1.7%) grade 2 reactions in the placebo group (P < 0.001). None of the reactions resulted in hospitalization.
[68] Kuna 2011	Alternaria	30 (987 injections)	1 patient had headache
[68] Kuna 2011	placebo	20 (702 injections)	2 patients reported mild facial flushing and redness

Comments on adverse reactions reported as events

Refid	Allergen	Number of patients in arm	Comments
[21] Durham 1999	Timothy grass	16	This group received immunotherapy for 3 years and now after randomization has been allowed to continue with the maintenance dose. It is reported that less than 2 % of the injections resulted in early or delayed local reactions larger than 3 cm. No substantial immediate or late systemic reactions were observed after allergen injection
[34] Klimek 1999	Grass mix	24	of the 7 unspecified systemic reactions 5 occurred as nasal/conjunctival

Refid	Allergen	Number of patients in arm	Comments
			symptoms one case of itching of palms and feet that disappeared without treatment and one case of paleness and anxiety that reversed with antihistamine and diazepam.
[10] Maestrelli 2004	Placebo	31	subcutaneous nodule at injection site
[23] McHugh 1990	Placebo	20	13 with pruritus and 10 with erythema
[23] McHugh 1990	Dermatophagoides pteronyssinus (purified-pharmalgen)	30	angioedema glottal or laryngeal edema (these reported on ref6150 7 with asthma 5 with asthma+ erythema 3 with rhinitis 5 with erythema or pruritus and 3 with erythema + other symptoms All reactions within 15 minutes all responded to treatment
[50] Munoz Lejarazu 1993	Timothy grass (seasonal)	18	6 local reactions in 5 patients.
[55] Nouri-Aria 2003 [40] Walker 2001	Placebo	22	the one unspecified systemic reaction was conjunctivitis
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass (Ag 19 25)	20	Unspecified reaction: Arthralgia=1 Tiredness=4 Headache=1 Conjunctivitis=2 flu-like symptoms=1. Subcutaneous nodules seen in 16 patients
[70] Osterballe 1982 [71] Osterballe 1981 [72] Osterballe 1980 [73] Osterballe 1982	Timothy grass (partially purified extract)	20	Unspecified systemic reaction: Tiredness=2 Arthralgia=1. Subcutaneous nodules were seen in 24 patients Local side effects are given for the entire study only: immediate type (within 30 mins) was seen in 7/40 patients delayed type (within 24 hrs) was seen in 28/40 pateints
[84] Reid 1986	Grass mix (grass extract included)	9	287 had "some local reaction" and 20 had a reaction of >25mm. Total injections: 321
[84] Reid 1986	Grass mix (grass extract not included)	9	Mild is any local reaction moderate was >25mm and total injections were 325.
[26] Van Metre 1980	Ragweed	15	10 systemic reactions requiring no treatment; 3 mild systemic reactions treated with antihistamines; 6 moderate reactions requiring epinephrine
[41] Zenner. 1996	Grass mix Rye- Secale cereale	45	paleness and anxiety: 1 episode

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APPENDIX E: SLIT EVIDENCE TABLES

TABLE 1.- STUDY CHARACTERISTICS SLIT

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
				Asthma		
D'Ambrosio, 1999 Italy[1]	Asthma	Seasonal	Single	Weeds: parietaria	No previous immunotherapy Positive skin test Monosensitized individuals only Minimum duration of disease: 2 years	Industry
Pajno, 2000 Italy[2]	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 USA[3]	Asthma	Perennial	Single	Animals: cat	Positive specific IgE test	Non-profit
Lue, 2006 Taiwan[4]	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 Taiwan[5]	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Positive skin test	Not stated
Sambugaro, 2003 Italy[6]	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
				Rhinitis		
Hordijk, 1998 Netherlands[7]	Rhinitis	Seasonal	Single	Grass mix	Positive skin test	Industry Government
Horiguchi, 2007 Japan[8]	Rhinitis	Seasonal	Single	Trees: Japanese cedar	No previous immunotherapy Positive specific IgE test Positive skin test Pregnancy	Government
Okubo, 2008 Japan[9]	Rhinitis	Seasonal	Single	Trees: Japanese cedar	Positive specific IgE test	Government

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Fujimura, 2011 Japan[10]	Rhinitis	Seasonal	Single	Trees: Japanese cedar	No previous immunotherapy Positive specific IgE test Minimum duration of disease: 2 years Excluded pregnant patients	Government
Tahamiler, 2007 Turkey[11]	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 Taiwan[12]	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 Netherlands[13]	Rhinitis	Perennial	Multiple	Dust mite: Dermatophagoides pterynossum and farinae	Age: Children 6-18 years Positive specific IgE test Minimum duration of disease: 1 year	Industry
Rhinoconjunctivitis						
D'Ambrosio, 1996 Italy[14]	Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Positive specific IgE test Positive skin test Monosensitized individuals only Excluded Pregnancy	Not stated
la Rosa, 1999 France-Italy[15]	Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Positive specific IgE test Positive skin test Monosensitized individuals only	Industry
Bowen, 2004 Canada[16]	Rhinoconjunctivitis	Seasonal	Single	Weeds: Ragweed	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Skoner, 2010 USA[17]	Rhinoconjunctivitis	Seasonal	Single	Weeds: Ragweed	No previous immunotherapy Positive skin test Minimum duration of disease: 2 years	Industry
Di Rienzo, 2006 Italy[18]	Rhinoconjunctivitis	Seasonal	Single	Trees: Mountain cedar	Age: 18 – 55 years Positive skin test Minimum duration of disease: 2 years	Not stated
Makino, 2010 Japan[19]	Rhinoconjunctivitis	Seasonal	Single	Trees: Japanese cedar	Age: adult No previous immunotherapy Positive specific IgE test Minimum duration of disease: 2 years	Government
Durham, 2002	Rhinoconjunctivitis	Seasonal	Single	Grass: Timothy grass	Age: adults	Industry

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
United Kingdom[20]					Positive skin test	Government
Novembre, 2004 Italy[21]	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Ott, 2008 Germany[22]	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Age: 18 – 60 years No previous immunotherapy Positive specific IgE test Positive skin test	Industry
Panzer, 2008 Czech Republic[23]	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Minimum duration of disease: 2 years	Industry
Roder, 2007 Netherlands[24]	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Positive specific IgE test	Industry
Sabbah, 1994 France[25]	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Positive specific IgE test Positive skin test	Industry Not stated
Asthma and Rhinitis						
Marogna, 2005 Italy[26]	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 Italy[27]	Asthma and Rhinitis	Seasonal	Single	Trees: Birch	Positive specific IgE test Positive skin test	Industry
Marogna, 2010 Italy[28]	Asthma/ 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 USA[29]	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 Italy[30]	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

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Stelmach, 2011 Poland[31]	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
Marogna, 2004 Italy[32]	Asthma and Rhinitis	Seasonal	Multiple	Trees: White birch Dust mites: Dermatophagoidespteronyssinus 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 Italy[33]	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
Marogna, 2008 Italy[34]	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 Spain[35]	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 Germany[36]	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 Australia[37]	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 United States[38]	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 Italy[39]	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

APPENDIX

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Bahceciler, 2001 Turkey[40]	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 France[41]	Asthma and Rhinitis	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	No previous immunotherapy Positive specific IgE test Positive skin test	Industry
Marogna, 2010 Italy[42]	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
Asthma and Rhinoconjunctivitis						
Pajno, 2004 Italy[43]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Age: children Positive skin test	Industry
Passalacqua, 1999 Italy[44]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	No previous immunotherapy Monosensitized individuals only Minimum duration of disease:2 years	Industry Government
Vervloet, 2007 France[45]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Bald-cypress	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry
Vourdas, 1998 France-Greece[46]	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Olive	Positive specific IgE test Positive skin test	50% of authors are industry
Pajno 2011 Italy[47]	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 Italy[48]	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 Multiple European countries[49]	Asthma and Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Positive specific IgE test Positive skin test Monosensitized individuals only	Industry
Pradalier, 1999	Asthma and	Seasonal	Multiple	Grass: Grass mix	Positive specific IgE test	Industry

APPENDIX

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
France[50]	Rhinoconjunctivitis				Positive skin test	
Sieber, 2012 Germany[51]	Asthma/ Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Positive specific IgE test Positive skin test Minimum duration of disease: 2 years Excluded patients with allergic disease	Industry
Valovirta, 2006 Finland[52]	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	Industry
de Blay, 2007 France[53]	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
Pozzan, 2010 Italy[54]	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 Spain[55]	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 Italy[56]	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 Spain[57]	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 2.- PATIENT CHARACTERISTICS- SLIT

Study	Patients randomized	Comparators	Age (years) (mean+/- SD)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Asthma						
[1] D'Ambrosio, 1999	30	SLIT Placebo	Mean:32 +/- 17 Mean:32 +/- 18	50/50 43/57	14/0 16/0	NR
[2] Pajno, 2000	24	SLIT Placebo	Mean:11(Range 8-15) Mean:12 (Range 8-15)	58/42 50/50	12/0 12/3	5
[3] Nelson, 1993	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
[4] Lue, 2006	20	SLIT Placebo	Mean:8 +/- 2 Mean:9 +/- 2	40/60 40/60	10/0 10/0	1
[5] Niu, 2006	110	SLIT Placebo	Mean:8 +/- 2 (Range 5-11) Mean:8+/- 2 (Range 5-12)	61/39* 58/42*	56/7 54/6	NR
[6] Sambugaro, 2003	58	8-day induction 15-day induction 20-day induction Untreated	Mean:19 (Range 4-43) Mean:26 (Range 5-42) Mean:17 (Range 6-41) Mean:23 (Range 10-37)	56/44 39/61 58/42 60/40	18/0 18/0 12/0 10/0	NR
Rhinitis						
[7] Hordijk, 1998	69	SLIT Placebo	Mean:28 Mean:28	52/48 43/57	27/8 30/6	NR
[8] Horiguchi, 2007	67	SLIT Placebo	Mean:27 +/- 5 Mean:26 +/- 6	51/49 46/54	43/2 24/2	9
[9] Okubo, 2008	61	SLIT Placebo	Mean:41/- 15 Mean:40+/- 15	49/51 32/68	37/0 22/0	NR
[10] Fujimura 2011	103	SLIT Placebo	44.4 (Range 16-73) 42.3 (Range 19-70)	34/66 22/78	51/15 37/10	NR
[11] Tahamiler, 2007	NR	SLIT /placebo SLIT alone	Mean:28+/- 10 (Range 12-51) Mean:26+/- 8 (Range 10-49)	54/46 54/46	67/NR 70/NR	2 3

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- SD)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
[12] Tseng, 2008	63	SLIT Placebo	Mean:10 +/- 3 Mean: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
[13] deBot 2011	257	SLIT Placebo	11.8 +/- 3.1 11.7 +/- 2.9	NR	125/17 126/15	1 year
Rhinoconjunctivitis						
[14] D'Ambrosio, 1996	40	SLIT Pharmacotherapy	Mean:30 (Range 18-41) Mean:34 (Range 19-67)	47/53 33/67	15/0 15/0	2 or more
[15] la Rosa, 1999 [58] Leonardi, 2009	41	SLIT Placebo	Mean:10 (Range 6-14) Mean:10 (Range 7-13)	65/35 57/43	20/5 21/4	3 4
[16] Bowen, 2004	83	SLIT Placebo	Mean: 38 (Range 14-58) Mean:35 (Range 16-56)	NR NR	37/15 37/11	19 17
[17] Skoner, 2010	115	High dose SLIT Medium dose SLIT Placebo	Mean:34 (Range 20-49) Mean:34 (Range 19-49) Mean:35 (Range 20-50)	33/67 26/74 48/53	36/5 39/8 40/5	NR
[18] Di Rienzo, 2006	34	SLIT Placebo	Mean:34+/- 10 (Range 18-55) Entire Study	47/53 Entire Study	19/1 15/1	NR
[19] Makino, 2010	25	SLIT Placebo	Mean:49+/- 15 Mean:48 +/- 13	67/34 69/31	9/0 15/1	2
[20] Durham, 2002	56	SLIT Placebo	Mean:34 (Range 21-53) Mean:34 (Range 21-55)	54/47 32/68	28/2 28/5	2
[21] Novembre, 2004	113	SLIT Control	Mean:9 (Range 5-14) Mean:8 (Range 4-16)	70/30 70/30	54/6 59/10	NR
[22] Ott, 2008	213	SLIT-rush Placebo	Mean:33+/- 11 Mean:34+/- 9	46/54 54/46	142/3 (99/3) 67/1 (46/1)	13
[23] Panzer, 2008	35	SLIT Placebo-SLIT	Mean:17 +/- 9 (Range 7-50) Mean:24 +/- 12 (Range 7-50)	55/45 60/40	20/0 15/0	NR

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- SD)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
[24] Roder, 2007	204	SLIT Placebo	Mean:13+/- 7 (Range 7-17) Mean:13+/- 3 (Range 6-17)	67/33 44/56	108/70 (64/26) 96/70 (50/24)	NR
[25] Sabbah, 1994	58	SLIT Placebo	Mean:23 +/- 10 (Range 13-43) Mean:27 +/- 12 (Range 13-51)	59/41 48/52	29/0 29/0	11 10
Asthma and Rhinitis						
[26] Marogna, 2005	79	SLIT Placebo	Mean:28 (Range 18-43) Mean:29 (Range 19-45)	55/45 57/44	39/10 40/17	NR
[27] Voltolini, 2009	24	SLIT Placebo	Mean:44+/- 9 Mean:40 +/- 7	50/50 30/70	14/1 10/1	NR
[28] Marogna 2010	33	SLIT Montelukast	NR	NR	17/1 16/3	2 years
[29] Amar, 2009	58	SLIT Monotherapy SLIT Multiple allergen Placebo	Mean 39 Mean 36 Mean 39	26/74 41/59 47/53	19/0 17/3 17/2	NR
[30] Marogna, 2009	51	SLIT Budesonide	Mean:27 +/- 1 (Range 17-41) Mean:27 +/- 1 (Range 19-41)	44/56 46/54	25/2 26/3	8 7
[31] Stelmach 2011	60	SLIT pre-coseasonal SLIT continuous Placebo	8.3 Range 5-17	65/35 74/26 61/39	17/3 19/1 18/2	2 years
[32] Marogna, 2004	511	SLIT Control	Mean:23 (Range 5-60) Mean:22 (Range 5-58)	56/44 63/37	319/48 192/22	NR
[33] Marogna, 2006	48	SLIT - birch SLIT - grass SLIT - birch + grass Control	Mean:28 Mean:27 Mean:26 Mean:27	NR NR NR NR	12/0 11/0 12/0 13/0	NR
[34] Marogna, 2008	216	SLIT Control	Mean:11+/- 0 Mean:10 +/- 0	72/38 60/40	144/14 72/6	NR
[35] Moreno-Ancillo, 2007	105	SLIT Placebo	Mean:29+/-10 (Range: 14-55) Mean:26 +/- 8 (Range: 14-55)	54/46 57/43	52/11 53/9	7
[36] Hirsch, 1997	30	SLIT Placebo	Mean:11 (Range 6-15) Mean:10 (Range 6-15)	67/34 67/33	15/1 15/0	5 (asthma), 5 (rhinitis) 3 (asthma), 3 (rhinitis)

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- SD)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
[37] O'Hehir, 2009 [37] O'Hehir, 2009	30	SLIT Placebo	Mean:29+/- 8 Mean:38+/- 11	NR NR	15/2 15/1	Minimum 2
[38] Bush 2011	31	SLIT high dose SLIT Low dose Placebo	30.6	50/50 10/90 27/73	10/1 10/3 11/6	2 years
[39] Tari, 1990	66	SLIT Placebo	Range 5-12 Range 5-12	Entire study 64/36	34/4 34/4	NR
{#376 Bahceciler, 2001	15	SLIT Placebo	Mean:12 (Range 8-18) Mean:12 (Range 7-15)	50/50 58/43	8/0 7/0	NR NR
[41] Guez, 2000	72	SLIT Placebo	Mean:30+/- 12 (Range 12-51) Mean:23 +/- 11 (Range 6-47)	39/61 42/58	36/11 36/22	10 8
[42] Marogna 2010	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
[43] Pajno, 2004 [59] Pajno, 2004	30	SLIT+ fluticasone Placebo+fluticasone	Mean:11 Mean:11	47/53 40/60	15/1 15/2	5 3
[44] Passalacqua,1999	30	SLIT Placebo	Mean:33 (Range 22-47) Mean:30 (Range 19-36)	67/34 33/67	15/1 15/2	3 4
[45] Vervloet, 2007	76	SLIT Placebo	Mean:39 (Range 22-60) Mean:39 (Range 19-60)	58/42 45/55	38/2 38/4	8 8
[46] Vourdas, 1998	70	SLIT Placebo	Mean:12 (Range 8-17) Mean:12 (Range 7-17)	74/37 67/34	34/1 36/1	4 4
[47] Pajno 2011	80	SLIT continuous; SLIT co-seasonal	11 Range 8-16	60/40 47/53	40/3 40/5	5.2 years 4.1 years
[48] Feliziani, 1995	34	SLIT Placebo	NR	NR NR	18/0 16/0	Minimum 2

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- SD)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
[49] Pfaar, 2007	185	SLIT Placebo	Mean:33 (Range 18-59) Mean:34 (Range 17-55)	66/34 59/41	94/45 91/36	NR
[50] Pradalier, 1999	126	SLIT Placebo	Mean:28+/- 11 (Range 8-50) Mean:30 +/- 12 (Range 7-58)	47/53 59/41	62/3 61/4	9 5
[51] Sieber 2012	213	SLIT followed by placebo Placebo	Range 7.9- 64.7	NR	142/10 67/4	NR
[52] Valovirta, 2006 [60] Savolainen, 2006	98	SLIT High dose SLIT Low dose Placebo	Mean 9 +/- 3 Mean 10 +/- 3 Mean 10 +/- 3	49/52 61/39 62/38	32/7 32/1 29/6	4 5 5
[53] de Blay, 2007	118	SLIT Placebo	Mean:24+/- 7 (Range 12 -41) Mean:27 +/- 8 (Range 12 -41)	56/44 61/39	61/9 57/8	6 6
[54] Pozzan 2010	52	SLIT Placebo	18 +/- 9 19+/-10	67/33 55/45	34/1 18/0	2 years
[55] Alvarez-Cuesta, 2007	50	SLIT Placebo	Mean:35 (Range 14-55) Entire study	NR NR	25/8 25/9	NR NR
[56] Ippoliti, 2003	86	SLIT Placebo	Median;9 (Range 5-12) Median;9 , (Range 7-11)	60/41 56/44	47/0 39/0	2 2
[57] Rodriguez, 2006	135	SLIT SLIT no 30d updosing	Mean:23+/- 11 (Range 7-55) Mean:22 +/- 10 (Range 7-55)	55/45 47/53	69/6 66/6	NR NR

TABLE 3.- INTERVENTION CHARACTERISTICS-SLIT

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
[1] D'Ambrosio, 1999	SLIT Parietaria Placebo	Conventional therapy	5 drops of 0.6 mcg/ml	199.5 BU	3 times a week,rush	12.77 Par j1 (cumulative)	9 months
[2] Pajno, 2000	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
[3] Nelson, 1993	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
[4] Lue, 2006	SLIT Dust mite Placebo	Conventional therapy	20 drops of 300 IR/mL	41824 IR	Daily	3000 Der F , 1700 Der P (cumulative)	6 months
[5] Niu, 2006	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
[6] Sambugaro, 2003	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
[7] Hordijk, 1998	SLIT Grass mix Placebo	Conventional therapy	9500 BU	NR	2 times a week	NR	10 months
[8] Horiguchi, 2007	SLIT Japanese cedar Placebo	Conventional therapy	1 mL of 1000 JAU	NR	Weekly	1.5 Cry j1 (maintenance)	7 months

APPENDIX

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
[9] Okubo, 2008	SLIT Japanese cedar Placebo	Conventional therapy	1 ml of 2000 JAU/ml	NR	Weekly	NR	6 months
[10] Fujimura 2011	SLIT Japanese Cedar placebo	Conventional therapy	2000 JAU	NR	Once a week	1.5-4.2 µg Cry j 1 (maintenance dose)	20 months
[11] Tahamiler, 2007	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
[12] Tseng, 2008	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
[13] deBot 2011	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
[14] D'Ambrosio, 1996	SLIT Parietaria Medication	Conventional therapy	5 drops of10 BU/ml	13 mcg	every other day	0.12 Par j 1 (maintenance)	8 months (mid Jan to end Sep) 5 months (unclear)
[15] La Rosa, 1999 [58] Leonardi, 2009	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
[16] Bowen, 2004	SLIT Ragweed Placebo	Conventional therapy	100 - 300 IR/ml	NR	Daily	116 Amb a 315 (per day)	3 months (estimated duration)
[17] Skoner, 2010	SLIT Ragweed High dose SLIT Ragweed Medium dose	ONLY rescue medication	48 mcg 4.8 mcg	4981 +/- 1487 mcg Amb a 1 498 +/- 185 Mcg Amb a 1	Daily	48Amb a1 (maintenance) 4.8Amb a1 (maintenance)	17 +/- 3 weeks

APPENDIX

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
[18] Di Rienzo, 2006	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)
[19] Makino, 2010	SLIT Japanese cedar Placebo	Conventional therapy	1 mL of 2000 JAU/mL	NR	Weekly	15 Cr j1, 2-5 Cr j2 (maintenance)	5 months
[20] Durham, 2002	SLIT Timothy Placebo	Conventional therapy	6 drops of 1 mg/ml	NR	Daily	900 Phl p5 (per month)	12-18 months 18 months
[21] Novembre, 2004	SLIT Grass mix symptomatic therapy	ONLY rescue medication	5 drops of 25 BU/ml	120 mcg	Daily	0.5 Group V major grass (maintenance)	3 years
[22] Ott, 2008	SLIT Grass mix Placebo	ONLY rescue medication	300 IR	22000 IR per season	Ultrarush, then daily	1500 Group V major grass (per season)	3 seasons 4 seasons
[23] Panzer, 2008	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
[24] Roder, 2007	SLIT Grass mix Placebo	Conventional therapy	9500 BU	1976000, 4.5 mg	2 times a week	21 Lol p5 (maintenance)	2 years
[25] Sabbah, 1994	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
[26] Marogna, 2005	SLIT Birch Placebo	Conventional therapy	102 mcg per year	NR	Daily	102 Bet v1 (per year)	3.5 years

APPENDIX

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
[27] Voltolini, 2009	SLIT Birch Placebo	Conventional therapy	300	13.8 IR per season	Daily	13.8 IR (6.9 µgBet v1 per season)	
[28] Marogna 2010	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
[29] Amar, 2009	SLIT Timothy-Monotherapy SLIT Timothy-Multiallergen therapy	Conventional therapy	19 mcg	571 mcg per month	Daily	19Phl p5 (maintenance)	15 months
[30] Marogna, 2009	SLIT Grass mix Inhaled Corticosteroids	Conventional therapy	5 drops of 10,000 RU/ml	70 mcg (yearly)	3 times a week	70 Phl p1 (per year)	5 years
[31] Stelmach 2011	SLIT pre-coseasonal - grass mix SLIT continuous – grass mix placebo	ONLY rescue medication	300IR	NR	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
[32] Marogna, 2004	SLIT Dust mite, birch, grass mix, parietaria, mugwort Pharmacotherapy	Conventional therapy	5 drops of 10,000 RU/ml	390 mcg Der p1/ Der p2, 70 mcg Phl p1, 70 mcg Par j1, 100 mcg Bet v1 (per year)	3 times a week	390 mcg Der p 1/Der p 2, 70 mcg Phl p 1, 70 mcg Par j 1, 100 mcg Bet v 1 (per year)	3 years
[33] Marogna, 2006	SLIT Birch alone SLITGrass alone SLITBirch+Grass Pharmacotherapy	Conventional therapy	100 mcg (monthly) 70 mcg (monthly)		every other day	100 mcg (per month) 70 mcg (per month)	4 years
[34] Marogna, 2008	SLIT Birch-Grass-Dust mite and Parietaria Conventional therapy	Conventional therapy	5 drops of 10,000 RU/ml	480 mcg of Der p1, 480 mcg Der p2, 40 mcg of Phl p 1,40 mcg Par j 1, 100 mcg of Bet v 1(per year)	3 times a week	480 mcg of Der p1, 480 mcg Der p2, 40 mcg of Phl p 1,40 mcg Par j 1, 100 mcg of Bet v 1 (per year)	3 years

APPENDIX

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
{#3703 Moreno-Ancillo, 2007	SLIT Grass mix and olive Placebo	NR	2 mcg grass, 3 mcg olive	NR	Daily	2 Group V major grass, 3 Oeuropaea Ole e1 (maintenance)	10 months
[36] Hirsch, 1997	SLIT Dust mite Placebo	Conventional therapy	7 drops of 11.9 mcg/ml=3.75 mcg	570 micrograms (per year)	3 times a week	570 Dep p1 (per year)	1 year
[37] O'Hehir, 2009 [37] O'Hehir, 2009	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
[38] Bush 2011	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 micrograms Def f 1 per day	12-18 months
[39] Tari, 1990	SLIT Placebo	ONLY rescue medication	15 drops of 500 STU/ml		3 times per week		18 months
{#376 Bahceciler, 2001	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
[41] Guez, 2000	SLIT Dust mite Placebo	Conventional therapy	20 drops of 300 IR/ml	90,000 IR	3 times a week	2200 Der p1, 1700 mcg Der f1 (cumulative)	24 months
[42] Marogna 2010	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.
[43] Pajno, 2004 [59] Pajno, 2004	SLIT Parietaria Placebo	Conventional therapy	5 drops of 10BU/ml	20.3 mcg	every other day	20.3 Par j1 (cumulative)	13 months

APPENDIX

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
[44] Passalacqua, 1999	SLIT Parietaria Placebo	ONLY rescue medication	5 drops of 10 BU/ml =12 mcg	256 BU	Daily	16 Par j1 (cumulative)	6 months
[45] Vervloet, 2007	SLIT Bald-cypress Placebo	ONLY rescue medication	300 IR	NR	Rush, Then daily	228 Jun a1 (maintenance)	120 days
[46] Vourdas, 1998	SLIT Olive Placebo	Conventional therapy	20 drops of 300 IR/ml	30000 IR/year	Daily	4050 Ole e 1 (per year)	Seasonal (5 to 6 months each year) for 2 years
[47] Pajno 2011	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
[48] Feliziani, 1995	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
[49] Pfaar, 2007	SLIT Grass mix Placebo	ONLY rescue medication	40 mcg (of group 5 grass allergen)	NR	Daily	40 Group V major grass (maintenance)	2 years
[50] Pradalier, 1999	SLIT Grass mix or dust mite (updosing) SLIT Grass mix or dust mite (No updosing)	Conventional therapy	2 mcg GroupV major grass, or 0.8/0.4 mcg Der p1/Der p2 2 mcg GroupV major grass, or 0.8/0.4 mcg Der p1/Der p2	NR	Daily	2 mcg Group V major grass, or 0.8/0.4 mcg Der p1/Der p2	3 months 2 months
[51] Sieber 2012	SLIT grass mix followed by placebo placebo	ONLY rescue medication	300 IR maintenance dose (one day ultra rush escalation from 30 IR to 300 IR in one hour)	66000 IR total over 3 seasons	Daily during pollen season (82-93 days) for 3 seasons	1500 µg Grp V major allergen per season, or 4500 total over study	Co-seasonal for 3 years; note follow-up season at year 4 where everyone had placebo

APPENDIX

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
[52] Valovirta, 2006 [60] Savolainen, 2006	SLIT Tree mix high dose SLIT Tree mix low dose	Conventional therapy	100,000 SQ-U/ml (per week) 12,000 SQ-U/ml (per week)	200,000 SQ-U per week =30 mcg 24,000 SQ-U per week or 3.6 mcg	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 18 months maintenance
[53] De Blay, 2007	SLIT Grass mix Placebo	ONLY rescue medication	300 IR	31800 IR	3 times a week	2750 Group 3 major grass (cumulative)	10 months
[54] Pozzan 2010	SLIT Alternaria placebo	ONLY rescue medication	0.12 micrograms Alt a 1 per day	NR	Daily	3.6 µg Alt a 1 per month	3 years
[55] Alvarez-Cuesta, 2007	SLIT Cat Placebo	Conventional therapy	5 drops of 0.51 mcg/ml	17.1 mcg Fel d 1.	Daily	0.51 Fel d1 (maintenance)	12 months
[56] Ippoliti, 2003	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
[57] Rodriguez, 2006	SLIT Dust mite Placebo	Conventional therapy	1.0 ml of 0.5 mcg/ml 2.0 Der f1	NR	Weekly	0.5 Der f1 (maintenance)	10 months

TABLE 4.- QUALITY ASSESSMENT-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
Asthma							
[1] D'Ambrosio 1999	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
[2] Pajno 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[3] Nelson 1993	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
[4] Lue 2006	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[5] Niu 2006	Low risk	Low risk	High risk	High risk	High risk	No	Medium risk
[6] Sambugaro 2003	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Rhinitis							
[7] Hordijk 1998	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[8] Horiguchi 2007	Low risk	Low risk	High risk	Low risk	Low risk	No	Medium risk
[9] Okubo 2008	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[10] Fujimura 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[11] Tahamiler 2007	Low risk	Low risk	High risk	High risk	Low risk	No	Medium risk
[12] Tseng 2008	Low risk	Low risk	High risk	High risk	Low risk	No	Medium risk
[13] deBot 2011	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
Rhinoconjunctivitis							
[14] D'Ambrosio 1996	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
[15] La Rosa 1999 [58] Leonardi, 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[16] Bowen 2004	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[17] Skoner 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[18] Di Rienz, 2006	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
[19] Makino 2010	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
[20] Durham 2002	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[21] Novembre, 2004	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
[22] Ott, 2008	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[23] Panzer, 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[24] Roder, 2007	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
[25] Sabbah, 1994	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
Asthma - Rhinitis							
[26] Marogna, 2005	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
[27] Voltolini, 2009	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[28] Marogna 2010	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
[29] Amar, 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[30] Marogna, 2009	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[31] Stelmach 2011	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
[32] Marogna, 2004	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
[33] Marogna, 2006	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
[34] Marogna, 2008	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
[35] Moreno-Ancillo, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[36] Hirsch, 1997	Low risk	Low risk	Low risk	High risk	Low risk	No	Medium risk
[37] O'Hehir, 2009 [37] O'Hehir, 2009	Low risk	Low risk	High risk	High risk	High risk	Yes or unclear	High risk
[38] Bush 2011	Low risk	High risk	Low risk	Low risk	High risk	Yes or unclear	Medium risk
[39] Tari, 1990	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[40] Bahceciler, 2001	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[41] Guez, 2000	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[42] Marogna 2010	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
Asthma - Rhinoconjunctivitis							
[43] Pajno, 2004 [59] Pajno, 2004	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[44] Passalacqua,1999	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[45] Vervloet, 2007	Low risk	Low risk	High risk	Low risk	High risk	Yes or unclear	Medium risk
[46] Vourdas, 1998	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[47] Pajno 2011	Low risk	Low risk	High risk	Low risk	High risk	No	Medium risk
[48] Feliziani, 1995	Low risk	Low risk	High risk	High risk	Low risk	No	Medium risk
[49] Pfaar, 2007	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk

APPENDIX

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
[50] Pradalier, 1999	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[51] Sieber 2012	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
[52] Valovirta, 2006 [60] Savolainen, 2006	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[53] De Blay, 2007	Low risk	Low risk	High risk	Low risk	High risk	Yes or unclear	Medium risk
[54] Pozzan 2010	Low risk	High risk	Low risk	Low risk	High risk	Yes or unclear	Medium risk
[55] Alvarez-Cuesta2007	Low risk	Low risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
[56] Ippoliti, 2003	Low risk	High risk	Low risk	Low risk	Low risk	No	Medium risk
[57] Rodriguez, 2006	Low risk	High risk	Low risk	Low risk	Low risk	Yes or unclear	Medium risk

TABLE 5.- ASTHMA AND ASTHMA COMBINED SCORES-SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[2] Pajno, 2000	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
[2] Pajno, 2000	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
[4] Lue, 2006	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
[5] Niu, 2006	Dust mite	SLIT Placebo	24 weeks	Unspecified asthma symptoms	0-3/day	0.11 0.05	0.04 0.06	SLIT vs Placebo p= 0.028
[36] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	pulmonary symptoms	0-3	0.36 0.07	0.07 0.28	Placebo pre vs post p=1545 SLIT vs Placebo p< 0.05
[40] Bahceciler, 2001	Dust mite	SLIT placebo	6 months	Asthma symptoms		0.64 0.33	0.3 0.26	SLIT pre vs post p <0.05
[56] Ippoliti, 2003	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
[13]* deBot 2011	Dust mite	SLIT placebo	2 years	Dyspnea/wheeze score		NR	0.21 0.11	SLIT vs Placebo p=0.01
[14] D'Ambrosio, 1996	Parietaria	SLIT Placebo	5 months	Rhinoconjunctivitis plus asthma symptom scores	0 = none	NR NR	4352 6134	SLIT vs Placebo p <0.05
[1] D'Ambrosio, 1999	Parietaria	SLIT Placebo	10 months	Unspecified Asthma plus rhinoconjunctivitis score	0-3	NR NR	NR NR	SLIT pre vs post p=0.001

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[43] Pajno, 2003	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
[43] Pajno, 2003	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
[20] Lima, 2002	Timothy	SLIT Placebo	18 months	Overall chest symptom scores	0-12/ day	NR NR	117 32	SLIT vs Placebo p= 0.64
[20] Lima, 2002	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
[26] Marogna, 2005	Birch	SLIT Placebo	3.5 years	Lung, nasal, eye symptoms	0-360	290 300	50 150	SLIT vs Placebo p<0.001
[27] Voltolini, 2010	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
[28]* Marogna 2010	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)	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
[23] Panzner, 2008	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
[23] Panzner, 2008	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[30] Marogna, 2009	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
[35] Moreno-Ancillo, 2007	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
[33] Marogna, 2007	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
[33] Marogna, 2007	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
[38] Bush 2011	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
[47]* Pajno 2011	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
[47] Pajno 2011	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
[52] Valovirta, 2006	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[52] Valovirta, 2006	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,
[54] Pozzan 2010	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
[32] Marogna, 2004	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 6.- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES- SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[1] D'Ambrosio, 1999	Parietaria	SLIT Placebo	10 months	Unspecified rhinitis symptom scores	0-12	NR NR	NR NR	SLIT pre vs post p= 0.04
[3] Nelson, 1993	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
[3] Nelson, 1993	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
[7] Hordijk, 1998	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
[7] Hordijk, 1998	Grass mix	SLIT Placebo	10 months	investigator rhinoconjunctivitis assessment	NS		3.21+/- 3.05 5.13+/- 3.6	SLIT vs Placebo p = 0.03
[8] Horiguchi, 2008	Japanese cedar	SLIT Placebo	7 months	sneezing	0-4	NR NR	0.98 1.2	SLIT vs Placebo p <0.0001
[8] Horiguchi, 2008	Japanese cedar	SLIT Placebo	7 months	Nasal secretion	0-4	NR NR	0.95 1.24	SLIT vs Placebo p <0.0001
[8] Horiguchi, 2008	Japanese cedar	SLIT Placebo	7 months	Nasal obstruction	0-4	NR NR	0.43 0.52	SLIT vs Placebo p =0.0028

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[9] Okubo, 2008	Japanese cedar	SLIT Placebo	end of cedar season, (April 5th)	total rhinitis symptom score; every day, between Feb 2 to Apr 5	0-9		5.1 5.9	SLIT pre vs post p= NS SLIT vs Placebo p= NS
[61] Stevens, 1984	Parietaria	SLIT Placebo	10 months	Nasal symptoms	0-12	64.1 64.7	42 76	SLIT vs Placebo NS
[11] Tahamiler, 2007	Dust mite	SLIT 2 years SLIT 3 years	6 years after start; end of second year, end of 3rd year	Nasal symptoms	0-3	2.3045 +/- 0.2982 2.366 +/- 0.3795	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
[13] deBot 2011	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
[28] Marogna 2010	Birch	SLIT birch; Monteleukast	5 years	0-3/upper airway symptom. 0-12/day		82.0 93.6	26.8 86.4	Arm 1 vs Arm 1 P<0.05; Arm 2 vs Arm 2 NS. SLIT vs Placebo p <0.05
[12] Tseng, 2008	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
[15] La Rosa, 1999	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
[16] Bowen, 2004	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
[16] Bowen, 2004	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
[16] Bowen, 2004	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
[16] Bowen, 2004	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[16] Bowen, 2004	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
[20] Lima, 2002	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
[23] Panzner, 2008	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
[24] Roder, 2007	Grass mix	SLIT Placebo	2 years	mean daily total of all rhinitis symptoms	0-15	NR NR	3.1 3.4	SLIT vs Placebo NS CI -0.66 - 0.5
[25] Sabbah, 1994	Grass mix	SLIT Placebo	17 weeks	Nasal symptom scores	0-7	NR NR	NR NR	SLIT vs Placebo p NS
[27] Voltolini, 2010	Birch	SLIT Placebo	1 year	Nasal obstruction score	0-3	2 2	1.5 2	SLIT vs Placebo p <0.05
[27] Voltolini, 2010	Birch	SLIT Placebo	1 year	Rhinorrhea symptom score	0-3	2 2	1 1.5	SLIT vs Placebo p <0.05
[30] Marogna, 2009	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
[35] Moreno-Ancillo, 2007	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
[36] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	nasal symptom score	0-3	1.4 0.48	0.84 0.34	SLIT vs Placebo p NS

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[37] O'Hehir, 2009	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
[40] Bahceciler, 2001	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
[41] Guez, 2000	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
[43] Pajno, 2003	Parietaria	SLIT Placebo	13 months	Nasal symptoms	0-3	NR	NR	SLIT vs Placebo NS
[45] Vervloet, 2007	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
[46] Vourdas, 1998	Olive	SLIT Placebo	pollen season Year 2	Rhinitis score	0-4		0.72 1.22	SLIT vs Placebo p NS
[50] Pradalier, 1999	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
[52] Valovirta, 2006	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
[53] De Blay, 2007	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
[56] Ippoliti, 2003	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
[62] Yonekura, 2010	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[17] Skoner, 2010	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	Arm 1 Vs. Arm 3 p = 0.005 Arm 2 Vs. Arm 3 p =0.19 Arm 2 Vs. Arm 1 p =0.51 (values are average for entire pollen season)
[21] Novembre, 2004	Grass mix	SLIT Placebo	3 years	Unspecified Rhinoconjunctivitis Symptom score				SLIT vs Placebo NS
[22] Ott, 2009	Grass mix	SLIT Placebo	3 years	VAS Rhinoconjunctivitis Symptom score		-1.94 -0.30	5.05 4.4	SLIT vs Placebo p = 0.015
[29] Amar, 2009	Timothy	SLIT-mono SLIT-Multi Placebo	15 months	Rhinoconjunctivitis Symptom score	0-3 0 = No symptom 3 = Severe	6.3 8.1 6.4	4.0 5.4 3.9	Arm 1 vs Arm 3 NS Arm 2 vs Arm 3 NS
[48] Feliziani, 1995	Grass mix	SLIT Placebo	End of pollen season	Rhinoconjunctivitis Symptom score	0-2	NR NR	109.7 209.4	SLIT vs Placebo p=0.01
[23] Panzner, 2008	Grass mix and Olive	SLIT Placebo	10 months	Rhinoconjunctivitis total symptoms score		NR NR	111.35 321.6	SLIT pre vs post p = 0.0076 Placebo pre vs post p = 0.293
[39] Tari, 1990	Dust mite	SLIT Placebo	18 months	Combined nasal and respiratory symptoms				SLIT vs Placebo p<0.05 at 12 months SLIT vs Placebo p<0.001 at 18 months

NS: Not significant

TABLE 7.- CONJUNCTIVITIS SYMPTOM SCORES-SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[13] deBot 2011	Dust mite	SLIT placebo	2 years	0-3/eye score, 0-9 /day		NR	SLIT 0.49, placebo 0.57	Arm 1 vs Arm 2 NS
[35] Moreno-Ancillo, 2007	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	Arm 1 Vs. Arm 1 p = 0.0092 Arm 2 Vs. Arm 2 p = 0.1401
[45] Vervloet, 2007	Mountain cedar	SLIT Placebo	120 days	Conjunctivitis total score	0-9	0.02 0	1.14 +/- 1.14 1.24+/-1.40	Arm 1 Vs. Arm 2 p = 0.95 Peak season
[46] Vourdas, 1998	Olive	SLIT Placebo	End of pollen season Year 2	4-point scale	0-4	NR NR	0.04 0.23	Arm 1 Vs. Arm p <0.05; only significant week 19
[25] Sabbah, 1994	Grass mix	SLIT Placebo	17 weeks	Ocular redness	0-6	0 0.4	1.5 4.5	Arm 1 Vs. Arm 2 p <0.05 Peak season
[25] Sabbah, 1994	Grass mix	SLIT Placebo	17 weeks	Ocular pruritus	0-7	0.5 0.5	2.5 4.5	Arm 1 Vs. Arm 2 p NS
[16] Bowen, 2004	Ragweed	SLIT Placebo	3 months (end of pollen season)	total conjunctivitis score	0-9	NR NR	1.96 +/- 1.9 2.38+/- 1.92	Arm 1 Vs. Arm 2 p= 0.35
[20] Lima, 2002	Timothy	SLIT Placebo	18 months; at peak season	unspecified		NR NR	462 550	Arm 1 Vs. Arm 2 p= 0.86 CI -18
[23] Panzner, 2008	Grass mix	SLIT Placebo	End of pollen season (September 2004)	ocular symptoms score	0-16/day	NR	60.20 185.67	Arm 2 vs. Arm 4 p= 0.4937 Arm 1 vs. Arm 2 p= 0.013
[53] De Blay, 2007	Orchard, Timothy and Regrass	SLIT Placebo	10 months	4-point scale	0-30	NR	7.79 11.18	Arm 1 Vs. Arm 2 p = 0.08

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[1] Purcello-D'Ambrosio, 1999	Parietaria	SLIT Placebo	10 months	unspecified	0-6	NR	NR	Arm 1 Vs. Arm 1 p= 0.04
[52] Valovirta, 2006	Tree Mix	SLIT HighDose SLIT LowDose Placebo	Whole pollen season	Total eye symptoms	0-9/day	NR	0.8 0.9 1.1	Arm 1 vs Arm 3, p=0.04, Arm 2 vs Arm 2 NS
[39] Tari, 1990	Dust mite	SLIT Placebo	18 months	Ocular symptoms				Arm 1 Vs. Arm 2 p NS

NS: Not significant

TABLE 8.- MEDICATION SCORES-SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[1]Purcello-D'Ambrosio, 1999	Parietaria	SLIT Placebo	10 months	Unspecified		NR NR	NR NR	Arm 1 Vs. Arm 1 p<0.05 60% Percentage improvement
[2] Pajno, 2000	Dust mite	SLIT Placebo	2 years	Unspecified		259.68 296	82.68 205.2	Arm 1 Vs. Arm 2 p <0.0001
[4] Lue, 2006	Dust mite	SLIT Placebo	6 months	Unspecified		1.7 +/- 1.08 1.25 +/- 0.72	1.0 +/- 0.94 1.1 +/- 1.15	Arm 1 Vs. Arm 1 p = 0.034 Arm 2 Vs. Arm 2 p= 0.432 Arm 1 Vs. Arm 2 p = 0.366
[5] Niu, 2006	Dust mite	SLIT Placebo	24 weeks	Medication scores antihistamines and oral corticosteroids				Arm 1 Vs. Arm 2 p No significant change
[9] Okubo, 2008	Japanese Cedar	SLIT Placebo	End of season (april)	Medication score			0.44 0.36	Arm 1 Vs. Arm 1 p NS Arm 2 Vs. Arm 2 p NS
[63] Troise, 1995	Parietaria	SLIT Placebo	Peak season (4 months)	0 to 3 grading the medications required	1-3	NR NR	25.6 250.2	Arm1 vs Arm 2 P<0.05 during peak season
[12] Tseng, 2008	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	Arm 1 Vs. Arm 1 p = 0.826 Arm 2 Vs. Arm 2 p = 0.312
[12] Tseng, 2008	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	Arm 1 Vs. Arm 1 p = 0 .932 Arm 2 Vs. Arm 2 p = 0.843 Arm 1 Vs. Arm 2 p= 0.74
[13] deBot 2011	Dust mite	SLIT; placebo	2 years	Proportion of days with rescue meds		NR	0.21 0.26	Arm 1 vs Arm 2 NS

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[15] La Rosa,	Parietaria	SLIT Placebo	2 years	Anti-rhinitis medication score				Arm 1 Vs. Arm 2 p NS
[16] Bowen, 2004	Ragweed	SLIT Placebo	3 months (end of pollen season)	Unspecified			1.05 +/- 1.60 1.26 +/- 1.24	Arm 1 Vs. Arm 2 p = 0.36
[17] Skoner, 2010	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	Arm 1 Vs. Arm 2 p= 0.59 Arm 1 Vs. Arm 3 p= 0.004 Arm 2 Vs. Arm 3 p = 0.12
[19] Makino, 2010	Japanese Cedar	SLIT Placebo	5 months	Unspecified			39.4 +/- 12.5 56.0 +/- 16.1	Arm 1 Vs. Arm 2 p= 0.42
[20] Lima, 2002	Timothy	SLIT Placebo	18 months	rescue medication use			1418 2569	Arm 1 Vs. Arm 2 p= 0.19 45% Percentage improvement Arm1
[22] Ott, 2009	Grass mix	SLIT Placebo	End of season 4	unspecified			0.07+/- 11.69 -0.98 +/- 2.61	Arm 1 Vs. Arm 2 p= 0.8397
[23] Panzner, 2008	Grass mix	SLIT Placebo	End of pollen season (September 2004)	rescue medication intake score		NR NR	4.60 13.93	Arm 1 Vs. Arm 2 p= 0.036
[24] Roder, 2007	Grass mix	SLIT Placebo	2 years	% rescue med free days			69.3 (3.4) 74.2 (3.2)	Arm 1 Vs. Arm 2 p=0.67
[26] Marogna, 2005	White Birch	SLIT Placebo	3 years	Doses of Salbutamol used per month		9 10	1.9 10.4	Arm 1 Vs. Arm 2 p< 0.001

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[28] Marogna 2010	Birch	SLIT monteleukast	5 years	1 point per nasal corticosteroid 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 Arms 1 vs Arm 2 p <0.05 Beta agonists: Arm 1 vs Arm 1 p<0.01, Arm 2 vs Arm 2 p =0.019; Arm 1 vs Arm 2 p<0.0001
[29] Amar, 2009	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
[30] Marogna, 2009	Grass mix	SLIT Placebo	5 years	Bronchodilators use		23.0 +/- 1.5 22.4 +/- 0.9	5.1 +/- 1.4 13.0 +/- 1.2	Arm 1 Vs. Arm 1 p= 0.001 Arm 2 Vs. Arm 2 p= 0.001 Arm 1 Vs. Arm 2 p= 0.01
[30] Marogna, 2009	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	Arm 1 Vs. Arm 2 p< 0.001
[33] Marogna, 2007	Birch and Grass	SLIT Birch alone SLITGrass alone SLITBirch+Grass Pharmacotherapy	4 years	Drug score during birch pollen season		70 68 70 60	15 30 10 62	Arm 1 Vs. Arm 4 p< 0.001 Arm 2 Vs. Arm 4 p< 0.001 Arm 3 Vs. Arm 4 p< 0.001
[33] Marogna, 2007	Birch and Grass	SLIT Birch alone SLITGrass alone SLITBirch+Grass Pharmacotherapy	4 years	drug score for grass pollen season		70 65 68 65	30 10 10 65	Arm 1 Vs. Arm 4 p< 0.01 Arm 2 Vs. Arm 4 p< 0.001 Arm 3 Vs. Arm 4 p< 0.001
[35] Marogna, 2007	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	Arm 1 Vs. Arm 1 p =0.55 Arm 2 Vs. Arm 2 p= 0.118

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[36] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	pulmonary symptom relief medication			5 8	Arm 1 Vs. Arm 2 p NS
[36] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	nasal symptom relief medication			3 1	Arm 1 Vs. Arm 2 p NS
[38] Bush 2011	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
[40] Bahceciler, 2001	Grass mix and Olive	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	Arm 1 Vs. Arm 2 p=0.028
[40] Bahceciler, 2001	Grass mix and Olive	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	Arm 1 Vs. Arm 1 p = 0.6 Arm 1 Vs. Arm 2 p = 0.67
[41] Guez, 200	Dust mite	SLIT Placebo	24 months	Unspecified	1- no max	9.2 10.2	4.1 (5.5) 6.1 (6.8)	Arm 1 Vs. Arm 2 p NS
[42] Marogna 2010	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)
[43] Pajno, 2004	Parietaria	SLIT Placebo	Pollen season (April-June)	Drug scores			0 2	Arm 1 Vs. Arm 2 p =0.192

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[44] Passalacqua 1999	Parietaria	SLIT Placebo	End of pollen season (8 months)	Drug intake scores means		115.5 137.4	42.3 83	Arm 1 Vs. Arm 1 p =0.008 Arm 2 Vs. Arm 2 p NS
[45] Vervloet, 2007	Mountain cedar	SLIT Placebo	4 months	Total medication score		NR NR	3.39 +/- 3.94 4.71+/- 5.0	Arm 1 Vs. Arm 2 p = 0.03
[46] Vourdas, 1998	Olive	SLIT Placebo	Pollen season Year 2	Unspecified				Arm 1 Vs. Arm 2 p NS
[25] Sabbah, 1994	Grass mix	SLIT Placebo	17 weeks	Consumption of specific medications				Nasal and eye dorps Cromoglycate –and terfenadine Arm 1 Vs. Arm 2 p<0.005 Betamethasone and dexchlopheniramine Arm 1 Vs. Arm 2 p<0.005
[47] Pajno 2011	Grass mix	Continous SLIT Co-seasonal SLIT	3 years	Percent reduction from baseline	1 topical med; 2 systemic meds	NR	70% reduction 50% reduction	Arm 1 vs Arm 2: NS difference in amount of reduction of medication use
[48] Feliziani, 1995	Grass mix	SLIT Placebo	End of pollen season	drug consumption for rhinoconjunctivitis symptoms		NR NR	24.05 76	Arm 1 Vs. Arm 2 p=0.002
[50] Pradalier, 1999	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	Arm 1 Vs. Arm 2 p NS

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[52] Valovirta, 2006	Tree mix	SLIT high dose SLIT low dose Placebo	Peak season	Unspecified	0-8		4.5 5.5 6.5	Arm 1 vs placebo p=0.06 whole season, p=0.04 during peak season; Arm 2 vs placebo p=0.72 whole season, p=0.83 during peak season
[53] De Blay, 2007	Grass mix	SLIT Placebo	10 months	Medication scores. 0-5 points per dose	0-66		7.18 +/- 11.6 9.15 +/- 10.8	Arm 1 Vs. Arm 2 p=0.11
[21] Novembre, 2004	Grass Mix	SLIT Conventional ther	3 years	Medication score	1 per medication	NR	NR	Arm 1 vs Arm 2 p=0.02
[39] Tari, 1990	Dust mite	SLIT Placebo	18 months	Medication score			20% reduction of in medicine consumption in active group No changes in placebo	
[54] Pozzan 2010	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	Arm 1 vs Arm 2 p=0.0001

NS: Not significant

TABLE 9.- COMBINED SYMPTOM AND MEDICATION SYMTPOM SCORES -SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[1] Purello-D'Ambrosio, 1999	Parietaria	SLIT Placebo	10 months	Nasal, eye, bronchial symptoms plus medication	0-27	NR NR	NR NR	Arm 1 Vs. Arm 1 p=0.04 45% improvementover placebo
[6] Sambugaro, 2003	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)
[8] Horiguchi, 2008	Japanese Cedar	SLIT placebo	7 months	Nasal symptoms plus medication	NR	NR NR	1.2 1.7	Arm 1 Vs. Arm 2 p<0.001
[9] Okubo, 2008	Japanese cedar	SLIT placebo	End of season (april)	Nasal symptoms plus medication	NR	NR NR	NR NR	Arm 1 Vs. Arm 2 NS
[10] Fujimura 2011	Japanese Cedar	SLIT placebo	20 months	0-4 nasal sx plus 0-2 per medication used per day	NR	NR	NR	Total SMS: Arm 1 vs Arm 2 NS (exact p value is not given, only NS) Peak season: Arm 1 vs Arm 2 p=0.02
[14] D'Ambrosio, 1996	Parieteria	SLIT Conventional therapy	8 months	Nasal, eye, bronchial symptoms plus medication	NR	NR NR	5247 7158	Arm1 vs Arm 2 P=0.037 during peak season
[17] Skoner, 2010	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	Arm 1 Vs. Arm 3 p =0.02, Arm 2 Vs. Arm 3 NS

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[18] Di Rienzo, 2006	Mountain Cedar	SLIT Placebo	0-12	Nasal, ocular symptoms plus medication		NR NR	NR NR	Arm 1 Vs. Arm 2 NS
[19] Makino, 2010	Japanese Cedar	SLIT Placebo	5 months	Nasal symptoms plus medications	NR	NR NR	122 166	Arm 1 Vs. Arm 2 NS
[21] Novembre, 2004	Grass Mix	SLIT Conventional therapy SLIT	3 years	Nasal, eye, bronchial symptoms plus medication	NR	NR NR	NR NR	Arm 1 Vs. Arm 2 NS
[22] Ott, 2009	Grass mix	Placebo SLIT	18 months	Nasal, eye, bronchial symptoms, plus medications		0.97 1.28	-1.76 -1.19	Arm 1 Vs. Arm 2 NS
[33] Marogna, 2007	Birch, Grass, Birch plus Grass	SLIT Birch alone SLITGrass alone SLITBirch+Grass Pharmacotherapy	End of season 4	Nasal, eye, bronchial symptoms, plus medications				All SLIT Arms: pre versus post–treatment intra-group comparison, p <0.05
[34] Marogna, 2008	Dust mite, birch, grass mix, parieteria	SLIT Placebo	3 years	Nasal, eye, bronchial symptoms, plus medications	0-750	140 145	40 100	Arm 1 vs Arm 2 P<0.001
[35] Mareno-Ancillo, 2007	Grass Mix and Olive	SLIT Placebo	10 months	Nasal, eye, bronchial symptoms plus medication	NR	1.89 1.76	1.23 1.10	Arm 1 Vs. Arm 2 NS
[41] Guez, 2000	Dust mite	SLIT Placebo	2 years	Nasal symptoms plus medications		13.0 14.3	6.4 9.2	Arm 1 vs Arm 1 p <0.01, Arm 1 Vs. Arm 2 p< 0.01

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[42] Marogna 2010	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		Arm 1: 417 Arm 2: 383 Arm 3: 412	5 yr, 20 yr: 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)
[44] Passalacqua, 1999	Parietaria	SLIT Placebo	8 months	Nasal, eye, bronchial symptoms plus medication		417.1 403.5	231.5 274.3	Arm 1 vs Arm 1 p =0.006, Arms 2 vs Arm 2 p +0.046444
[47] Pajno 2011	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	Arm 1 vs Arm 2 NS
[49] Pfaar, 2008	Grass mix	Placebo SLIT	1.5 years	Nasal, eye, bronchial symptoms plus medication		527 442	214 453 9.15 +/- 10.8	Arm 1 Vs. Arm 2 p= 0.002

TABLE 10.- ALLERGY CHALLENGES AND FUNCTIONAL OUTCOMES: PFT-SLIT

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[11] Tahamiler, 2007	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	Arm 1 Vs. Arm 1 p<.05 Arm 2 Vs. Arm 2 p<.05

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[29] Amar, 2009	Timothy	SLIT Timothy mono SLIT Timothy multi Placebo	15 months	nasal provocation	0-5	1.9 1.7 2.3	2.5 2.2 2.1	Arm 1 vs Arm 3 p =0.03 Arm 2 Vs. Arm 3 p=0.11
[36] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	nasal provocation (acoustic rhinometry)	SBU/ml 40% reduction nasal flow	1240 470	1380 1790	Arm 1 vs Arm 1 p <0.001 Arm 2 Vs. Arm 2 NS Arm 1 vs Arm 2 NS
[44] Passalacqua 1999	Parietaria	SLIT Placebo	End of pollen season (8 months)	nasal provocation ASNC	0-12	8 8	4 6.5	Arm 1 vs Arm 1 p<0.001 Arms 2 vs Arm 2 p <0.01 Arm 1 Vs. Arm 2 p =0.0001
[55] Alvarez-Cuesta, 2007	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 Arm 1 Vs. Arm 2 p =0.002
[15] La Rosa, 1999	Parietaria	SLIT Placebo	2 years	ocular conjunctival provocation test	0-3	NR NR	NR NR	Arm 1 Vs. Arm 2 p =0.02
[20] Lima, 2002	Timothy	SLIT Placebo	18 months; at peak season	ocular provocation challenge scores		NR NRI	3200 3200	Arm 1 Vs. Arm 2 p=0.18
[55] Alvarez-Cuesta, 2007	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	Arm 1 Vs. Arm 1 p < 0.001 Arm 2 Vs. Arm 2 p =0.327 Arm 1 Vs. Arm 2 p =0.118

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[55] Alvarez-Cuesta, 2007	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	Arm 1 vs Arm 1 p=0.003 Arm 2 vs Arm 2 p=0.263 Arm 1 vs Arm 2 p=0.118
[4] Lue, 2006	Dust mite	SLIT Placebo	6 months	FEV1		75 (graph) 80 (graph)	90 (graph) 82 (graph)	Arm 1 Vs. Arm 1 p = 0.001 Arm 2 Vs. Arm 2 p =0.48 Arm 1 Vs. Arm 2 p =0.93
[5] Niu, 2006	Dust mite	SLIT Placebo	24 weeks	FEV1		85 90	95 90	Arm 1 vs Arm 1 p=0.048 Arm1 vs Arm 2 NS
[56] Ippoliti, 2003	Dust mite	SLIT Placebo	6 months	FEV1		83.4 80.7	92.6 81.2	Arm 1 Vs. Arm 1 p < 0.001 Arm 2 Vs. Arm 2 p NS Arm 1 vs Arm 2 NR
[4] Lue, 2006	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.
[5] Niu, 2006	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[6] Sambugaro, 2003	Dust mite-grass mix-ragweed and Parietaria	SLIT/ 8-d induction SLIT/ 15-d induction SLIT/ 15-d induction	2 years	FEV1				All 3 SLIT arms had improvement FEV1 pre/post tx p<0.05
[32] Marogna, 2004	Dust mite, birch, grass mix, parietaria, mugwort	SLIT Pharmacotherapy	3 years	Metacholine challenge				pre/post tx SLIT: significant reduction in M CH positive cases; not significant in controls
[33] Marogna, 2007	Birch and Grass	SLIT Birch alone SLITGrass alone SLITBirch+Grass Pharmacotherapy	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
[34] Marogna, 2008	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
[55] Alvarez-Cuesta, 2007	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	Arm 1 Vs. Arm 1 p <0.001 Arm 2 Vs. Arm 2 p NS Arm 1 Vs. Arm 2 p < 0.0001
[28] Marogna 2010	Birch; (GINA Criteria for asthma dx)	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	FEV1 96.2(1.2); PD20 919.3(85.7); MEF 85.5(2.2) FEV1 81.2(1.4); PD20 478.7	FEV1: Arm 1 vs Arm 2 p<0.0001 PD20: Arm 1 vs Arm 1 P<0.001; Arm 2 vs Arm 2 P=0.019 Arm 1 vs Arm 2 p=0.001 MEF: Arm 1 vs Arm 2 p<0.0001

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
						288.6(44.9); MEF 64.3(2.1)	(76.2); MEF 67.7(1.8)	
[27] Voltolini, 2010	Birch	SLIT Placebo	2 years	GINA Asthma severity				SLIT vs placebo post tx: GINA asthma severity decreased (p<0.05)
[30] Marogna, 2009	Grass mix	SLIT Inhaled Corticosteroids	5 years	PD20				post tx SLIT vs controls: significant difference in PD20.
[31] Stelmach 2011	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
[38] Bush 2011	Dust mite	SLIT High dose; SLIT low dose; placebo	12-18 months	PD20 with antigen challenge		70 ±18 NR NR	101+13 NR NR	Arm 1 vs Arm 3 p=0.04 Arm 2 vs Arm 3 NS
[39] Tari, 1990	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
[42] Marogna 2010	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	Arm 1: Signficance lost after yr 8, Arm 2 vs Arm 2 p <0.05; Arm 3 vs Arm 3 p <0.05

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

TABLE 11.- SECONDARY OUTCOMES-SLIT

Study	ARMS	QOL	Adherence	Disease modification	Prevention of asthma	Development of new sensitivities
[5] Niu, 2006	SLIT Placebo	NR	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
[37] O'Hehir, 2009	SLIT Placebo	RQLQ significantly improved SLIT pre versus post-treatment score, p <0.01	NR	NR	NR	NR
[9] Okubo, 2008	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	NR	NR	NR	NR
[10] Fujimura 2011	SLIT Placebo	JRQLQ: SLIT vs Placebo p<0.01	NR	NR	NR	NR
[13] deBot 2011	SLIT placebo	PRQLQ Adol RQLQ	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

Study	ARMS	QOL	Adherence	Disease modification	Prevention of asthma	Development of new sensitivities
[17] Skoner, 2010	High dose SLIT Medium dose SLIT Placebo	RQLQ RQLQ RQLQ	91.6 +/- 9.7 93.1 +/- 7.8 NR	NR	NR	NR
[18] Di Rienzo, 2006	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)	NR	NR	NR	NR
[19] Makino, 2010	SLIT Placebo	Japanese Juniper RQLQ; 9/5 +/- 8.3 when compared to placebo p=0.048 15.9 +/- 19.6	NR	NR	NR	NR
[21] Novembre, 2004	SLIT Control	NR	NR	NR	At the end of study 8 developed asthma At the end of study 18 developed asthma	NR
[64] Ring, 2004	SLIT Placebo	pediatric and adolescent QOL(PRQLQ/AdolQLQ) no significant difference between groups	no significant difference between groups	NR	NR	NR

Study	ARMS	QOL	Adherence	Disease modification	Prevention of asthma	Development of new sensitivities
[27] Voltolini, 2010	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	NR	NR	NR	NR
[28] Marogna 2010	SLIT Monteleukast	NR	SLIT adherence >80% in 10 patients, >60% in 5 patients; Monteleukast adherence >80% 14 pts.	NR	NR	NR
[30] Marogna, 2009	SLIT Placebo	NR	more than 80% in 17/23 patients and more than 60% in 4/23 patients more than 80% in all patients	NR	NR	NR
[32] Marogna, 2004	SLIT Control	NR	>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)
[34] Marogna, 2008	SLIT Control	NR	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
[35] Moreno-Ancillo, 2007	SLIT Placebo	Overall QOL improved in all areas p=0.006 QOL improved in all areas p=0.260	NR	VAS p=0.006 VAS p=0.184	NR	NR

APPENDIX

Study	ARMS	QOL	Adherence	Disease modification	Prevention of asthma	Development of new sensitivities
[36] Hirsch, 1997	SLIT Placebo	NR	8/15 were compliant 10/15 were compliant	NR	NR	NR
[65] Tabar, 2005	Cluster Conventional	NR	5 didn't complete initial phase 4 didn't complete initial phase	NR	NR	NR
[42] Marogna 2010	SLIT 3 yrs, SLIT 4 yrs, SLIT 5 yrs.	NR	NR	NR	NR	New sensitivities: SLIT 3--21.4%, SLIT 4—12.5%, SLIT 5 11.7%
[49] Pfaar, 2008	SLIT Placebo	NR	18.1% discontinued 10.9% discontinued	NR	NR	NR
[52] Valovirta, 2006	SLIT dose 1 SLIT dose 2 Placebo	NR	NR	NR	After a follow up for 5 years asthma developed in 2/10 children. After a follow up for 5 years asthma developed in 6/10 children After a follow up for 5 years asthma developed in 6/10 children	NR
[62] Yonekura, 2010	SLIT Placebo	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	NR	NR

QOL:QUALITY OF LIFE, RVAS: VISUAL ANALOG SCALE, RQLQ

TABLE 12.- BIOMARKERS –SLIT

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[29] Amar, 2009	Timothy Monotherapy			Reported	increased by .05; p = .005	0.93	Reported	increased by .07; p = .02	
[29] Amar, 2009	Multiallergen therapy			Reported	increased by .03; not significant	0.93	Reported	increased by .10; p = .008	
[29] Amar, 2009	Placebo			Reported	decreased by .01; NS. Significant difference among all 3 arms (p = .02)	0.81	Reported	decreased by .06; NS. Significant difference among all 3 arms (p = .02)	
[40] Bahceciler, 2001	SLIT						Reported	pre: median 420 (range 42-2751); post: 295 (40-1701)	Total IgE levels were reported but no significant difference was found between arm 1 and arm 2.
[40] Bahceciler, 2001	Placebo						Reported	pre: median 405 (range:197-5967); post: 536 (166-3948)	
[16] Bowen, 2004	SLIT			Reported	Significantly increased (p < .001) compared to placebo	15.9	Reported	Significantly increased (p < .001) compared to placebo	
[16] Bowen, 2004	Placebo			Reported		16.9	Reported		
[14] D'Ambrosio,									"No statistically significant change could be detected in specific IgE

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
1996									and IgG4 in either group."
[53] De Blay, 2007	SLIT			Reported					
[53] De Blay, 2007	Placebo			Reported					
[53] De Blay, 2007									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. Measurement of anti-Dactylis specific IgG4 antibodies at inclusion showed a significantly (P = .03) higher baseline level for the SLIT group (Table 1). This difference was more marked at the end of the study. The anti-Dactylis specific IgG4 antibody level increased from a mean +/- SD of 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 = .001) (Fig 4). The Spearman rank correlation between the anti-Dactylis specific

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
									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 = .08) but not for the placebo group (r = 0.02, P = .87).
[66] Eifan, 2010	SLIT						Df = 51.1; Dpt = 59.4	Reported	significant decrease om IgE D.f at 12 months (p=0.04)
[41] Guez, 2000	Active SLIT			Reported	no change	25.3 (derp) 18.8 (derf)	Reported	decreased slightly	
[41] Guez, 2000	Placebo			Reported	no change	37 (derp) 31 (derf)	Reported	lower too	
[36] Hirsch, 1997	SLIT	Reported	NS			39.1 kU/l	Reported	Increased more than placebo, P<0.01	compliance is reported
[36] Hirsch, 1997	Placebo	Reported	NS	Reported	decreased, p<0.05	33.3 kU/l	Reported	increased, p<0.01	
[67] Horak, 1998	SLIT	Reported	same as IgE				Reported	increased slightly, not significant	skin prick tests done. unchanged in active group and rise in the placebo
[67] Horak, 1998	Placebo	Reported	Same as IgE				Reported	slight decrease (not significant)	
[7] Hordijk, 1998	SLIT	Reported	significantly higher than placebo	Reported	no significant change from baseline		Reported	no significant change from baseline	

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[7] Hordijk, 1998	Placebo	Reported	increased significantly	Reported	no significant change from baseline		Reported	no significant change from baseline	
[8] Horiguchi, 2008	SLIT			Reported	increased significantly in the active group but not in the placebo and the a significant difference was observed between the groups (p<0.05)	4.18 (cedar pollen RAST)	Reported	no change	The Th1/Th2 levels, IL-4 and IL-5 are reported
[8] Horiguchi, 2008	Placebo			Reported	no change	4.14 (cedar pollen RAST)	Reported	no change	
[56] Ippoliti, 2003	SLIT								The other lad measures reported are CD40+ Bcells, serum ECP, IL-13 and ACTH levels.
[15] La Rosa, 1999	SLIT			Reported	significant increase in levels after 2 yrs (p=0.02)		Reported	no significant difference between the groups	
[15] La Rosa, 1999	Placebo			Reported	no significant change in levels		Reported		
[20] Lima, 2002	SLIT			Reported	increased	250 KU/L +/- 257	Reported	no change at the end	IL-12 mRNA levels reported in sublingual biopsies
[20] Lima, 2002	Placebo			Reported	no change	189 KU/L +/- 251	Reported	no change at the end	

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[4] Lue, 2006	SLIT			Reported	Staistically significant increase within group and when compared to placebo p=0.026	500 IU/L (from graph)	Reported	Increased within group, not statistically significant when compared with placebo	
[4] Lue, 2006	Placebo			Reported	no major change	400 IU/L (from graph)	Reported	no major change	
[26] Marogna, 2005	SLIT								eosinophil counts 61% of patients had no eos in nasal smear in SLIT vs 14% in placebo p <0.01
[33] Marogna, 2007	SLIT								The biomarker reported is 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
[68] Mauro, 2007	SLIT			Reported	increase, not significant	52.8 kU/L	Reported	increased	
[69] Mungan, 1999	SLIT			Reported	there was a significant increase in levels at the 12th month following therapy, p<0.05	505.05 (kU/L)	Reported	No changes observed in IgE levels in the 6th and 12th months of therapy compared to baseline	
[69] Mungan, 1999	SLIT						Reported	no difference from baseline; baseline value=311.89 kU/L	

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[69] Mungan, 1999	Placebo			Reported		288.40 (kU/L)	Reported	No changes observed in IgE levels in the 6th and 12th months of therapy compared to baseline	
[69] Mungan, 1999	Placebo						Reported	no difference from baseline; baseline value=288.40	
[3] Nelson, 1993	SLIT	Reported	mean values before and after treatment are 2.7+/-0.13 and 2.81+/-0.16 (arbitrary units) respectively (p value=NS)			0.86 (PRU) +/-0.36	Reported	mean values before and after treatment are 0.86+/-0.36 and 1.00+/-0.35 PRU respectively (p value=NS)	no effect of treatment on IgG or IgE levels.
[3] Nelson, 1993	Placebo	Reported	mean values before and after treatment are 2.57+/-0.13 and 2.58+/-0.11 (arbitrary units) respectively (p			-0.12 (PRU) +/-0.27	Reported	mean values before and after study are -0.12+/-0.27 and 0.05+/-0.32 PRU respectively (p value=NS)	

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
			value=NS)						
[5] Niu, 2006	SLIT					829.8	Reported	The change in total IgE from baseline to 24 weeks is 129.7 +/- 460.6,	also specific IgE was reported, no significant change.
[5] Niu, 2006	Placebo					780.6	Reported	The change in total IgE from baseline to 24 weeks is - 85.1 +/- 59.8 (group difference, p value= 0.063)	
[37] O'Hehir, 2009	SLIT			Reported	Mean Der p1 baseline value=596, at 1 year= 800, Mean Der p2 baseline value=274, at 1 year= 528		Reported	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 IgG4 Der p 1= 0.57, IgG4 Der p 2= 0.17 IL-10= 0.18

APPENDIX

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[37] O'Hehir, 2009	Placebo			Reported	Mean Der p1 baseline value=82, at 1 year= 279, Mean Der p2 baseline value=31, at 1 year= 99		Reported	Mean Der p1 baseline value=32, at 1 year= 28, Mean Der p2 baseline value=8, at 1 year= 6	
[38] Bush 2011	High dose; Low dose; placebo			IgG4 significantly increase in Arm 1 compared to placebo. No sig change in low dose group			Specific IgE no significant change over study		
[22] Ott, 2009	SLIT-rush			Reported	At follow-up: 0.02 +/- 0.30	13.35	Reported	At follow-up: 5.74 +/- 16.88	
[22] Ott, 2009	Placebo			Reported	At follow-up: -0.03 +/- 0.10 (between groups p value= 0.518)	7.78	Reported	At follow-up: 2.02 +/- 9.78 (between groups p value= 0.2578)	
[2] Pajno, 2000	SLIT	Reported	Mean at baseline: 33.0, after 2 years: 31.3	Reported	Mean at baseline: 2.85, after 2 years: 2.53	45.4	Reported	Mean at baseline: 45.4, after 2 Baseline: 52.2, after 2 years: 65.3, Between group differences NS years: 52.6	

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[2] Pajno, 2000	Placebo	Reported	Mean at baseline: 26.0, after 2 years: 31.9, Between group differences NS	Reported	Mean at baseline: 2.7, after 2 years: 2.66, Between group differences NS	52.2	Reported	Mean at baseline: 52.2, after 2 years: 65.3, Between group differences NS	
[23] Panzner, 2008	SLIT	Reported	Baseline: 27.13+/- 17.46, End of 1 yr: 47.82+/- 13.68 (pvalue: 0.0240)			20	Reported	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
[23] Panzner, 2008	Placebo	Reported	Baseline: 56.97+/- 22.79, End of 1 yr: 67.67+/- 21.49 (pvalue: 0.3038)			15	Reported	Baseline: 47.21+/- 14.79, End of 1 yr: 53.48+/- 20.81 (pvalue: 0.1373)	
[44] Passalacqua 1999									Neutrophils, eosinophils and ICAM expression on nasal epithelium (early inflammation is reduced after SLIT, p= 0.05 for neutrophils and ICAM)

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[47] Pajno 2011				Both groups had significant increase in specific IgG4 at end of study compared to baseline			Baseline specific IgE: Arm 1- 11.2, Arm 2- 9.9		
[49] Pfaar, 2008	SLIT			Reported	at end of 1.5 years SLIT vs Placebo: p value <0.001		Reported	there was no consistent trend for change in either group	Other lab measure reported was IgG1 values. At end of 1.5 years SLIT vs Placebo: p value <0.001 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.
[49] Pfaar, 2008	Placebo			Reported			Reported		
[70] Piazza, 1993	SILT	HDM	Reported	Baseline to 24 months : NS change	Reported	Baseline to 24 months : NS change		Reported	Baseline to 24 months : NS change
[50] Pradalier, 1999	SLIT			Reported	Baseline: 5.7+/- 3.8%; end of study: 8.7+/- 10.9% (p<0.0001)	91.3	Reported	Baseline: 91.3+/- 239.9; end of study: 244.5+/- 459.1 (p<0.0001)	

APPENDIX

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[50] Pradalier, 1999	Placebo			Reported	Baseline: 6.0+/- 3.3%; end of study: 6.8+/- 4.5% (p=0.002) Between group comparison p<0.03	78.8	Reported	Baseline: 78.8+/- 105.9; end of study: 144.0+/- 231.0 (p<0.0001) between group comparision p<0.04	
[51] Sieber 2012	None reported					SLIT: total IgE 198; placebo 258	Baseline SLIT specific IgE 27; placebo 29	No significant difference in baseline values	
[1] Purello-D'Ambrosio, 1999	SLIT			Reported	Baseline: 2.52+/- 0.333; 10 months: 2.57+/- 0.411 (p=0.7798)	14.058	Reported	Baseline: 14.058+/- 14.136; 10 months: 19.304+/- 24.763 (p value=0.0277)	
[1] Purello-D'Ambrosio, 1999	Placebo			Reported	Baseline: 2.6637+/- 0.6637 ; 10 months: 2.5850+/- 0.704 (p=0.3519)	17.42	Reported	Baseline: 17.42+/- 13.12; 10 months: 22.19+/- 20.295 (p=0.034)	
[71] Quirino, 1996	SLIT		Reported	significant difference before and after	Reported	significant difference before and after		Reported	insignificant difference before and after

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[72] Scadding, 1986	SLIT						Reported	Reports pre and post values for each patient	
[72] Scadding, 1986	Placebo						Not reported		
[17] Skoner, 2010	High dose SLIT	Reported	mean change: 2.29 +/- 3.97	Reported	mean change: -0.09 +/- 0.77		Reported	mean change: 19.75 +/- 56377	
[17] Skoner, 2010	Medium dose SLIT	Reported	mean change: 1.69 +/- 3.98	Reported	mean change: 0.64 +/- 1.65		Reported	mean change: 25.93 +/- 52.83	
[17] Skoner, 2010	Placebo	Reported	mean change: -0.08 +/- 1.81	Reported	mean change: -0.09 +/- 0.77		Reported	mean change: 2.55 +/- 4.14	
[73] Stelmach, 2009	SLIT			Reported	0.31 µg/ L	549.3 (kU/L)	Reported	496.4 kU/L	
[73] Stelmach, 2009	Placebo			Reported	0.25 µg/L	424.6 (kU/L)	Reported	503.4 kU/L	
[39] Tari, 1990	SLIT	Reported	5.23 +/- 3.1 significant increase p<0.001.	Reported	10.71 +/- 3.81		Reported	no change	
[39] Tari, 1990	Placebo	Reported	2.32 +/- 1/42 no change	Reported	2.78 +/- 2.02		Reported	significant rise	

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[63] Troise, 1995	SLIT	Reported	(%) 32.6+/- 12.7 before 34.6 +/-7.9 after	Reported	(%) 20.7 +/- 5.4 before 27.8 +/- 8.2 after		Reported	(total kU/l) 209+/- 238 before 232 +/- 236 after	
[63] Troise, 1995	Placebo	Reported	(%) 28.2+/- 5.2 before 28.1 +/- 10.1 after	Reported	(%) 23 +/-7.4 before 28.2 +/- 7.1 after		Reported	(total kU/l) 182+/- 150 before 190 +/- 126 after	
[12] Tseng, 2008	SLIT					Der p: 129, Der f: 170	Reported	change from baseline to 24th week s 40.8 +/- 76.1 p value: 0.008	
[12] Tseng, 2008	SLIT						Reported	change from baseline to 24th week s 49.0 +/- 73.9 p value: 0.002	
[12] Tseng, 2008				Reported	change from baseline to 24th week 772.9 +/- 1,002.8 p-value: <0.001				
[12] Tseng, 2008				Reported	change from baseline to 24th week s 710 +/- 990.9 p value: 0.002				
[12] Tseng, 2008	Placebo					Der p: 98, Der f: 119	Reported	change from baseline to 24th week is 21.0 +/- 46.7 p-value: 0.018	

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[12] Tseng, 2008	Placebo						Reported	change from baseline to 24th week s 24.2 +/- 43.3 p value: 0.004	
[12] Tseng, 2008	Placebo			Reported	change from baseline to 24th week -92.4 +/- 290.1 change from baseline to 24th week 772.9 +/-				
[12] Tseng, 2008	Placebo			Reported	change from baseline to 24th week s -6.4 +/- 280.1 p value: 0.889				
[52] Valovirta, 2006									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.
[45] Vervloet, 2007	SLIT			Reported	Baseline: 171.8+/- 74.3, after treatment: 481.6 +/- 623.4	18.9 specific (not total) IgE to Juniperus	Reported	Baseline specific IgE: 9.1+/- 11.1, after treatment: 38.8 +/- 35.1	

Study	Arms	IgG	Finding	IgG4	Finding	Mean IgE baseline	IgE	Finding	COMMENTS
[45] Vervloet, 2007	Placebo			Reported	Baseline: 198.0+/- 165.3, after treatment: 267.1 +/- 370.4 (p value :0.03)	23.3	Reported	Baseline: 11.3+/- 14.4, after treatment: 20.4 +/- 23.4 (p value :0.04)	
[46] Vourdas, 1998	SLIT			Reported			Reported		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.
[46] Vourdas, 1998	Placebo			Reported			Reported		

TABLE 13. SLIT-SAFETY

SLIT Local Reactions Reported as PERCENT OF PATIENTS WITH REACTIONS

Study	SLIT Allergen	Number of Patients in Arm	Percent of Patients with Local Reactions [1]	Severity
[37] O'Hehir, 2009	Dust mite	15	60	moderate
	Placebo	15	7	
[2] Pajno, 2000	Dust mite	12	8	mild
[11] Tahamiler, 2007	Dust mite 2 years	137	52	unspecified
	Dust mite 3 years			
[3] Nelson, 1993	Cat	20	40	mild
	Placebo	21	19	mild
[53] De Blay, 2007	Grass Mix	61	80	unspecified
	Placebo	57	19	unspecified
[21] Novembre, 2004	Grass mix	54	2	mild
	Control			
[49] Pfaar, 2008	Grass mix	94	62	mild
	Placebo	91	20	mild
[50] Pradalier, 1999	Grass mix	62	3	mild
	Placebo	61	2	mild
[26] Marogna, 2005	Birch	39	14	mild
	Placebo			
[8] Horiguchi, 2008	Japanese Cedar	43	26	mild
	Placebo	24	8	mild
[9] Okubo, 2008	Japanese Cedar	37	16	mild
	Placebo			

Study	SLIT Allergen	Number of Patients in Arm	Percent of Patients with Local Reactions [1]	Severity
[18] Di Rienzo, 2006	Mountain Cedar	19	37	
	Placebo	15	20	
[46] Vourdas, 1998	Olive	34	3	unspecified
	Placebo			
[52] Valovirta, 2006	Tree mix-high	32	50	unspecified
	Tree mix-low	33	36	unspecified
	Placebo	32	25	
[33] Marogna, 2007	Birch	11	9	mild
	Grass mix	12	8	mild
	Birch plus Grass mix	13	8	mild
[16] Bowen, 2004	Ragweed	43	51	unspecified
	Placebo			
[14] D'Ambrosio, 1996	Parietaria	15	0	unspecified
	Placebo			
[32] Marogna, 2004	Dust mite, Birch, Weed mix, Grass mix	319	1	unspecified
	Placebo			
[34] Marogna, 2008	Dust mite, Birch, Parietaria, Grass mix	144	0.7	unspecified
	Placebo			
[51] Sieber 2012	SLIT	142	6	NR
	Placebo	67	2	NR
[31] Stelmach 2011	SLIT (2SLIT arms reported together)	40	45	
	placebo	20	15.3	
[38] Bush 2011	High dose SLIT	10	40	Milld-moderate
	Low dose SLIT	10	30	Mild-moderate

Study	SLIT Allergen	Number of Patients in Arm	Percent of Patients with Local Reactions [1]	Severity
	placebo	11	20	moderate
[42] Marogna 2010	SLIT 3yrs	19	16	mild
	SLIT 4 yrs	21	5	mild
	SLIT 5 yrs	17	12	mild
[54] Pozzan 2010	SLIT	34	17	mild
	placebo			
[13] deBot 2011	SLIT	125	11.2	unspecified
	placebo	126	14.3	unspecified

Local SLIT Reactions Reported as Number of Event

Study	Arm	N in Arm	Number of Events	Number of Events per Patient [1]	Severity
[36] Hirsch, 1997	Dust mite	15	6	0.4	mild
	Placebo	15	1	0.07	mild
[7] Hordijk, 1998	Grass mix	27	3	0.11	mild
	Placebo	30	1	0.03	mild
[23] Panzner, 2008	Grass mix	20	11	0.55	unspecified
	Placebo	15	1	0.07	unspecified
[20] Lima, 2002	Timothy grass	28	380	13.57	mild
	Placebo				
[25] Sabbah, 1994	Grass Mix	29	4	0.14	unspecified
	Placebo	29	1	0.03	unspecified
[45] Vervloet, 2007	Bald Cypress	38	3	0.08	unspecified

Study	Arm	N in Arm	Number of Events	Number of Events per Patient [1]	Severity
	Placebo				
[46] Vourdas, 1998	Olive	32	8	0.25	unspecified
	Placebo	32	2	0.13	mild
[35] Moreno-Ancillo, 2007	Grass mix and Olive	52	92	1.77	mild
	Placebo	53	14	0.26	mild
[15] La Rosa, 1999	Parietaria	20	5	0.25	moderate
	Placebo	21	4	0.19	
[57] Rodriguez, 2006	Dust mite and Grass mix-updosing	69	30	0.43	unspecified
	Dust mite and Grass mix-no updosing	66	46	0.70	unspecified[1]
[29] Amar, 2009	Timothy	19	21	1.11	
	Timothy plus Tree mix and Weed mix	17	11	0.65	
	Placebo	17	1	0.06	
[51] Sieber 2012	SLIT	142	35		NR
	placebo	67	17		NR
[38] Bush 2011	High dose -Low dose SLIT				
	placebo	11	9		moderate
[13] deBot 2011	SLIT	125	92.0		NR
	placebo	126	93.7		NR

SLIT Systemic Reactions: Rhinitis/Nasal Reactions Reported as a Percent of Patients

Study	SLIT Allergen	Number of Patients in Arm	Percent of Patients with Rhinitis/Nasal Reactions[1]	Severity
[52] Valovirta, 2006	Tree mix	33	3	unspecified
	Placebo	32	3	unspecified
[39] Tari, 1990	Dust mite	32	25	Severe-authors noted this subjects exceed maximum dose
	Placebo			
[11] Tahamiler, 2007	Dust mite 2 years	137	37	mild
	Dust mite 3 years			
[6] Sambugaro, 2003	Dust mite, Grass mix, Tree mix	18	6	mild
	Placebo			
[41] Guez, 2000	Dust mite			
	Placebo	36	3	unspecified
[50] Pradalier, 1999	Grass Mix	62	6.5	unspecified
	Placebo			
[51] Sieber 2012	SLIT	142	35	NR
	placebo	67	17	NR
[38] Bush 2011	High dose -Low dose SLIT			
	placebo	11	9	moderate
[13] deBot 2011	SLIT	125	92.0	NR
	placebo	126	93.7	NR

SLIT Systemic Reactions: Cutaneous: (rash/urticaria/angioedema) Reported as a Percent of Patients

Study	SLIT Allergen	Number of Patients in Arm	Percent of Patients with Cutaneous Reactions[1]	Severity
[8]Horiguchi, 2008	Japanese Cedar	42	4.8	mild
[32]Marogna, 2004	Dust mite, Birch, Weed mix, Grass mix	319	1.3	mild
[34]Marogna, 2008	Birch and Grass mix	144	0.7	mild
[3]Nelson, 1993	Placebo	21	4.8	mild
[21]Novembre, 2004	Grass mix	54	1.9	mild
	Placebo	59	1.7	mild
[50] Pradalier, 1999	Grass mix	62	3.2	unspecified
	Placebo	61	9.8	unspecified
[39]Tari, 1990	Dust mite	30	10	unspecified
[51] Sieber 2012	SLIT	142	5	NR
	Placebo	67	4	NR
[13] deBot 2011	SLIT	125	56.8	NR
	placebo	126	65.1	NR

SLIT Systemic Reactions: Lower Respiratory Reactions Reported as a Percent of Patients

Study	SLIT Allergen	Number of Patients in Arm	Percent of Patients with Lower Respiratory Reactions[1]	Severity
[50] Pradalier, 1999	Grass mix	62	7 bronchospasm	unspecified
	Placebo	61	3 bronchospasm	unspecified
[39] Tari, 1990	Dust mite	32	34 asthma	9% severe asthma- these subjects were noted to have exceeded maximum dose. 25% mild asthma
[36] Hirsch, 1997	Dust mite	15	7 bronchial	unspecified
	Placebo			

[51] Sieber 2012	Dust mite	142	13	NR
	Placebo	67	4	NR
[38] Bush 2011	High dose	10	10	moderate
	Low dose			
	Placebo			
[13] deBot 2011	Dust mite	125	67.2	NR
	placebo	126	69.0	NR

SLIT Systemic Reactions: Lower Respiratory Reactions Reported as Number of events

Study	SLIT Allergen	Number of Patients in Arm	Number of Events	Number of Events per Patient[1]	Severity
[7] Hordijk, 1998	Grass mix	27	3 respiratory	0.03	Mild-no treatment required
	Placebo	30	1 respiratory	0.11	Mild-no treatment required
[3] Nelson, 1993	Cat	20	2 (1 asthma, 1 cough)	0.10	unspecified
	Placebo	21	6 (5 asthma, 1 cough)	0.29	unspecified
[41] Guez, 2000	Placebo	36	1 asthma	0.03	unspecified
[32] Marogna, 2004	Dust mite, Birch, Weed mix, Grass mix	319	1 asthma	0.05	unspecified
[34] Marogna, 2008	Birch and Grass mix	144	1 asthma	0.007	unspecified
[23] Panzner, 2008	Grass mix	20	6 lower respiratory	0.30	unspecified

SLIT Systemic Reactions: Gastrointestinal (nausea/pain/diarrhea) Reported as a Percent of Patients with Reaction

Study	SLIT Allergen	N in arm	Percent of Patients with Gastrointestinal Reactions	Severity
[53] De Blay, 2007	Grass mix	61	19.7	unspecified
	Placebo	57	7	unspecified
[32] Marogna, 2004	Dust mite, Birch, Weed mix, Grass mix	319	4	unspecified
[34] Marogna, 2008	Birch, Grass mix	144	0.7	unspecified

[3] Nelson, 1993	Cat	20	15	unspecified
[21] Novembre, 2004	Grass mix	54	1.2	unspecified
[70] Piazza, 1993	Dust mite	14	14.3	moderate
[50] Pradalier, 1999	Grass mix	62	3.2	unspecified
	Placebo	61	3.3	unspecified
[11] Tahamiler, 2007	Dust mite	137	14	mild
[39] Tari, 1990	Dust mite	32	11.4	unspecified
[52] Valovirta, 2006	Tree mix-high	32	3.1	unspecified
	Tree mix-low	33	6	unspecified
[16] Bowen, 2004	Ragweed	43	21	unspecified
[51] Sieber 2012	SLIT	142	15	NR
	Placebo	67	6	NR
[38] Bush 2011	High dose SLIT	10	10	mild
	Low dose SLIT	10	10	moderate
	placebo	11	0	
[13] deBot 2011	SLIT	125	68.0	NR
	placebo	126	60.3	NR
[31] Stelmach 2011	SLIT (arm 1 + 2 reported together)	40	6	NR
	placebo	20	5.6	NR

SLIT Systemic Reactions: Gastrointestinal (nausea/pain/diarrhea) Reported as Number of Events

Study	SLIT Allergen	N in arm	Number of Events	Number of Events per Patient[2]	Severity
[7]	Grass Mix	27	1	0.03	unspecified

Hordijk, 1998	Placebo	30	1	0.04	unspecified
[15] La Rosa, 1999	Parietaria	20	19	0.95	unspecified
	Placebo	21	1	0.05	unspecified
[25] Sabbah, 1994	Grass mix	29	1	0.03	unspecified
	Placebo	29	1	0.03	unspecified
[45] Vervloet, 2007	Bald Cypress	38	4	0.11	unspecified
	Placebo	38	1	0.03	unspecified

SLIT Systemic Reactions: Cardiovascular Reported as Number of Events

Study	SLIT Allergen	N in arm	Number of Events	Number of Events per Patient[3]	Severity
[52] Valovirta, 2006	Tree mix-high	32	3	0.09	mild
[45] Vervloet, 2007	Bald BaldCypress	38	1-Facial flushing	0.03	mild

SLIT Systemic Reactions: Ocular Reactions Reported as a Percent of Patients

Study	SLIT Allergen	Number of Patients in Arm	Percent of Patients with Ocular Reactions[1]	Severity
[49] Pfaar, 2008	Grass mix	94	6.4	unspecified
	Placebo	91	2.2	unspecified
[39] Tari, 1990	Dust mite	30	20	unspecified

SLIT Systemic Reactions: Ocular Reactions Reported as Number of Events

Study	SLIT Allergen	Number of Patients in Arm	Number of Events	Number of Events per Patient[4]	Severity
[74] Sabbah, 1994	Dust mite and Grass mix-updosing	69	5	0.07	unspecified
	Dust mite and Grass mix- no updosing	66	2	0.03	unspecified
[46] Vourdas, 1998	Olive	32	1	0.03	unspecified

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APPENDIX F. SLIT vs SCIT EVIDENCE TABLES

TABLE 1.- STUDY CHARACTERISTICS SLIT vs SCIT

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple Allergen	Allergen	Inclusion criteria	Funding source
Mauroa, 2007[1]	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]	Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	No previous immunotherapy Positive specific IgE test Positive skin test	Not stated
Tahamile, 2006[3]	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]	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]	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]	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
[7] Yukselen 2011 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
[8] Keles 2011 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 2.- PATIENT CHARACTERISTICS- SLIT vs SCIT

Study	Patients randomized	Comparators	Age (years) (mean+/- SD)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Mauroa, M., 2007[1]	47	SLIT SCIT	39 (Range 18-57) 40 (Range 20-59)	60/40 45/55	20/5 20/1	NR NR
Piazza, I., 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, R., 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, M.S., 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, A.O., 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, D., 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
[7] Yukselen 2011	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
[8] Keles 2011	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 3.- INTERVENTION CHARACTERISTICS- SLIT vs SCIT

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 mcg Bet v 1 3.28 mcg Bet v 1	11182 mcg 51mcg	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

APPENDIX

Study	Arms	Conventional/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
[7] Yukselen 2011	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
[8] Keles 2011	SCIT SLIT SCIT (build-up)+SLIT (maintenance) Pharmacotherapy	Rescue	44.12 mcg of Der p1 and 62.1 mcg of Df1 52.8 mcg of Der p1 and 52.8 mcg of Df1 43.2 mcg of Der p1 and 43.2 mcg of Df1	NR	Monthly 3 times a week 3 times a week	44.12 mcg of Der p1 and 62.1 mcg of Df1 52.8 mcg of Der p1 and 52.8 mcg of Df1 43.2 mcg of Der p1 and 43.2 mcg of Df1 (Maintenance phase)	1 year

TABLE 4.- QUALITY ASSESSMENT- SLIT vs SCIT

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
[7] Yukselen 2011	Low risk	High risk	High risk	Low risk	Low risk	No	Moderate risk
[8] Keles 2011	Low risk	High risk	High risk	Low risk	Low risk	No	Moderate risk

TABLE 5.- ASTHMA AND ASTHMA COMBINED SCORES- SLIT vs SCIT

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	SLIT, pre vs post, p=NS SCIT, pre vs post, p<0.01 Placebo, pre vs post, p=NS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[7] Yukselen 2011	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
[8] Keles 2011	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 6.- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES SLIT vs SCIT

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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
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 the 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
[7] Yukselen 2011	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
[8] Keles 2011	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 7.- 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
[7] Yukselen 2011	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
[8] Keles 2011	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
Eifan2010[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
[7] Yukselen 2011	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 8.- MEDICATION SCORES SLIT vs SCIT

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 vs Pharmacotherapy, p=0.26 SLIT vs Pharmacotherapy, p=0.03
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 vs post, p=0.01 SCIT, pre vs post, p=0.01 Placebo, pre vs 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 vs Placebo, p<0.002 SCIT vs Placebo, p<0.002 SCIT vs SLIT, p=NS
[7] Yukselen 2011	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
[7] Yukselen 2011	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
[8] Keles 2011	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

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[8] Keles 2011	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
[8] Keles 2011	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 9. COMBINED SYMPTOM MEDICATION SCORES, SCIT versus 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 vs post, p<0.001 SLIT, pre vs post, p<0.01 at 3 months but at 2 years p=NS(
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 vs SCIT, p=NS

TABLE 10.- ALLERGY CHALLENGES AND FUNCTIONAL OUTCOMES: PFT SLIT vs SCIT

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	Arm 1, pre vs post, p<0.05 Arm 2, 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	Arm1, pre vs post, p=NS Arm2, pre vs post, p=NS Arm3, pre vs post, p=NS
[7] Yukselen 2011	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
[7] Yukselen 2011	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

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[8] Keles 2011	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
[8] Keles 2011	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 11.- BIOMARKERS –SLIT SLIT vs SCIT

Study	Allergen	Arms	Time of measure	Biomarker	Value Pre	Value post	Units	Comparative values
IgE								
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 vs post, p= NS SCIT, pre vs 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

APPENDIX

Study	Allergen	Arms	Time of measure	Biomarker	Value Pre	Value post	Units	Comparative values
Eifan2010 [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 vs post, p=0.03 SCIT vs Pharmacotherapy, p=0.03 SLIT, pre vs post, p=0.04 Pharmacotherapy, pre vs post, p=NS D.pt specific: SCIT vs Pharmacotherapy, p=0.03
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
[8] Keles 2011	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
[7] Yukselen 2011	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
[8] Keles 2011	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 12. SAFETY SLIT vs SCIT

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,M.S.,2004[4]	Birch	23	13	56.5	mild
Mungan.D.,1999[6]	Dust mite	15	1	6.7	mild
Tahamiler,R.,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,M.,2007[1]	Tree pollen	20	4	0.2	mild
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.D.,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,M.,2007[1]	Tree pollen	20	3	0.15	moderate
Piazza,I.,1993[2]	Dust mite	17	3	0.18	moderate
Tahamiler,R.,2006[3]	Dust mite	96	10	0.1	mild
Eifan,A.O.,2010[5]	Dust mite	16	1	0.06	mild

SLIT Systemic Reactions Reported as a Percent of Patients					
Study	**SLIT Allergen**	**Number of patients in arm**	**Number of patients with reactions**	**Percent of Patients with reactions**	**Severity**
Gastrointestinal (nausea/pain/diarrhea)					
Khinchi,2004[4]	Birch	23	1	4.4	mild
Mungan.1999[6]	Dust mite	15	1	6.7	mild
Piazza,I 1993[2]	Dust mite	14	2	14.3	moderate
Tahamiler,, 2006[3]	Dust mite	97	12	12.4	mild
Respiratory (rhinitis/asthma)					
Tahamiler, 2006[3]	Dust mite	97	30	30.9	mild
Unspecified					
Khinchi,2004[4]	Birch	23	21	91.3	15 mild, 6 moderate
SCIT Systemic Reactions Reported as a Percent of Patients					
Study	**SCIT Allergen**	**Number of patients in arm**	**Number of patients with reactions**	**Percent of Patients with reactions**	**Severity**
Gastrointestinal (nausea/pain/diarrhea)					
Khinchi,2004[4]	Birch	24	1	4.2	mild
Respiratory (rhinitis/asthma)					
Eifan,A.O., 2010[5]	Dust mite	16	2	12.5	severe
Mungan.D 1999[6]	Dust mite	10	1	10	mild
Keles 2011[8]	Dust mite	11	2	18.2	moderate
Unspecified					
Khinchi,2004[4]	Birch	24	14	58.3	mild

SCIT Systemic Reactions Reported as Number of Events					
Study	**SCIT Allergen**	**Number of patients in arm**	**Number of events**	**Number of events per patient**	**Severity**
Respiratory (rhinitis/asthma)					
Mauroa,2007[1]	Tree pollen	20	2	0.1	1 mild, 1 moderate
Cutaneous (rash/urticaria/angioedema)					
Mauroa,2007[1]	Tree pollen	20	1	0.05	mild

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APPENDIX G. PEDIATRICS

PEDIATRICS SUBCUTANEOUS

TABLE 1. - STUDY CHARACTERISTICS SCIT - PEDIATRICS

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Asthma						
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,M., 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 Denmark-Finland[6]	Asthma	Perennial	Single	Animals: Dogs	Age: 5-18 years No previous immunotherapy Positive specific IgE test Positive skin test	Governme nt Non-profit
Adkinson,. 1997 USA[7]	Asthma	Seasonal and Perennial	Multiple	Trees : white oak Dust mites : Dermatophagoides pteronyssinus and farinae 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	Governme nt Industry
Rhinoconjunctivitis						
Moller, 2002 Niggeman, 2006 Multiple European countries[8]	Rhinoconjunctivitis	Seasonal	Multiple	Trees: Birch Grass: Timothy grass	Positive skin test	Not stated

Study, Author, Year, Country	Diagnosis	Seasonal or Perennial	Single or Multiple allergen	Allergen	Inclusion criteria	Funding source
Asthma and Rhinitis						
Akmanlar, 2000 Turkey[9]	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[10]	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[11]	Asthma and Rhinitis	Seasonal and Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus Grass: Perennial ryegrass Weeds: Parietaria	No previous immunotherapy Positive skin test	Not stated
Asthma and Rhinoconjunctivitis						
Kuna 2011 Poland[12]	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
Dreborg 1986 Multiple European countries[13]	Asthma and Rhinoconjunctivitis	Perennial	Single	Mold: Cladosporium	No previous immunotherapy Positive specific IgE test Positive skin test	Industry

TABLE 2.- PATIENT CHARACTERISTICS SCIT - PEDIATRICS

Study	Patients randomized	Comparators	Age (years) (mean+/- S.D)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
Asthma						
1 Hill, 1982	20	SCIT Placebo	Range 9-14 Range 9-14	Entire study 65/35	11/NR 9/NR	3 3
2 Altintas 1999	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
3 Pifferi 2002	29	SCIT no treatment	11 +/- 3 10 +/- 2	Entire Study 55/45	15/0 14/4	NR

APPENDIX

Study	Patients randomized	Comparators	Age (years) (mean+/- S.D)	Sex % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean years affected)
[4] Van Bever 1990	19	SCIT Placebo (after 1 year of SCIT)	12.2 (Range 8- 16) 12 (Range 9-14)	NR	9/NR 10/NR	NR
[5] Schubert 2009	34	SCIT Cluster SCIT Classic	10 8.5	NR NR	20/2 14/2	NR
[6] Valovirta 1986	27	SCIT Placebo	11 (Range 5-18) 10.5 (Range 5-16)	60/40 58/42	15/0 12/0	NR
[7] Adkinson 1997	121	SCIT Placebo	9 +/- 2 9 +/- 2	80/20 76/24	61/8 60/3	greater than 1 greater than 1
Rhinoconjunctivitis						
[8] Niggeman 2006	205	SCIT Control (conventional therapy)	10.7 (6-14)	138/70	103/6 102/8	4.7
Asthma and Rhinitis						
[9] Akmanlar 2000	18	Rush SCIT Conventional SCIT	7 +/- 2.6 9 +/- 4	NR NR	9/0 9/0	NR
[10] Hedlin 1999	32 3 dropouts in all the study	SCIT SCIT and Placebo	11.7 (Range 7-16) 12 (Range 10-16)	53/57 43/57	15/NR 14/NR	NR
[11] Cantani 1997	300	SCIT Control (drug-treated)	Entire study 4 (Range 3.-7)	Entire study 58/42	151/NR 149/NR	NR
Asthma and Rhinoconjunctivitis						
[12] Kuna 2011	50	SCIT Placebo	12 +/-4 11 +/-4	50/50 50/50	30/ 20/	2 years
[13] Dreborg 1986	30	SCIT Placebo	11 (Range 5-17) 11 (Range 5-17)	NR	16/NR 14/NR	NR

*** This study evaluates five-year follow-up of SIT. Children at initial onset of SIT were 6-14 years of age.**

Studies included in this table explicitly stated that their population of interest was <=18 years of age.

TABLE 3. INTERVENTION CHARACTERISTICS –SCIT - PEDIATRICS

Study	ARMS	Conventional /Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[1] Hill, 1982	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
[14] Jacobsen, 2007	SCIT Control						
[2] Altintas 1999	SCIT Dust mite Adsorbed Aluminum SCIT Dust mite Adsorbed calcium	NR	50000 -100000 SQ (target) 60000 - 100000 SQ (actual) 6 -10 IR (10 IR 1/1000w/v)	NR	Every 4 weeks	NR	2 years
[3] Pifferi 2002	SCIT Dust mite HDM No treatment	conventional therapy	800 U	24758.33 U (mean)	4 -6 weeks	NR	3 years
[4] Van Bever 1990	SCIT Dust mite Cluster 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
[5] Schubert 2009	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
[6] Valovirta	SCIT Dog alum-precipitated	NR	100,000 SQ U (Range from 8000 to	NR	6 weeks	NR	1 year

APPENDIX

Study	ARMS	Conventional /Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
1986	Placebo		50000 in 4/15 subjects)				
[7] Adkinson 1997 [15]	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 group1 (Grass mix– timothy, orchard, perennial ryegrass) 6 µg Alt a1 Not reported for Bermuda grass, English plantain, white oak, Cladosporium, Aspergillus fumigatus	27 months
[8] Moller 2002 Niggeman 2006 Jacobsen 2007	SCIT Grass and Birch alum-precipitated Placebo	conventional therapy	100000 SQU/mL	NR	Every 6 weeks	20 mcg Phl p 5 - 12 mcg Bet v 1	3 years
[9] Akmanlar 2000	SCIT Dust mite Rush SCIT Dust mite Conventional	conventional therapy	100000 SQ-U 50000- 100000 SQ-U	NR	Biweekly Every 4 weeks		3 years
[10] Hedlin 1999	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

Study	ARMS	Conventional /Rescue therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major allergen content	Duration of treatment
[11] Cantani 1997	SCIT Dust mite, Parietaria, ryegrass alum-precipitated Pharmacotherapy	conventional therapy	500 BU per month	26000 BU	Every 4 weeks		3 years
[12] Kuna 2011	SCIT Placebo	ONLY rescue therapy	2.0 ml (5000 TU/ml) or the highest tolerated dose	24.6 ml (range, 21.8-31.6 ml) =123,000 TU (range, 109,000-158,000 TU).	every 4 to 6 weeks for up to 3 years	Alternaria alternata. Alt a 1, 8 mcg/mL	3 years
[13] Dreborg 1986	SCIT Cladosporium Placebo	conventional therapy	100000 BU (reached after 18 weeks	NR	Every 4 weeks		10 months

BU: Biological units, SQU: standard quality units, PNU: Protein Nitrogen Unit, AU Allergy unit, mcg 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 4.- QUALITY ASSESSMENT – SCIT – 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
[1] Hill 1982	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
[14]Moller 2002 Niggeman 2006 Jacobsen 2007	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	Medium risk
[2] Altintas 1999	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
[3] Pifferi 2002	Low risk	High risk	High risk	Low risk	Low risk	No	Medium risk
[4] Van Bever 1990	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[5] Schubert 2009	Low risk	High risk	High risk	High risk	High risk	No	High risk
[6] Valovirta 1986	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk

[7] Adkinson 1997 [15] Limb 2006	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk
[9] Akmanlar 2000	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
[10] Hedlin 1999	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[11] Cantani 1997	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
[12] Kuna 2011	Low risk	Low risk	Low risk	Low risk	High risk	Yes or unclear	Medium risk
[13] Dreborg 1986	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

TABLE 5-ASTHMA SYMPTOM SCORES – SCIT-PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[7] Adkinson, 1997	Multiple	SCIT Placebo	last follow up	PEFR		81.9 84.8	2.5 -1.4	Pre vs. Post (SCIT), p = 0.5
[11] Cantani, 1997	Dust mites, ryegrass and parietaria	SCIT Placebo	Year 3	Mean percentage of NIGHTS with asthma			40 66	SCIT vs. Placebo p<0.0005
[13] Dreborg 1986	Cladosporium	SCIT Placebo	10 week period during peak season	Unspecified	0-3			SCIT vs. Placebo p>0.05

TABLE 6-COMBINED ASTHMA AND RHINOCONJUNCTIVITIS SYMPTOM SCORES – SCIT-PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[12] Kuna 2011	Alternaria	SCIT Placebo	Baseline-3yr			SCIT: 13.8 Placebo 11.2	scit: 2.3 plac: 21.4	SCIT pre vs Post p<0.001 Placebo pre vs post p<0.001 Pre SCIT vs Placebo: p>0.05 Post: SCIT vs Placebo, p=0.001
[13] Dreborg, 1986	Cladosporium	SCIT Placebo	10 week period during peak season	Unspecified nasal symptom scores	0-3			SCIT vs Placebo p> 0.05

TABLE 7- ASTHMA MEDICATION SCORES – SCIT- PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value Post	Comparative values
[3] Pifferi, 2002	Dust mites:	SCIT Pharmacotherapy	3 years	Days of therapy/year (Salbutamol)		40 50	7 40	SCIT vs. Placebo, p <0.01
[3] Pifferi, 2002	Dust mites:	SCIT Pharmacotherapy	3 years	Days of therapy/year (systemic steroids)		22 25	1 12	SCIT vs. Placebo, p <0.01
[7] Adkinson, 1997	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)	Pre vs. Post (SCIT) p <0.001 Pre vs. Post (Placebo), p <0.001 SCIT vs. Placebo, p =0.37 (Mean difference Pre = o.11; Post = 0.22)
[11] Cantani, 1997	Dust mites: Parietaria-ryegrass	SCIT Placebo	3 year	Mean drug usage for asthma attacks		NR	52 180	SCIT vs. Placebo p= 0.0003

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value Post	Comparative values
[1] Hill, 1982	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)	Pre vs. Post (SCIT) p <0.05 Pre vs. Post (Placebo) p NS
[1] Hill, 1982	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)	Pre vs. Post (SCIT) p NS Pre vs. Post (Placebo) p NS

TABLE 8- COMBINED SYMPTOM-MEDICATION SCORES – PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[2] Altintas 1999	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.
[12] Kuna 2011	Alternaria	SCIT 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 9- ASTHMA PFT RESULTS – PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	Value Pre	Value post	Comparative values
[7] Adkinson, 1997	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)
[13] Dreborg, 1986	Cladosporium	SCIT Placebo	6 months	Mean PEF	290 310	280 340	SCIT vs. Placebo p NS

TABLE 10- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES – PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[12] Kuna 2011	Alternaria	SCIT Placebo	baseline and 4 yrs after study	VAS visual analog scale Nasal challenge	0-600	baseline: Scit 207 Plac 199	4yrs: SCIT 67 Placebo: 185	SCIT pre vs Post: p<0.05 Placebo pre vs post: p=0.7 SCIT vs Placebo: p=0.04
[13] Dreborg, 1986	Cladosporium	SCIT Placebo	10 week period during peak season	Unspecified nasal symptom scores	0-3			SCIT vs Placebo p> 0.05
[16] Moller, 2002	Grass and/or birch	SCIT Placebo	3 years	VAS – rhinitis symptoms	0-100 mm			SCIT vs Placebo p<0.01

TABLE 11- RHINITIS AND RHINOCONJUNCTIVITIS COMBINED SYMPTOMS AND MEDICATION SCORES

Study	Allergen	Arms	Time of measure	Scale description	Score	Value Pre	Value post	Comparative values
[12] Kuna 2011 (SMS)	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 12- OCULAR SYMPTOM SCORES – PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[13] Dreborg, 1986	Cladosporium	SCIT Placebo	10 weeks	None	0-3			SCIT vs Placebo p>0.05
[16] Moller, 2002	Grass and/or birch	SCIT Placebo	3 years	VAS – Ocular symptoms	0-100mm			SCIT vs Placebo p<0.05

TABLE 13 – TOTAL SECONDARY OUTCOMES –PEDIATRICS- SCIT

RefId	ARMS	QOL	Adherence	Prevention of asthma	Development of new sensitivities
[3] Pifferi, 2002	SCIT no treatment			asthma exacerbation per year, baseline: 8; after 3 years: 1 asthma exacerbation per year, baseline: 8.5; after 3 years: 4.5 (SIT vs Control: p<0.01)	0 new sensitizations 4 new sensitizations SIT vs Control: p=0.01
[4] Van Bever, 1990	SCIT Placebo (after 1 year of SCIT)			Severity of Late asthma reactivity is measured. Before randomization: 20.78% +/- 8.57; after 1 year: 23% +/- 13.67 (p value= 0.525) Before randomization: 24.9% +/- 13.35; after 1 year: 31.2% +/- 13.47 (p value= 0.038)	
[6] Valovirta, 1986	SCIT Placebo	Number of days with asthma : 29.3 +/- 29.0 Number of days with asthma : 35.6 +/- 18.3			
[7] Adkinson, 1997	SCIT Placebo		92.6% NR		
[11] Cantani, 1997	SCIT Control (drug-treated)	Reported - Not significant Difference			
[12] Kuna 2011	SCIT placebo	In children up to 12 y SCIT Baseline: 4.19 SCIT 3rd yr: 5.8 P=0.008 QOL increased Place baseline: 4.8 Plac 3yr: 3.9 P=0.19			

RefId	ARMS	QOL	Adherence	Prevention of asthma	Development of new sensitivities
		QOL decreased Scit vs plac at 3 yr: signif diff, p=0.04 In adol (12-18y) SIT mean baseline, 3y: 3.9, 6.5; p=0.005 Plac base, 3y: 4.3, 4.2; p=0.715 Sit vs plac at 3y: sig diff: p=0.018 Parents of children QOL similar increase in SLIT group, decrease in plac gp			
Moller, 2002[16] Niggemann, 2006[8]	SCIT Placebo			N=151 children without asthma at beginning of study. 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 More children in control group reported increased asthma symptoms after 3 years (40 controls/20 active), p<0.05 Asthma scores increased in control group vs active after 3 years (p<0.01) (control: baseline 5.4, 3 years: 11.9) (active: baseline 5.0) 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)	

TABLE 14. SCIT – CHALLENGES SCORES

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[7] Adkinson, 1997	Cats	SCIT Placebo	last follow up	PEFR		81.9 84.8	2.5 -1.4	Pre vs. Post (SCIT), p = 0.5
[7] Adkinson, 1997	Cats	SCIT Placebo	last follow up	Bronchial provocation to methacholine		0.23 0.32	0.41 0.39	SCIT vs. Placebo, p = 0.99
[13] Dreborg, 1986	Cladosporium	SCIT Placebo	10 week period during peak season	Conjunctival provocation tets		NR NR	NR NR	SCIT vs. Placebo p>0.05 Pre vs. Post (SCIT), p=0.01
[13] Dreborg, 1986	Cladosporium	SCIT Placebo	10 week period during peak season	Bronchial provocation test		NR NR	NR NR	SCIT vs. Placebo p<0.05 Pre vs. Post (SCIT), p<0.01
[9] Akmanlar, 2000	Dust mites	SCIT-Rush SCIT-conventional	3 years	Allergen bronchial provocation test		20470 20470		SCIT Rush vs. SCIT Conventional, p=0.41 (6 months)
[2] Altintas, 1999	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

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[10] Hedlin, 1999	Cat, dust mite, Birch, Timothy	SCIT Placebo	1 year	Allergen bronchial provocation, PC-20		1900 1400	100000 5600 (SQU/ml)	Pre vs. Post (SCIT), p<0.001 Pre vs. Post (placebo), p<0.01 SCIT vs. Placebo, p=0.001
[10] Hedlin, 1999	Cat, dust mite, Birch, Timothy	SCIT Placebo	1 year	Histamine bronchial provocation		0.18 0.28	1.68 0.54 (mg/ml)	Pre vs. Post (SCIT), p=0.002 Pre vs. Post (Placebo), p<0.05 SCIT vs. Placebo, p=NS
[8] Niggemann, 2006	Timothy grass, Birch	SCIT Placebo	5 years	Ocular provocation test				SCIT vs. Placebo, p<0.001
[8] Niggemann, 2006	Timothy grass, Birch	SCIT Placebo	5 years	Methacholine challenge test				SCIT vs. Placebo, p=NS
[3] Pifferi, 2002	Dust mite	SCIT No treatment	3 years	Methacholine PD20 FEV1		93.5 374.5	997.7±974.0 (70% improvement) 388.5±516.4 (20% improvement)	
[6] Valovirta, 1986	Dogs	SCIT Placebo	1 year	Conjunctival provocation test				SCIT vs. Placebo, p<0.001
[6] Valovirta, 1986	Dogs	SCIT Placebo	1 year	Bronchial provocation test		0.13	0.25	Pre vs. Post (SCIT), p<0.1 SCIT vs. Placebo, p=NS
[4] Van Beaver, 1990	Dust mite	SCIT Placebo	1 year	Allergen bronchial provocation, PD 20%		5.53±0.81 5.93±0.63	5.20±1.59 5.72±0.87	SCIT, Pre vs. Post, p=0.801 Placebo, Pre vs. Post, p=0.059

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[16] Moller, 2002	Grass and/or birch	SCIT Placebo	3 years	Conjunctival Provocation test		NR	NR	SCIT vs placebo, p<0.001
[16] Moller, 2002	Grass and/or birch	SCIT Placebo	3 years	Methacholine bronchial provocation test Seasonal PC20 mean (range)		10.4 (32-0.13) mg/mL 11.1 (32-0.03) mg/mL	14.9 (32-0.15) mg/mL 12.2 (32-0.11) mg/mL	OR= 1.43 (0.8-2.7)*

*** Odds ratio for improvement of bronchial hyperresponsiveness (BHR) after 3 years of treatment did not show a significant increased odds for SCIT compared to placebo. BHR was measured as change from baseline (season 0).**

TABLE 15. SAFETY

Study	Allergen	Number of patients in arm	Percent of patients with local reactions	Severity
[9] Akmanlar, 2000	Other dust mites: Both Der P and F	18	17	Moderate
[2] Altintas 1999	Dermatophagoides pteronyssinus	34	18	Unspecified
[12] Kuna 2011	Alternaria	7 of 50 patients		Unspecified
[13] Dreborg 1986	Cladosporium	16	25	Unspecified

Local reactions reported as events

Study	Allergen	Number of patients in arm	Number of events	Number of events per patient	Severity
[5] Schubert, 2009	Unspecified dust mites (classic schedule)	10	80	8	Unspecified
[5] Schubert, 2009	Unspecified dust mites (cluster schedule)	20	185	9.25	Unspecified
[6]Valovirta, 1986	Placebo	12	251	20.91667	Mild
[6] Valovirta, 1986	Dogs	15	309	20.6	Mild

Cutaneous reactions reported as patients

Refid	Allergen	Number of Patients in arm	Percent of patients with cutaneous reactions	Severity
[11] Cantani , 1997	Dermatophagoides pteronyssinus Percentennial, Parietaria officinalis	151	2	Unspecified
[12] Kuna 2011	Alternaria	4 patients after 11 injections with local edema	1.1% of all injections	Unspecified
[13] Dreborg 1986	Cladosporium	16	19	Unspecified

SCIT Respiratory Reactions

Respiratory reactions reported as patients

Refid	Allergen	Number of Patients in arm	Percent of patients with respiratory reactions	Severity
[9]	Other dust mites: Both Der P and F (conventional schedule)	9	22	Severe
[9]	Other dust mites: Both Der P and F (rush schedule)	9	33	Severe
[11]	Dermatophagoides pteronyssinus, Percentennial ryegrass, Parietaria officinalis	151	1	Unspecified

SCIT Gastrointestional Reactions

Gastrointestional reactions reported as patients

Refid	Allergen	Number of Patients in Arm	Percent of patients with gastrointestinal reactions	Severity
[9] Akmanlar, 2000	Both Der P and F	18	17	Mild

Gastrointestional reactions reported as events

Refid	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
[5] Schubert, 2009	Unspecified dust mites (cluster schedule)	20	10 2	0.5 0.1	Mild Moderate
	Unspecified dust mites (classic schedule)	10	6 1	0.6 0.1	Mild Moderate

SCIT Unspecified Reactions

Unspecified reactions reported as patients

Refid	Allergen	Number of Patients in Arm	Percent of patients with unspecified reactions	Severity
[13] Dreborg 1986	Cladosporium	16	25	Unspecified
[1] Hill, 1982	Ryegrass	11	9	Unspecified

Systemic Reactions reported as Events

Refid	Allergen	Number of Patients in arm	Number of events	Number of events per patient	Severity
[10] Hedlin, 1999	Cats, Dermatophagoides pteronyssinus, White birch, Timothy grass (plus pollen extract)	15	5	0.333333	Unspecified

SCIT Comments on Adverse Reactions

Comments on adverse reactions reported as patients

Refid	Allergen	Number of patients in arm	Comments
[7] Adkinson,. 1997	White oak, Dermatophagoides pteronyssinus, Dermatophagoides farina, Short ragweed, Grass mix, AlternariaBermuda grass, English plantain, Cladosporium, As Percentgillus Placebo	61 60	Numbers were reported but adverse events were not specified. 21 AEs in 61 children Numbers were reported but adverse events were not specified. 4 AEs in 60 children
[9] Akmanlar, 2000	Other dust mites: Both Der P and F (Conventional schedule) Other dust mites: Both Der P and F (Rush schedule)	9 9	bronchospasm bronchospasm. 3 patients with local reactions were described as follows: local swelling larger than 3 cm, making it necessary to adjust updosing in Conventional IT. These patients could not attain the optimum maintenance dose (100,00 SQ). One reached 20,000 SQ; others reached 60,000 and 80,000 SQ.
[12] Kuna 2011	Alternaria	1 1 1	headache after 1 injection mild facial flushing, redness after every injection of placebo – 38 injections mild flushing, after 8 placebo injections

PEDIATRICS SUBLINGUAL

TABLE 16. - STUDY CHARACTERISTICS SLIT - PEDIATRICS

Refld, Author, Year, Country	Diagnosis	Seasonal OR Perennial	Single or multiple Allergen	Allergen	Inclusion criteria	Funding source
Asthma						
[17] Pajno, 2000 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
[18] Lue, 2006 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)
[19] Niu, 2006 Taiwan	Asthma	Perennial	Multiple	Dust mites: Dermatophagoides pteronyssinus and farinae	Positive skin test	Not stated
Rhinitis						
[20] deBot, 2011 Netherlands	Rhinitis	Perennial	Multiple	Dust mite: Dermatophagoides pterynossum and farinae	Age: Children 6-18 years Positive specific IgE test Minimum duration of disease: 1 year	Industry
[21] Tseng, 2008 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
Rhinoconjunctivitis						
[22] la Rosa, 1999 France-Italy	Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Positive specific IgE test Positive skin test Monosensitized individuals only	Industry
[23] Novembre, 2004 Italy	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	No previous immunotherapy Positive skin test Monosensitized individuals only	Industry

Refld, Author, Year, Country	Diagnosis	Seasonal OR Perennial	Single or multiple Allergen	Allergen	Inclusion criteria	Funding source
4784 Roder, 2007 The Netherlands	Rhinoconjunctivitis	Seasonal	Multiple	Grass: Grass mix	Positive specific IgE test	Industry
[24] Stelmach, 2011 Poland	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
Asthma and Rhinitis						
[25] Marogna, 2008 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
[26] Hirsch, 1997 Germany	Asthma and Rhinitis	Perennial	Single	Dust mites: Dermatophagoides pteronyssinus	Age: children No previous immunotherapy Positive specific IgE test Positive skin test	Not stated
[27] Bahceciler, 2001 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
Asthma and Rhinoconjunctivitis						
[28] Pajno, 2004 Italy	Asthma and Rhinoconjunctivitis	Seasonal	Single	Weeds: parietaria	Age: children Positive skin test	Industry
[29] Vourdas, 1998 France-Greece	Asthma and Rhinoconjunctivitis	Seasonal	Single	Trees: Olive	Positive specific IgE test Positive skin test	50% of authors are industry
[30] Pajno 2011 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
[31] Valovirta, 2006 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	Industry

Refld, Author, Year, Country	Diagnosis	Seasonal OR Perennial	Single or multiple Allergen	Allergen	Inclusion criteria	Funding source
[32] Ippoliti, 2003 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
[33] Tari, 1990	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

TABLE 17.- PATIENT CHARACTERISTICS SLIT - PEDIATRICS

Study	Patients randomized	Comparators	Age in years (mean-range)	Gender % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean number of years affected with disease
Asthma						
[17] Pajno, 2000	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
[18] Lue, 2006	20	SLIT Placebo	7.7 +/- 1.8 Mean:8.6 +/- 1.8	40/60 40/60	10/0 10/0	1 year 1 year
[19] Niu, 2006	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	NR NR
Rhinitis						
[20] deBot, 2011 Netherlands	257	SLIT Placebo	11.8 +/- 3.1 11.7 +/- 2.9	NR	125/17 126/15	1 year
[21] Tseng, 2008	63	SLIT Placebo	9.7 +/- 3.3 9.7 +/- 3	73/2.7 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
Rhinoconjunctivitis						
[22] La Rosa, 1999	41	SLIT Placebo	10 (Range 6-14) 10 (Range 7-13)	65/35 57/43	20/5 21/4	3 years 4 years

APPENDIX

Study	Patients randomized	Comparators	Age in years (mean-range)	Gender % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean number of years affected with disease
[23] Novembre, 2004	113	SLIT Controls	8.96 (Range 5-14) 7.74 (Range 4-16)	70/30 70/30	54/6 59/10	NR NR
[34] Roder, 2007	204	SLIT Placebo	12.9 +/- 2.6 (Range 7-17) 12.5 +/- 2.9 (Range 6-17)	67/33 44/56	108/70 (64/26) 96/70 (50/24)	NR NR
[24] Stelmach 2011	60	SLIT pre-coseasonal SLIT continuous Placebo	8.3 Range 5-17	65/35 74/26 61/39	17/3 19/1 18/2	2 years
Asthma and Rhinitis						
[25] Marogna, 2008	216	SLIT Control	10.7 +/- 0.43 10.0 +/- 0.3	72/38 60/40	144/14 72/6	NR NR
[26] Hirsch, 1997	30	SLIT Placebo	11.3 (Range 6-15) 9.92 (Range 6-15)	66/34 66/34	15/1 15/0	4.5 years (asthma), 5 years (rhinitis) 2.5 years (asthma), 3 years (rhinitis)
[27] Bahceciler, 2001	15	SLIT Placebo	12.4 (Range 7.8-18) 12 (Range 7.3-15)	50/50 57/43	8/0 7/0	NR NR
Asthma and Rhinoconjunctivitis						
[28] Pajno, 2004	30	SLIT+ fluticasone Placebo+fluticasone	11 11	47/53 40/60	15/1 15/2	4.7 years 3.1 years
[29] Vourdas 1998	70	SLIT Placebo	12 (Range 8-17) 12 (Range 7-17)	73/27 66/34	34/1 36/1	4 years 4 years
[30] Pajno 2011	80	SLIT continuous; SLIT co-seasonal	11 Range 8-16	60/40 47/53	40/3 40/5	5.2 years 4.1 years
[31] Valovirta, 2006	98	SLIT dose 1 SLIT dose 2 Placebo	9.0 +/- 2.7 9.6 +/- 3.1 9.9 +/- 3.0	48/52 61/39 62/38	32/7 32/1 29/6	4.1 years 5.0 years 4.6 years

Study	Patients randomized	Comparators	Age in years (mean-range)	Gender % male/female	Patients enrolled/ dropouts	Duration of Disease (Mean number of years affected with disease
[32] Ippoliti, 2003	86	SLIT Placebo	Median 9 (Range 5-12) Median 9 (Range 7-11)	59.5/40.5 56.4/43.6	47/0 39/0	1.8 years 1.6 years
[33] Tari, 1990	66	SCIT Placebo	Range 5-12 Range 5-12	Entire study 63.8/36.2	34/4 32/4	NR NR

TABLE 18. INTERVENTION CHARACTERISTICS –SLIT - PEDIATRICS

Ref ID	ARMS	Conventional/ Rescue therapy	Maintenance Dose (unless otherwise noted)	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
[17] Pajno, 2000	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
[18] Lue, 2006	SLIT Dust mite Placebo	conventional therapy	20 drops of 300 IR/mL	41824 IR	Daily	3000 Der F , 1700 Der P (cumulative)	6 months
[19] Niu, 2006	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
[20] deBot 2011	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
[21] Tseng, 2008	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

APPENDIX

Ref ID	ARMS	Conventional/ Rescue therapy	Maintenance Dose (unless otherwise noted)	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
[22] La Rosa, 1999 [35] Leonardi, 2009	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
[23] Novembre, 2004	SLIT Grass mix symptomatic therapy	ONLY rescue medication	5 drops of 25 BU/ml	120 mcg	Daily	0.5 Group V major grass (maintenance)	3 years
[34] Roder, 2007	SLIT Grass mix Placebo	conventional therapy	9500 BU	1976000, 4.5 mg	2 times a week	21 Lol p 5 (maintenance)	2 years
[24] Stelmach 2011	SLIT pre-coseasonal -grass mix SLIT continuous – grass mix placebo	ONLY rescue medication	300IR	NR	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
[25] Marogna, 2008	SLIT Birch /Grass conventional therapy	conventional therapy	5 drops of 10,000 RU/ml	480 mcg of Der p1, 480 mcg Der p2, 40 mcg of Phl p 1, 40 mcg Par j 1, 100 mcg of Bet v 1 (per year)	3 times a week	480 mcg of Der p1, 480 mcg Der p2, 40 mcg of Phl p 1, 40 mcg Par j 1, 100 mcg of Bet v 1 (per year)	3 years
[26] Hirsch, 1997	SLIT Dust mite Placebo	conventional therapy	7 drops of 11.9 mcg/ml=3.75 mcg	570 micrograms (per year)	3 times a week	570 Dep p1 (per year)	1 year
{#376 Bahceciler, 2001	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

APPENDIX

Ref ID	ARMS	Conventional/ Rescue therapy	Maintenance Dose (unless otherwise noted)	Cumulative Dose	Maintenance Dosing Interval	µg of major protein	Duration of treatment
[28] Pajno, 2004 [36] Pajno, 2004	SLIT Parietaria Placebo	conventional therapy	5 drops of 10 BU/ml	20.3 mcg	every other day	20.3 Par j 1 (cumulative)	13 months
[30] Pajno 2011	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
[29] Vourdas, 1998	SLIT Olive Placebo	conventional therapy	20 drops of 300 IR/ml	30000 IR/year	Daily	4050 Ole e 1 (per year)	seasonal (5 to 6 months each year) for 2 years
[31] Valovirta, 2006 [37] Savolainen, 2006	SLIT Tree mix SLIT Tree mix	conventional therapy	100,000 SQ-U/ml (per week) 12,000 SQ-U/ml (per week)	200,000 SQ-U per week =30 mcg 24,000 SQ-U per week or 3.6 mcg	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 18 months maintenance
[32] Ippoliti, 2003	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
[33] Tari, 1990	SLIT Placebo	ONLY rescue medication	15 drops of 500 STU/ml		3 times per week		18 months

TABLE 19.- RISK OF BIAS – 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
[17] Pajno, 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[18] Lue, 2006	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[20] deBot 2011	Low risk	High risk	High risk	Low risk	High risk	Yes or unclear	High risk
[19] Niu, 2006	Low risk	Low risk	High risk	High risk	High risk	No	Medium risk
[21] Tseng, 2008	Low risk	Low risk	High risk	High risk	Low risk	No	Medium risk
[22] La Rosa, 1999 [35] Leonardi, 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[23] Novembre, 2004	Low risk	High risk	High risk	High risk	High risk	Yes or unclear	High risk
[34] Roder, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Yes or unclear	Low risk
[24] Stelmach 2011	Low risk	Low risk	High risk	Low risk	High risk	No	Moderate risk
[25] Marogna, 2008	Low risk	High risk	High risk	High risk	Low risk	Yes or unclear	High risk
[26] Hirsch, 1997	Low risk	Low risk	Low risk	High risk	Low risk	No	Medium risk
[33] Tari, 1990	Low risk	High risk	High	Low risk	Low risk	Yes or unclear	Medium risk
[27] Bahceciler, 2001	Low risk	Low risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk
[28] Pajno, 2004 [36] Pajno, 2004	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	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
[29] Vourdas, 1998	Low risk	Low risk	Low risk	High risk	Low risk	Yes or unclear	Medium risk
[30] Pajno 2011	Low risk	Low risk	High risk	Low risk	High risk	No	Moderate risk
[31] Valovirta, 2006 [37] Savolainen, 2006	Low risk	High risk	High risk	Low risk	Low risk	Yes or unclear	Medium risk 3

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 20-ASTHMA AND ASTHMA COMBINED SYMPTOM SCORES –SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[17] Pajno, 2000	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
[17] Pajno, 2000	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
[18] Lue, 2006	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
[19] Niu, 2006	Dust mite	SLIT Placebo	24 weeks	Unspecified asthma symptoms	0-3/day	0.11 0.05	0.04 0.06	SLIT vs Placebo p= 0.028
[26] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	pulmonary symptoms	0-3	0.36 0.07	0.07 0.28	Placebo pre vs post p=1545 SLIT vs Placebo p< 0.05

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[33] Tari, 1990	Dust mite	SLIT Placebo	18 months	Lung symptom score	0-3			SLIT pre vs post p 0.001 SLIT vs Placebo NS
[27] Bahceciler, 2001	Dust mite	SLIT placebo	6 months	Asthma symptoms		0.64 0.33	0.3 0.26	SLIT pre vs post p <0.05
[32] Ippoliti, 2003	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
[20]* deBot 2011	Dust mite	SLIT placebo	2 years	Dyspnea/wheeze score		NR	0.21 0.11	SLIT vs Placebo p=0.01
[28] Pajno, 2003	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
[28] Pajno, 2003	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
[30]* Pajno 2011	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
[30] Pajno 2011	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
[31] Valovirta, 2006	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

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[31] Valovirta, 2006	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,

TABLE 21- RHINITIS AND RHINOCONJUNCTIVITIS SYMPTOM SCORES – SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[20] deBot 2011	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
[21] Tseng, 2008	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
[22] La Rosa, 1999	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
[34] Roder, 2007	Grass mix	SLIT Placebo	2 years	mean daily total of all rhinitis symptoms	0-15	NR NR	3.1 3.4	SLIT vs Placebo NS CI -0.66 - 0.5
[26] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	nasal symptom score	0-3	1.4 0.48	0.84 0.34	SLIT vs Placebo p NS
[33] Tari, 1990	Dust mite	SLIT Placebo	18 months	Nasal symptom score	0-3			SLIT pre vs post p = 0.001 SLIT vs Placebo p NR
[27] Bahceciler, 2001	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

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[28] Pajno, 2003	Parietaria	SLIT Placebo	13 months	Nasal symptoms	0-3	NR	NR	SLIT vs Placebo NS
[29] Vourdas, 1998	Olive	SLIT Placebo	pollen season Year 2	Rhinitis score	0-4		0.72 1.22	SLIT vs Placebo p NS
[31] Valovirta, 2006	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
[32] Ippoliti, 2003	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
[23] Novembre, 2004	Grass mix	SLIT Placebo	3 years	Unspecified Rhinoconjunctivitis Symptom score				SLIT vs Placebo NS

TABLE 22- CONJUNCTIVITIS SYMPTOM SCORES -SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[33] Tari, 1990	Dust mite	SLIT Placebo	18 months	Ocular symptoms	0-3			SLIT pre Vs. post p NS
[20] deBot 2011	Dust mite	SLIT placebo	2 years	0-3/eye score, 0-9 /day		NR	SLIT 0.49, placebo 0.57	SLIT vs Placebo NS
[31] Valovirta, 2006	Tree Mix	SLIT HighDose SLIT LowDose Placebo	Whole pollen season	Total eye symptoms	0-9/day	NR	0.8 0.9 1.1	Arm 1 vs Arm 3, p=0.04, Arm 2 vs Arm 2 NS
[29] Vourdas, 1998	Olive	SLIT Placebo	End of pollen season Year 2	4-point scale	0-4	NR NR	0.04 0.23	Arm 1 Vs. Arm p <0.05; only significant week 19

TABLE 23.- MEDICATION SCORES- SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[19] Niu, 2006	Dust mite	SLIT Placebo	24 weeks	Medication scores antihistamines and oral corticosteroids				Arm 1 Vs. Arm 2 p No significant change
[21] Tseng, 2008	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	Arm 1 Vs. Arm 1 p = 0 .932 Arm 2 Vs. Arm 2 p = 0.843 Arm 1 Vs. Arm 2 p= 0.74
[20] deBot 2011	Dust mite	SLIT; placebo	2 years	Proportion of days with rescue meds		NR	0.21 0.26	Arm 1 vs Arm 2 NS
[22] La Rosa,	Parietaria	SLIT Placebo	2 years	Anti-rhinitis medication score				Arm 1 Vs. Arm 2 p NS
[34] Roder, 2007	Grass mix	SLIT Placebo	2 years	% rescue med free days			69.3 (3.4) 74.2 (3.2)	Arm 1 Vs. Arm 2 p=0.67
[26] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	pulmonary symptom relief medication			5 8	Arm 1 Vs. Arm 2 p NS
[26] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	nasal symptom relief medication			3 1	Arm 1 Vs. Arm 2 p NS
[27] Bahceciler, 2001	Grass mix and Olive	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	Arm 1 Vs. Arm 2 p=0.028
[27] Bahceciler, 2001	Grass mix and Olive	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	Arm 1 Vs. Arm 1 p = 0.6 Arm 1 Vs. Arm 2 p = 0.67

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[30] Pajno 2011	Grass mix	Continous SLIT Co-seasonal SLIT	3 years	Percent reduction from baseline	1 topical med; 2 systemic meds	NR	70% reduction 50% reduction	Arm 1 vs Arm 2: NS difference in amount of reduction of medication use
[31] Valovirta, 2006	Tree mix	SLIT high dose SLITlow dose Placebo	Peak season	Unspecified	0-8		4.5 5.5 6.5	Arm 1 vs placebo p=0.06 whole season, p=0.04 during peak season; Arm 2 vs placebo p=0.72 whole season, p=0.83 during peak season

TABLE 24- COMBINED SYMPTOM AND MEDICATION SCORES- SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[23] Novembre, 2004	Grass Mix	SLIT Conventional therapy	3 years	Nasal, eye, bronchial symptoms plus medication	NR	NR	NR	SLIT vs Placebo NS
[25] Marogna, 2008	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

TABLE 25. SLIT – CHALLENGES SCORES- SLIT– PEDIATRICS

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[26] Hirsch, 1997	Dust mite	SLIT Placebo	1 year	nasal provocation (acoustic rhinometry)	SBU/ml 40% reduction nasal flow	1240 470	1380 1790	Arm 1 vs Arm 1 p <0.001 Arm 2 Vs. Arm 2 NS Arm 1 vs Arm 2 NS
[22] La Rosa, 1999	Parietaria	SLIT Placebo	2 years	ocular conjunctival provocation test	0-3	NR NR	NR NR	Arm 1 Vs. Arm 2 p =0.02
[18] Lue, 2006	Dust mite	SLIT Placebo	6 months	FEV1		75 (graph) 80 (graph)	90 (graph) 82 (graph)	Arm 1 Vs. Arm 1 p = 0.001 Arm 2 Vs. Arm 2 p =0.48 Arm 1 Vs. Arm 2 p =0.93
[19] Niu, 2006	Dust mite	SLIT Placebo	24 weeks	FEV1		85 90	95 90	Arm 1 vs Arm 1 p=0.048 Arm1 vs Arm 2 NS
[32] Ippoliti, 2003	Dust mite	SLIT Placebo	6 months	FEV1		83.4 80.7	92.6 81.2	Arm 1 Vs. Arm 1 p < 0.001 Arm 2 Vs. Arm 2 p NS Arm 1 vs Arm 2 NR
[18] Lue, 2006	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.

APPENDIX

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[19] Niu, 2006	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
[24] Stelmach 2011	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
[25] Marogna, 2008	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
[27] Bahceciler, 2001	Dust Mite	SLIT Placebo	6 months	Peak Expiratory Flow				PEF Significant improvement vs placebo. FEV1, PC20 no significant improvement vs placebo
[33] Tari, 1990	Dust mite	SLIT Placebo	12 months	Nasal provocation challenge				SLIT vs Placebo p= 0.01
[33] Tari, 1990	Dust mite	SLIT Placebo	12 months	Bronchial provocation challenge	FEV with dust mite challenge	SLIT group 280.8 +/- 16.4	SLIT group 502 +/- 26.6	SLIT vs Placebo p< 0.05

Study	Allergen	Arms	Time of measure	Scale description	SCORE	Value Pre	Value post	Comparative values
[33] Tari, 1990	Dust mite	SLIT Placebo	12 months	PFT: FEV1 Metacholine challenge	PFT			SLIT pre vs post p< 0.05

TABLE 26 – TOTAL SECONDARY OUTCOMES –SLIT– PEDIATRICS

Study	ARMS	QOL	Adherence	Disease modification	Prevention of asthma	Development of new sensitivities
[19] Niu, 2006	SLIT Placebo	NR	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
[20] deBot 2011	SLIT placebo	PRQLQ Adol RQLQ	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
[23] Novembre, 2004	SLIT Control	NR	NR	NR	At the end of study 8 developed asthma At the end of study 18 developed asthma	NR

Study	ARMS	QOL	Adherence	Disease modification	Prevention of asthma	Development of new sensitivities
[38] Ring, 2004	SLIT Placebo	pediatric and adolescent QOL(PRQLQ/AdolQLQ) no significant difference between groups	no significant difference between groups	NR	NR	NR
[25] Marogna, 2008	SLIT Control	NR	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
[26] Hirsch, 1997	SLIT Placebo	NR	8/15 were compliant 10/15 were compliant	NR	NR	NR
[31] Valovirta, 2006	SLIT dose 1 SLIT dose 2 Placebo	NR	NR	NR	After a follow up for 5 years asthma developed in 2/10 children. After a follow up for 5 years asthma developed in 6/10 children After a follow up for 5 years asthma developed in 6/10 children	NR

- Outcomes not reported Maintenance control, Prevention of Sinusitis, Prevention of Otitis and Convenience

TABLE 27 – BIOMARKERS - SLIT– PEDIATRICS

Study	Arms	IgG	Finding	IgG4	Finding	Mean baseline Ig E	IgE	Finding	COMMENTS
[27] Bahceciler, 2001	SLIT						Reported	pre: median 420 (range 42-2751); post: 295 (40-1701)	Total IgE levels were reported but no significant difference was found between arm 1 and arm 2.
[27] Bahceciler, 2001	Placebo						Reported	pre: median 405 (range:197-5967); post: 536 (166-3948)	
[26] Hirsch, 1997	SLIT	Reported	no significant change			39.1 kU/l	Reported	Increased more than placebo, P<0.01	compliance is reported
[26] Hirsch, 1997	Placebo	Reported	no significant change	Reported	decreased, p<0.05	33.3 kU/l	Reported	increased, p<0.01	
[32] Ippoliti, 2003	SLIT								The other lad measures reported are CD40+ Bcells, serum ECP, IL-13 and ACTH levels.
[22] La Rosa, 1999	SLIT			Reported	significant increase in levels after 2 yrs (p=0.02)		Reported	no significant difference between the groups	
[22] La Rosa, 1999	Placebo			Reported	no significant change in levels		Reported		

Study	Arms	IgG	Finding	IgG4	Finding	Mean baseline Ig E	IgE	Finding	COMMENTS
[18] Lue, 2006	SLIT			Reported	Staistically significant increase within group and when compared to placebo p=0.026	500 IU/L (from graph)	Reported	Increased within group, not statistically significant when compared with placebo	
[18] Lue, 2006	Placebo			Reported	no major change	400 IU/L (from graph)	Reported	no major change	
[19] Niu, 2006	SLIT					829.8	Reported	The change in total IgE from baseline to 24 weeks is 129.7 +/- 460.6,	also specific IgE was reported, non significant change.
[19] Niu, 2006	Placebo					780.6	Reported	The change in total IgE from baseline to 24 weeks is - 85.1 +/- 59.8 (group difference, p value= 0.063)	
[17] Pajno, 2000	SLIT	Reported	Mean at baseline: 33.0, after 2 years: 31.3	Reported	Mean at baseline: 2.85, after 2 years: 2.53	45.4	Reported	Mean at baseline: 45.4, after 2 Baseline: 52.2, after 2 years: 65.3, Between group differences NSyears: 52.6	

Study	Arms	IgG	Finding	IgG4	Finding	Mean baseline Ig E	IgE	Finding	COMMENTS
[33] Tari, 1990	SLIT	Reported	5.23 +/- 3.1 significant increase p<0.001.	Reported	10.71 +/- 3.81		Reported	no change	
[33] Tari, 1990	Placebo	Reported	2.32 +/- 1/42 no change	Reported	2.78 +/- 2.02		Reported	significant rise	
[21] Tseng, 2008	SLIT					Der p: 129, Der f: 170	Reported	change from baseline to 24th week s 40.8 +/- 76.1 p value: 0.008	D. farinae
[21] Tseng, 2008	SLIT						Reported	change from baseline to 24th week s 49.0 +/- 73.9 p value: 0.002	D. pteronyssinus only. See other sheet for D.f.
[21] Tseng, 2008				Reported	change from baseline to 24th week 772.9 +/- 1,002.8 p-value: <0.001				D. farinae
[21] Tseng, 2008				Reported	change from baseline to 24th week s 710 +/- 990.9 p value: 0.002				D. pteronyssinus only. See other sheet for D.f.

Study	Arms	IgG	Finding	IgG4	Finding	Mean baseline Ig E	IgE	Finding	COMMENTS
[21] Tseng, 2008	Placebo					Der p: 98, Der f: 119	Reported	change from baseline to 24th week is 21.0 +/- 46.7 p-value: 0.018	
[21] Tseng, 2008	Placebo						Reported	change from baseline to 24th week s 24.2 +/- 43.3 p value: 0.004	
[21] Tseng, 2008	Placebo			Reported	change from baseline to 24th week -92.4 +/- 290.1 change from baseline to 24th week 772.9 +/-				
[21] Tseng, 2008	Placebo			Reported	change from baseline to 24th week s -6.4 +/- 280.1 p value: 0.889				
[31] Valovirta, 2006									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

Study	Arms	IgG	Finding	IgG4	Finding	Mean baseline Ig E	IgE	Finding	COMMENTS
									evaluated.
[29] Vourdas 1998	SLIT			Reported			Reported		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.
[29] Vourdas 1998	Placebo			Reported			Reported		
[30] Pajno 2011				Both groups had significant increase in specific IgG4 at end of study compared to baseline			Baseline specific IgE: Arm 1- 11.2, Arm 2- 9.9		

TABLE 28 – SAFETY - SLIT– PEDIATRICS

Local SLIT Reactions Reported as Number of Events					
RefID	**Arm**	**N in Arm**	**Number of Events**	**Number of Events per Patient [1]**	**Severity**
[26] Hirsch, 1997	Dust mite	15	6	0.4	mild
	Placebo	15	1	0.07	mild

[29] Vourdas 1998	Olive	32	8	0.25	unspecified
	Placebo	32	2	0.13	mild
[22] La Rosa, 1999	Parietaria	20	5	0.25	moderate
	Placebo	21	4	0.19	

Local SLIT Reactions Reported as PERCENT OF PATIENTS WITH REACTIONS				
RefID	**SLIT Allergen**	**Number of Patients in Arm**	**Percent of Patients with Local Reactions [1]**	**Severity**
[17] Pajno, 2000	Dust mite	12	8	mild
[23] Novembre, 2004	Grass mix	54	2	mild
[29] Vourdas 1998	Olive	34	3	unspecified
[31] Valovirta, 2006	Tree mix-high	32	50	unspecified
	Tree mix-low	33	36	unspecified
	Placebo	32	25	
[25] Marogna, 2008	Dust mite, Birch, Parietaria, Grass mix	144	0.7	unspecified

[5]

SLIT Systemic Reactions: Cardiovascular Reported as Number of Events					
Refid	**SLIT Allergen**	**N in arm**	**Number of Events**	**Number of Events per Patient[6]**	**Severity**
[31] Valovirta, 2006	Tree mix-high	32	3	0.09	mild

[5] Percent of patient with local reactions = the percent of patients in that arm of the study with local reactions. Arms of the study where no reactions were reported are not displayed on this table.

[6] Number of events per patient =number of events reported in arm ÷ number of patients in arm. Arms of studies which did not report any events are not displayed on the table.

[7]SLIT Systemic Reactions: Cutaneous: (rash/urticaria/angioedema) Reported as a Percent of Patients				
Study	**SLIT Allergen**	**Number of Patients in Arm**	**Percent of Patients with Cutaneous Reactions[1]**	**Severity**
[25] Marogna, 2008	Birch and Grass mix	144	0.7	mild
[23] Novembre, 2004	Grass mix	54	1.9	mild
	Placebo	59	1.7	mild
	Placebo	61	9.8	unspecified
[33] Tari, 1990	Dust mite	30	10	unspecified

SLIT Systemic Reactions: Gastrointestinal (nausea/pain/diarrhea) Reported as Number of Events					
Study	**SLIT Allergen**	**N in arm**	**Number of Events**	**Number of Events per Patient[8]**	**Severity**
[22] La Rosa, 1999	Parietaria	20	19	0.95	unspecified
	Placebo	21	1	0.05	unspecified

SLIT Systemic Reactions: Gastrointestinal (nausea/pain/diarrhea) Reported as a Percent of Patients with Reactions

[7] Percent of patient with local reactions = the percent of patients in that arm of the study with local reactions. Arms of the study where no reactions were reported are not displayed on this table.

[8] Number of events per patient =number of events reported in arm ÷ number of patients in arm. Arms of studies which did not report any events are not displayed on the table.

Refid	SLIT Allergen	N in arm	Percent of Patients with Gastrointestinal Reactions[19]	Severity
[25] Marogna, 2008	Birch, Grass mix	144	0.7	unspecified
[23] Novembre, 2004	Grass mix	54	1.2	unspecified
[33] Tari, 1990	Dust mite	32	11.4	unspecified
[31] Valovirta, 2006	Tree mix-high	32	3.1	unspecified
	Tree mix-low	33	6	unspecified

SLIT Systemic Reactions: Lower Respiratory Reactions Reported as a Percent of Patients				
Refid	**SLIT Allergen**	**Number of Patients in Arm**	**Percent of Patients with Lower Respiratory Reactions[1]**	**Severity**
[33] Tari, 1990	Dust mite	32	34 asthma	9% severe asthma- these subjects were noted to have exceeded maximum dose. 25% mild asthma
[26] Hirsch, 1997	Dust mite	15	7 bronchial	unspecified

SLIT Systemic Reactions: Rhinitis/Nasal Reactions Reported as Number of Events					
Refid	**SLIT Allergen**	**Number of Patients in Arm**	**Number of Events**	**Number of Events per Patient[10]**	**Severity**
[25] Marogna, 2008	Birch and Grass mix	144	1 asthma	0.007	unspecified

[9] Percent of patient with local reactions = the percent of patients in that arm of the study with local reactions. Arms of the study where no reactions were reported are not displayed on this table.

[10] Percent of patient with local reactions = the percent of patients in that arm of the study with local reactions. Arms of the study where no reactions were reported are not displayed on this table.

[2]Number of events per patient =number of events reported in arm ÷ number of patients in arm

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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 No SIT Not an RCT

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. It does not meet ALL the inclusion criteria No original data Other reason for exclusion (specify): case report

A. J. Frew, R. J. Powell, C. J. Corrigan and S. R. Durham Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. Part of 10070

A. Mitsch and K. J. Drachenberg Positive results in a primary multicentric study. Specific immunotherapy administered sublingually. Foreign language

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 criteria not a quantifiable dose

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 criteria not a quatifiable dose

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 criteriaose not quantifiable

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 criterianot a quantifiable dose

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 criteriaoes not meet cTherapy NOT AVAILABLE in the U.S

Aarnoudse, A. L., van den Berge, H., Bijl, A. M., and Stricker, B. H. [A localized reaction to sublingual immunotherapy]. Ned Tijdschr Geneeskd 2006; 150 (29): 1632-4. Dutch

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 No SIT

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 criteriaoes not apply to any of the key questionsNo SIT

Aas, K. [Allergen extract and hyposensitization]. Arb Paul Ehrlich Inst Georg Speyer Haus Ferdinand Blum Inst Frankf A M 78; 73 3-6.Foreign language

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.Does not apply to any of the key questionsNo 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

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 criteriaposter only

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 criteriaoseOther reason for exclusion (specify):not really a control group, no harms

Adachi, M., Furuya, A., Kobayashi, H., Iijima, M., Kokubu, F., Okada, T., and Takahashi, T. [The effect of specific hyposensitization with house dust on the late asthmatic response (LAR)]. Arerugi 86; 35 (1): 31-9.Chinese/Japanese

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.Polish

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

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 data Other 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.It does not meet ALL the inclusion criteria Other reason for exclusion (specify):editorial

Adkinson, N. F. Jr Immunotherapy for allergic rhinitis. N Engl J Med 99; 341 (7): 522-4.No original dataOther 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.It does not meet ALL the inclusion criteriaoes 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 criteriaase seriesNo SIT

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.Other reason for exclusion (specify):Rhinits not confirmed by skin tests/RAST

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 No original dataOther reason for exclusion (specify):review

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 criteriaoes not apply to any of the key questionsOther 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 criteria Other reason for exclusion (specify):no harms

Akbas, Y. and Saatci, M. R. [Monitoring the efficacy of immunotherapy by symptom scores and the skin prick test in patients with allergic rhinitis]. Kulak Burun Bogaz Ihtis Derg 2003; 10 (6): 221-5.Turkish

Akcakaya, N. Hassanzadeh, A. Camcioglu, Y. and Cokugras, H. Local and systemic reactions during immunotherapy with adsorbed extracts of house dust mite in children. Ann Allergy Asthma Immunol 2000; 85 (4): 317-21.obs case series

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 dataOther reason for exclusion (specify):SLIT Review 2006

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 dataOther reason for exclusion (specify):review

Alemany-Vall, R. [Sensitization against mould fungi]. Allerg Asthma (Leipz) 68; 14 (3): 84-9.Foreign language

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.Excluded foreign language

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

Ali, M. Ramanarayanan, M. P. Nalebuff, D. J. Fadal, R. G. and Willoughby, J. W. Serum concentrations of allergen-specific IgG antibodies in inhalant allergy: effect of specific immunotherapy. Am J Clin Pathol 83; 80 (3): 290-9.obs case series

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

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. I. [Multicenter drug surveillance of sublingual immunotherapy in allergic patients]. Allergol Immunopathol (Madr) 95; 23 (4): 153-9.Foreign language

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 criteriaMethod 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.obs case series

Alonso, A., Prestisimone, R. E., Trotta, M., and Vaela, M. R. [Histologic and immunologic study of recurring endonasal polyposis in relation to desensitization therapy]. Allergol Immunopathol (Madr) 76; 4 (2): 121-30.Foreign language

Alvarez J M N Costs of specific immunotherapy (Brief record). Journal of Investigational Allergology and Clinical Immunology ; ,It does not meet ALL the inclusion criteriaoes not apply to any of the key questionsNo SITNo original dataOther reason for exclusion (specify):brief article on cost of asthma

Alzakar, R. H. and Alsamarai, A. M. Efficacy of immunotherapy for treatment of allergic asthma in children. Allergy Asthma Proc 2010; 31 (4): 324-30.excluded at data abstraction

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.Exclude but Keep for harms analysis

Anania, A., Marino, G., and Cascio, G. [Effect of specific immunotherapy on peripheral T-lymphocytes in atopic patients]. Minerva Med 96; 87 (6): 263-7.Foreign language

Anaphylaxis-rhinitis-hyposensitization. Hautarzt 97; 48 (8 Suppl): 4-6.Foreign language

Andersen, N. H., Jeppesen, F., Schioler, T., and Osterballe, O. Treatment of hay fever with sodium cromoglycate, hyposensitization, or a combination. Allergy 87; 42 (5): 343-51.Excluded at data abstraction

Anderson, J. A. Lane, S. R. Howard, W. A. Leiken, S. and Oppenheim, J. J. The effect of hyposensitization on alternaria-induced lymphocyte blastogenesis. Cell Immunol 74; 10 (3): 442-9.It does not meet ALL the inclusion criteriaoes not apply to any of the key questions

Andre, C. and Fadel, R. Anaphylaxis caused by allergen sublingual immunotherapy?. Allergy 2007; 62 (10): 1220-1.ritu.sharma,Therapy NOT AVAILABLE in the U.S

Andre, C. Perrin-Fayolle, M. Grosclaude, M. Couturier, P. Basset, D. Cornillon, J. Piperno, D. Girodet, B. Sanchez, R. Vallon, C. Bellier, P. and Nasr, M. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. Int Arch Allergy Immunol 2003; 131 (2): 111-8.Therapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):SLIT oral (aqueous arm) vs SLIT (Tablet)

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 Other reason for exclusion (specify):Inadequate control

Andri, L. Senna, G. and Mezzelani, P. Safety of specific immunotherapy. Ann Allergy 94; 72 (3): 285-6.It does not meet ALL the inclusion criteria-allergic asthma not confirmed by pulm lung function per article

Anon Homoeopathy ineffective for treating asthma triggered by dust-mite allergy. Pharmaceutical Journal ; ritu.sharma,No SITNo original data

Anon Rhinovac no tratamento das rinites alqrgicas em pacientes pedibtricos: estudo multicWntrico. Folha mqd 93; 106 (3): 97-102.Excluded foreign language

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.It does not

meet ALL the inclusion criteriaStudy 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

APPELMAN, H. B. UNTOWARD REACTIONS TO EMULSION THERAPY OF POLLENOSIS. REPORT OF TWO CASES. JAMA 64; 187 1030-1.It does not meet ALL the inclusion criteriaTherapy NOT AVAILABLE in the U.S

ARBESMAN, C. E. and REISMAN, R. E. HYPOSENSITIZATION THERAPY INCLUDING REPOSITORY: A DOUBLE-BLIND STUDY. J Allergy Clin Immunol 64; 35 12-7.obs case series

ARBESMAN, C. E., REISMAN, R. E., and KUNZ, M. L. CLINICAL AND IMMUNOLOGIC EVALUATION OF A PURIFIED FRACTION OF RAGWEED POLLEN (DELTA). A DOUBLE-BLIND STUDY. J Allergy Clin Immunol 65; 36 29-38.Excluded at data abstraction

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.It does not meet ALL the inclusion criteriaTherapy NOT AVAILABLE in the U.S

Ariano, R. Incorvaia, C. La Grutta, S. Marcucci, F. Pajno, G. Sensi, L. Di Cara, G. Sieber, J. Yacoub, M. R. and Frati, F. Safety of sublingual immunotherapy started during the pollen season. Curr Med Res Opin 2009; 25 (1): 103-7.It does not meet ALL the inclusion criteriaoes not apply to any of the key questions

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

Ariano, R. Spadolini, I. and Panzani, R. C. Efficacy of sublingual specific immunotherapy in Cupressaceae allergy using an extract of Cupressus arizonica. A double blind study. Allergol Immunopathol (Madr) 2001; 29 (6): 238-44.non random trial investigator

Ariano, R., Berto, P., Incorvaia, C., Di Cara, G., Boccardo, R., La Grutta, S., Puccinelli, P., and Frati, F. Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma. Ann Allergy Asthma Immunol 2009; 103 (3): 254-9.Excluded at data abstraction

Arifhodzic, N. Behbehani, N. Duwaisan, A. R. Al-Mosawi, M. and Khan, M. Safety of subcutaneous specific immunotherapy with pollen allergen extracts for respiratory allergy. Int Arch Allergy Immunol 2003; 132 (3): 258-62.obs case series

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.Does not apply to any of the key questionsOther 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 criteriaOther reason for exclusion (specify):no dose

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.nonR CT

Asai, S. [Effect of hyposensitization therapy on nasal allergy (author's transl)]. Nippon Jibiinkoka Gakkai Kaiho 76; 79 (8): 850-61.Foreign language

Asaoku, Y. [Clinical study of immunotherapy for bronchial asthma using purified mite feces antigen]. Nihon Kokyuki Gakkai Zasshi 2000; 38 (2): 92-9.Chinese/Japanese

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 immunotherapy on patients with mite-positive bronchial asthma using purified mite feces antigen fractions]. Arerugi 95; 44 (7): 692-700.Chinese/Japanese

Aschan, G. Irander, K. and Olofsson, J. Hyposensitization in allergic rhinitis--a comparison of aqueous extracts and Allpyral by means of rhinomanometry. J Otolaryngol 78; 7 (5): 444-9.It does not meet ALL the inclusion criteriaOther reason for exclusion (specify):no dose

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

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.patient preference

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 criteriaoes not apply to any of the key questions

Atienza Martin, F. J., Marquez Ramirez, P., Perez Jigato, R., Perez Errazquin, I., Alonso Perez, M., and Lopez Bueno, N. [Use of specific immunotherapy in the Basic Health Area of Campina Sur (Moguer-Huelva)]. Aten Primaria 2000; 26 (3): 169-71.Foreign language

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.Foreign language

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.Foreign language

Baeza Bacab, Manuel A, Graham Zapata, Luis F, and Sierna Monge, Juan Josq Luis Lineamientos para el tratamiento de la rinitis alqrgica. Bol. mqd. Hosp. Infant. Mqx 99; 56 (1): 38-46.Excluded foreign language

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M. I. Garcimartin, R. Barranco, M. Vazquez De La Torre Gaspar, F. J. Ruano, N. B.-L. N, E. S. E and et al. Effect of grass pollen immunotherapy on asthma quality of life [Abstract]. Meeting abstract

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dose/concentration "given in detail elsewhere", another studyDoes not apply to any of the key questions

Wilcock, L. K. Francis, J. N. and Durham, S. R. Aluminium hydroxide down-regulates T helper 2 responses by allergen-stimulated human peripheral blood mononuclear cells. Clin Exp Allergy 2004; 34 (9): 1373-8.It does not meet ALL the inclusion criterianon clinical outcomesDoes not apply to any of the key questionsNo SIT

Wilkinson, P. and Taudorf, E. Clinical trial of hyposensitisation in hay fever: two methods of relating symptom scores to daily pollen counts. Allergy 84; 39 (6): 463-8.It does not meet ALL the inclusion criteriaoes not apply to any of the key questionsNo original dataOther reason for exclusion (specify):methodology paper

Wilson, C. W. Black, J. H. McEwen, L. M. and Ganderton, M. A. The treatment of allergic rhinitis and asthma by percutaneous desensitisation. J Ir Med Assoc 67; 60 (360): 205-6.It does not meet ALL the inclusion criteriasthma not confirmed by PFTs; no relevant comparison groupTherapy NOT AVAILABLE in the U.S Other reason for exclusion (specify):used enzymes

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Yang, G. M. [Effects of desensitization and immunologic changes in patients with allergic asthma]. Zhonghua Jie He He Hu Xi Za Zhi 89; 12 (6): 359-60, 382.Chinese/Japanese

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Yoo, Y. S. Cho, O. H. Kim, E. S. and Jeong, H. S. Effect of asthma management education program on stress and compliance of patients with allergic asthma to house dust mite. Taehan Kanho Hakhoe Chi 2005; 35 (4): 686-93.Does not apply to any of the key questionsNo SIT

Yuksel, H. Tanac, R. Gousseinov, A. and Demir, E. Sublingual immunotherapy and influence on urinary leukotrienes in seasonal pediatric allergy. J Investig Allergol Clin Immunol 99; 9 (5): 305-13.It does not meet ALL the inclusion criteriaose and units not clearly specified- dose noted in "drops" and "IR"Exclude but Keep for harms analysis

Yunginger, J. W. and Gleich, G. J. Seasonal changes in IgE antibodies and their relationship to IgG antibodies during immunotherapy for ragweed hay fever. J Clin Invest 73; 52 (5): 1268-75.It does not meet ALL the inclusion criteria measurements; no cx endpts

Yunginger, J. W. and Gleich, G. J. Seasonal changes in IgE antibodies and their relationship to IgG antibodies during immunotherapy for ragweed hay fever. J Clin Invest 73; 52 (5): 1268-75.It does not meet ALL the inclusion criterianon clinical outcomes

Yuta A, Miyamoto Y, Hattori R, Ogihara H, Takeuchi K, and Majima Y The influence of medical economy from the aspect of medical direct costs by a

difference of the number of the pollen scattering on an allergen-specific immunotherapy for Japanese cedar pollinosis (Brief record). Japanese Journal of Allergology ; Brief Record

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Zavazal, V. [The significance of infection for the allergic disorders of the respiratory tract. IV. The results of immunotherapy in patients with bronchial asthma and vasomotor rhinitis]. Allerg Asthma (Leipz) 65; 11 (6): 278-85.Foreign language

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