Table E3. Evidence table SCIT studies

Author, date	Study design	Setting	Eligibility	Participants (number, gender, age, and descriptive	Asthma type,* severity (e.g. on ICS?)	Allergy type (mono/multi, allergens,	Intervention (type, dose, duration)	Control	Follow-up (from start	Outcomes	Results reported by authors†	Critical appraisal‡	Comments
Adkinson, 1997[45]	Double blind, placebo controlled, parallel group RCT Placebo carameli zed saline + histamin e	?		121 allergic children with perennial asthma Mean age 9.2 (range 5.4 to 14) years, 79% boys	Perennial asthma 34% ICS, 13% systemic	80% dust mite, 77% ragweed, 69% rye grass	Subcutaneo us multiple allergen immunother apy Median 6 (range 2 to 7) allergen extracts	Placebo	?	Symptom scores Medication scores PEF rates Nonspecific BHR (methacholin FEV_1)	SCIT not useful in moderate to severe perennial allergic asthma	Study useful, however low rate of ICS	Allocation concealm ent unclear
Altintas, 1999[46]	Open placebo controlled RCT multiple groups	university		34 poorly controlled mild to moderate asthmatics aged 4 to 18 years; 30 patients in 3 groups, 5 placebo	ICS use not specified, no medical details on asthma	Mono-sensitization *Dermatophago ides pteronyssinus*	Subcutaneou s immunothera py with adsorbed or aqueous *Dermatophag oides pteronyssinus* extracts (in different dilutions)	Placebo		Symptom medication score IgE and IgG4 level Bronchial provocation tests	SCIT is useful and safe; no conclusion on asthma	Study not useful No data on ICS,	Allocation concealme nt unclear Study designed to compare 3 different abstracts of immunothe rapy
Dreborg, 1986[47]	RCT, double blind Freeze dried carameliz ed histamine placebo	European		30 children with *Cladosporium* allergy, aged 5 to 17 years	Clinical history suggesting mold-induced asthma and/or rhinoconjunct ivitis ICS not stated	*Cladosporium* allergy	*10 months Cladosporium* subcutaneous immunothera py Or placebo	Placebo		Symptoms Medication PEF (no SD reported) Allergen specific BHR	Decrease in medication score, but not in symptom score Lower medication score in verum group	Study not useful No information on asthma medication No fixed study medication scheme	Allocation concealme nt unclear Asthma diagnosis not specified, (worsening of asthma in the *Cladospori*

													um season)
Hill, 1982[48]	Single blind RCT, rye grass pollen placebo	University Australia		20 asthmatic children, aged 9 to 14 years, with rye grass pollen allergy, positive at bronchoprovocation	ICS N=1 beclomethason N=8 cromoglycate		Subcutaneous immunotherapy with aqueous rye grass pollen extract	Placebo		Symptoms Medications (medians only reported, no SD)	no evidence that limited hyposensitization with a pollen extract is of any clinical benefit in seasonal asthma despite evidence of an immunological response.	Study not useful Primary outcome = IgE and IgG levels	No allocation concealment
Johnstone, 1961[49]	RCT, double blind, 4-year follow up Buffered saline control	United States general hospital		173 children with perennial asthma Severity = number of days of wheeze/year Placebo: n=41	No medication mentioned at all, no medication scores		Subcutaneous immunotherapy with relevant allergen extracts, administered by 3 regimens	Placebo		Asthma symptoms reported by mother Number of new allergies developing	Less new allergies developing Less symptoms and asthma attacks in the last year in the group 4	Study not useful No asthma medication scores	Allocation concealment unclear 4 different groups, 1 placebo (n=41) Group 2-4 different strength SCIT Last year single blind
Johnstone, 1968[50]	RCT, double blind Buffered saline control			130 children with perennial asthma; Severity = number of days of wheeze/year RCT, double blind Buffered saline control	No medication mentioned, no medication scores		Subcutaneous immunotherapy with relevant allergens administered by 3 regimens	Placebo		Asthma symptoms reported by mother	More children in SCIT group high dose overgrowing asthma at the age of 16 than placebo	Study not useful No asthma medication scores	Allocation concealment unclear 14-years follow up of Johnstone 1961
Price, 1984[51]	RCT, double blind			25 children with perennial asthma, aged 5 to 15 years	Asthma severity not specified asthma		Subcutaneous immunotherapy with *Dermatophag*	Placebo		Symptoms Medication Lung function Bronchoprovocation	Loss of late reaction on bronchoprovocation Only one out of 6	Study not useful Bronchoprovocation is	Continuation of study by Warner 1978 for second

	Saline placebo control				medication not specified		*oides pteronyssinus* extracts				children with severe asthma improved	surrogate outcome;	year with placebo group crossed over to active immunotherapy
Tsai, 2010[34]	RCT, no blinding, no intervention in control group	University hospital, Taiwan		40 children (21 boys), aged 5-14 years (average 8,5) >1 year moderate persistent to severe asthma, all monosensitized to house dust mite	Moderate persistent to severe asthma, using daily medication, most patient at least on ICS	House dust mite, diagnosed by SPT or specific antibody test	Subcutaneous injections of extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* (10000 AU/ml), initial dose 0,5AU/ml once a week. Dosage was increased weekly by 25-100% to reach optimal maintenance dose, with respect to local or systemic reaction. Maintenance therapy every 2 weeks during at least 3 months	No intervention	6 months (last follow-up)	Primary: Medication score (5 point scale, modified GINA) Secondary: PEF, asthma symptom score, number of contacts with health care providers	Mean medication score declined after 6 months in both groups; no significant between group differences. Both groups had reduction of asthma symptoms after 6 months, but no between group differences. There was no difference in PEF. Patients in the intervention group had more clinical visits than the control group, but no difference in emergency room or hospitalization	Very few patients, no blinding, randomization procedure not clear	
Valovirta, 1984[52]	RCT, double blind Caramel histamine placebo control	?		27 asthmatic children allergic to dog dander, aged 5 to 18 years	Asthma severity not specified asthma medication not specified		Subcutaneous immunotherapy with aluminium hydroxide bound dog	Placebo		Symptoms Allergen specific BHR	The decrease in bronchial sensitivity was less marked than that in conjunctival sensitivity and	Study not useful No asthma medication scores	Primary outcome dog dander sensitivity, not asthma 2 authors connected

							dander extract				statistically not significant		to pharmaceutical company
Warner, 1978[53]	RCT, double blind Tyrosine placebo control	University, United Kingdom		51 asthmatic children, aged 5 to 14 years, with positive *Dermatophagoides pteronyssinus* challenge	ICS n=12, cromoglycate n=24 SABA n=14	House dust mite, SPT and bronchoprovocation positive	Subcutaneous immunotherapy with tyrosine adsorbed *Dermatophagoides pteronyssinus* extracts	Placebo	1 year	Symptoms Medication Lung function (PEF, FEV 0.75) Allergen specific BHR	Less asthma medication in active group, but no difference in control or immediate response on bronchoprovocation	Useful; however incomparable low level of ICS	Allocation concealment unclear No fixed medication scheme
Zielen, 2010[35]	RCT, single blind, no control intervention	Multinational, multicenter		56 children with asthma GINA treatment II-III, on ICS, house dust mite (positive SPT), positive conjunctival provocation, significant RAST response	All on ICS, GINA II-III treatment	House dust mite SPT, provocative	SCIT with allergens extracted from *Dermatophagoides pteronyssinus* in 2 strengths: A: 1000 TU/ml; B: 10000 TU/ml. Initial therapy: weekly increasing doses strength A, followed by B. After reaching max individually tolerated dose, dosage intervals were increased to 6 weeks	No immunotherapy, only maintenance therapy with ICS	2 years	Primary: change in ICS dose steps to achieve asthma control Secondary: change in pre-bronchodilatory PEF, immunologic changes, nonspecific bronchial hyperreactivity	Less asthma medication in SCIT group as compared to control group, no change in asthma control, higher increase in PEF in intervention group. Adverse events in 97% in both groups	Block randomization. Multicenter, multinational is possible bicenter, binational. Conflict of interest in authors	

Abbreviations: AU: dosing units; BHR: bronchohyperreactivity; FEV1: forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; ml: millilitres; n: number; PEF: peak expiratory flow; RAST: radioallergent sorbent test; RCT: randomized controlled trial; SABA: short-acting beta agonist; SCIT: subcutaneous immunotherapy; SD: standard deviation; SPT: skin prick test; TU: dosing units

** Doctors diagnosed asthma? Stable/seasonal asthma? Mild/severe asthma?*

† Asthma symptoms, allergy/rhinitis symptoms, asthma control, (disease specific) quality of life, exacerbations, lung function, adverse reactions and/or complications

‡ e.g. randomization procedure, blinding, risk of bias