**AIT for allergic rhinoconjunctivitis: a systematic review and meta-analysis**

**Tables and figures to accompany main paper**

**Table 1a: Characteristics of SCIT studies (n=61 studies, reported in 63 papers)**

| **Study****(First author, y, country)** | **Allergen(s) type** | **Allergen no.** | **Comparator** | **AIT Protocol** | **Short-term effectiveness** | **Long-term effectiveness** | **Safety** | **Quality of life** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Grass pollen(s)** | **Tree pollen(s)** | **Weed(s)** | **Mold(s)** | **House dust mite** | **Cat** | **Dog** | **Other(s)** | **Single** | **Multiple** | **Placebo** | **Routine care** | **Active** |  |  |  |
| **Pre-seasonal** | **Co-seasonal** | **Continuous** | **Conventional** | **Cluster** | **Semi-rush** | **Rush** | **Ultra-rush** | **Rx duration** | **Product type/****Name (manufacturer)** | **Symptom score** | **Medication score** | **Combined score** | **Symptom score** | **Medication score** | **Combined score** |
| Alvarez-Cuesta, 2005, Spain | X | X |  |  |  |  |  |  |  | X | X |  |  |  |  | X | X |  |  |  |  | 1 y | Glutaraldehyde-polymerized extracts / NR (Laboratorios LETI, S.L.) | X | X |  |  |  |  | X | X |
| Ariano, 1999, Italy |  |  | X |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 1 y | Glutaraldehyde modified allergoid extract of *Parietaria judaica (50%) & Parietaria officinalis*  (50%)/ Purethal® |  |  | X |  |  |  | X |  |
| Arvidsson, 2002, Sweden  |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  |  | X | X |  |  |  | 2 y | Birch depot extract adsorbed onto aluminum hydroxide / Alutard SQ ® | X | X |  |  |  |  | X |  |
| Balda, 1998, Germany |  | X |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 7 w | Purified and standardized extracts composed of equal parts of *Corylus avellana, Alnus glutinosa, and Betula verrucosa* / ALK7 Frűhbltihermischűng® | X | X |  |  |  |  | X |  |
| Bodtger, 2002, Denmark |  | X |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  | X |  |  |  | 1 y | *Betula verrucosa* extract / Soluprick SQ® (ALK-Abello´) | X | X |  |  |  |  | X |  |
| Bousquet, 1987, France | X |  |  |  |  |  |  |  | X |  | X |  | X | X | X |  |  |  |  | X |  | 10 m | Six-mixed grass-pollen allergoid and standardized orchard grass-pollen extract / Alyostal ST® (Stallergenes) | X | X |  |  |  |  | X |  |
| Bousquet, 1989, France | X |  |  |  |  |  |  |  | X |  |  |  | X | X | X |  |  |  |  | X |  | 8 m | SCIT with a high-molecular-weight formalinized allergoid (HMW-GOID) vs SCIT with unfractionated allergoid (GOID) vs SCIT with standardized extract vs placebo / NR | X | X |  |  |  |  | X |  |
| Bousquet, 1990, France | X |  |  |  |  |  |  |  | X |  | X |  | X | X | X |  |  |  |  | X |  | NR | High-molecular weight mixed grass pollen allergoids / NR | X | X |  |  |  |  | X |  |
| Bousquet, 1991, France | X | X | X |  |  |  |  |  |  | X | X |  |  | X |  |  |  |  |  | X |  | 1 y | Standardized extracts from orchard grass (*Dactylis glomerata*), olive (*Olea europaea*), plane tree (*Platanus occidentalis*), mugwort (*Artemisia vulgaris*), and *Parietaria ofjicinalis* pollens / NR (manifactured by Stallergenes) |  |  | X |  |  |  | X |  |
| Bozek, 2016, Poland | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 3 y | Pollen mixture extract solution of grass pollens (*Agrostis stolonifera, A odoratum, Arrhenatherum elatius, D glomerata, Festuca rubra, Holcus lanatus, Lolium perenne, P pratense, P pratensis, Secale cereal, and Loe edasi*) / Purethal grasses ( HAL Allergy BV) | X | X | X |  |  |  | X | X |
| Brunet, 1992, Canada |  |  | X |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 3 m | Alum-precipitated aqueous ragweed extracts / NR | X | X |  |  |  |  | X |  |
| Ceuppens, 2009, Belgium & the Netherlands |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 18 m | Glutaraldehyde-modified birch pollen extract adsorbed onto aluminium hydroxide /PURETHAL® Birch |  |  | X |  |  |  | X |  |
| Chakraborty, 2006, India |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 2 y | *Phoenix sylvestris* *Roxb* or sugar palm allergoid extract / NR |  |  | X |  |  |  | X |  |
| Charpin, 2007, France |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 15 m | Standardized, aluminum hydroxide-adsorbed *Juniperus ashei* extract/ Alustal® (Stallergenes) | X | X |  |  |  |  | X | X |
| Colas, 2006, Spain |  |  | X |  |  |  |  |  | X |  | X |  |  |  |  | X |  | X |  |  |  | 1 y | Depigmented and glutaraldehyde polymerized extract of *Salsola kali* absorbed onto aluminium hydroxide/ NR (supplied by Laboratorios LETI, SL.) | X | X |  |  |  |  | X | X |
| Corrigan, 2005, UK | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 2 y | Aluminium-adsorbed six-grass pollen allergoid / Allergovit® | X | X |  |  |  |  | X | X |
| Crimi, 2004, Italy |  |  | X |  |  |  |  |  | X |  | X |  |  |  |  | X |  | X |  |  |  | 3 y | Intact *Parietaria judaica* extract adsorbed onto aluminum hydroxide / Alutard SQ® | X | X |  |  |  |  | X |  |
| Dokic, 2005,Macedonia |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  | X |  |  |  |  | 3 y | Aluminium hydroxide adsorbed *D.pt*. allergoid / NR (Allergopharma) | X | X |  |  |  |  | X |  |
| Dolz, 1996, Spain | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  | X |  |  |  | X |  | 3 y | Grass-pollen allergen extract (*Phleum, Dactylis, Lolium*) adsorbed onto aluminum hydroxide / Alutard SQ® (ALK-Abelló) | X | X |  |  |  |  | X |  |
| Drachenberg, 2001, Germany and Austria | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 4-7 w | Tyrosine-adsorbed glutaraldehyde-modified grass pollen extract containing monophosphoryl lipid A as adjuvant / Pollinex Quattro ® | X | X | X |  |  |  | X |  |
| Drachenberg, 2002, Germany  |  | X |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 4-7 w | L-tyrosine-adsorbed birch, alder, hazel pollen allergoids treated with glutaraldehyde plus monophosphoryl lipid-A (MPL) / Pollinex Quattro ® |  |  | X |  |  |  | X |  |
| DuBuske, 2011, USA, Canada, UK, Austria | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 4-8 w | Modified Allergen Tyosine Adsorbate (MATA) consisting of a mixture of modified pollen allergens from 13 grass species adsorbed onto tyosine/ Pollinex Quattro, PollinexComplete; Allergy Therapeutics, U.K. |  |  | X |  |  |  | X |  |
| Durham , 1999, UKPrimary study Varney, 1991 | X |  |  |  |  |  |  |  | X |  | X |  | X |  |  | X | X |  |  |  |  | 3 y | Standardized, aluminum hydroxide–adsorbed, depot grass pollen vaccine / Alutard SQ® (ALK Abelló) |  |  |  | X | X |  | X |  |
| Ewan , 1988, UK |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  | X |  |  | 3 m | Partially purified extract of *D. pteronysinus* / Pharmalgen® | X |  |  |  |  |  | X |  |
| Fell, 1988, UK | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  |  |  |  |  | X | 1 injection | Enzyme (glucuronidase) potentiated grass pollen allergens / (Pharmacia) | X | X |  |  |  |  |  |  |
| Ferrer, 2005, Spain |  |  | X |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 20 m | Biologically standardized extract of *Parietaria judaica* adsorbed onto aluminium hydroxide gel / Pangramin ®Depot, ALK-ABELLÓ | X | X | X |  |  |  | X | X |
| Frew, 2006, UK | X |  |  |  |  |  |  |  | X |  | X |  | X | X | X |  | X |  |  |  |  | 1 y | Standardized depot preparations of grass pollen extract / Alutard SQ grass pollen® (ALK-Abello´) | X | X |  |  |  |  | X | X |
| Grammer, 1982, USA |  |  | X |  |  |  |  |  | X |  | X | X |  | X |  |  | X |  |  |  |  | 15 w | Polymerized ragweed extract (PRW)/NR | X |  |  |  |  |  | X |  |
| Grammer, 1983, USA | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 4 m | Six grass pollen allergoid prepared by polymerization with glutaraldehyde / NR | X | X |  |  |  |  | X |  |
| Grammer, 1984, USA |  |  | X |  |  |  |  |  | X |  | X | X |  | X |  |  | X |  |  |  |  | >30 m (UR) | Polymerized ragweed extract / NR |  |  | X |  |  | X | X |  |
| Grammer, 1987, USA | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 4 m | Polymerized ragweed extract / NR |  |  | X |  |  |  | X |  |
| Höiby, 2010, Sweden & Germany |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 18 m | Depigmented polymerized birch pollen (Betula alba) extract adsorbed onto aluminium hydroxide/ Depigoid ®(Laboratorios LETI Sl) |  |  | X |  |  |  | X |  |
| Horst, 1989, France |  |  |  | X |  |  |  |  | X |  | X |  |  |  |  | X |  |  |  | X |  | 1 year | lyophilized and standardized Alt extract Stallergnes Laboratories |  |  | X |  |  |  | X |  |
| Iliopoulos, 1991, USA |  |  | X |  |  |  |  |  | X |  | X |  |  | X | X |  | X |  |  |  |  | ~8 m  | Short ragweed extract / NR (Greer Laboratories,Lenoir, N.C.) |  |  | X |  |  |  | X |  |
| James, 2011, UK | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 2/4 y | *Phleum pratense* extract adsorbed with aluminum hydroxide / Alutard SQ ® |  |  |  | X |  | X |  |  |
| Juniper, 1990, Canada |  |  | X |  |  |  |  |  | X |  |  | X |  | X | X |  | X |  |  |  |  | 6 w  | Modified ragweed tyosine adsorbate / Pollinex® (Bencard Allergy Service) | X | X |  |  |  |  | X |  |
| Jutel, 2005, Poland  | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  | X |  |  |  |  | 8-9 m | Five recombinant grass pollen allergens / NR (Allergopharma) |  |  | X |  |  |  | X | X |
| Kleine-Tebbe, 2014, Spain, Germany & Austria | X |  |  |  |  |  |  |  | X |  | X |  | X |  |  | X | X |  |  |  |  | 1 y | Aluminium hydroxide adsorbed Phleum pratense extract / AVANZ ® Phleum pratense (ALK) | X | X |  |  |  |  | X |  |
| Klimek, 2014, Germany  | X |  | X |  |  |  |  |  |  | X | X |  |  | X | X |  |  | X |  |  |  | 1 y | Glutaraldehyde-modified high polymerized allergen extract containing 6 grasses (60%) and rye pollen adsorbed onto aluminum hydroxide / CLUSTOID® (ROXALL Medizin) | X | X | X |  |  |  | X |  |
| Kuna, 2011, Poland |  |  |  | X |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 3 y | *Alternaria alternata* extract in a depot formulation with aluminum hydroxide / Novo-Helisen Depot ® A alternata 100% (Allergopharma) | X | X | X |  |  |  | X | X |
| Leynadier, 2001, France | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 1 y | Standardized five-grass-pollen (equal parts of: orchard, meadow, rye, sweet vernal and timothy) depot extract adsorbed onto calcium phosphate / Phostal® (Stallergenes) | X | X | X |  |  |  | X |  |
| Metzger, 1981, England |  |  | X |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 5 w | Glutaraldehyde-modified, tyosine-adsorbed short ragweed extract / NR (Beecham Laboratories) | X |  |  |  |  |  | X |  |
| Mirone , 2004, Italy |  |  | X |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 1y (DBRCT) | *Ambrosia artemisiifolia* absorbed onto aluminium hydroxide and suspended in phenolated (0.4% w/v) saline solution / NR (ALK-Abello`) | X | X |  |  |  |  | X |  |
| Olsen, 1995, Denmark | X | X | X |  |  |  |  |  |  | X |  |  | X |  |  | X | X |  |  |  |  | 2 y | Aluminium hydroxide adsorbed extracts of standardized extracts of *Betula, Phleum and Artemisia* / Alutard® SQ (ALK) | X |  |  |  |  |  | X |  |
| Ortolani, 1994, Italy |  |  | X |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 1 y | Partially purified alginate-conjugated extract of *Parietaria judaica* / Conjuvac Parietaria ® (Dome Hollister-Stier) |  |  | X |  |  |  | X |  |
| Pastorello, 1992, Italy  | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  | X |  |  |  |  | 5-12m  | Formalinized depot 6 grass allergoid absorbed onto aluminum hydroxide / NR (Allergopharma) |  |  | X |  |  |  | X |  |
| Patel, 2012, Canada  |  |  |  |  |  | X |  |  | X |  | X |  | X |  |  |  |  | X |  |  |  | 3 m | Fel d 1–derived peptide antigen (Cat-PAD) / NR (Bachem and Patheon) | X\* |  |  | X\* |  |  | X |  |
| Pauli, 2008, Austria, Denmark, France, Italy & Sweden |  | X |  |  |  |  |  |  | X |  | X |  | X |  |  | X | X |  |  |  |  | 2 y | Aluminum hydroxide–adsorbed vaccines of birch pollen extract, *rBet v 1*, and *nBet v 1* / NR (Stallergenes SA) | X | X |  |  |  |  | X |  |
| Pfaar, 2010, Lithuania, Poland & Germany |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 19 m | Standardized depigmented and glutaraldehyde-polymerized tree pollen extract (33% *Corylus avellana*, 33% *Alnus glutinosa*, 34% *Betula alba*) adsorbed onto aluminium hydroxide / Depigoid(Laboratorios LETI SL, Tres Cantos, Spain), | X |  | X |  |  |  | X |  |
| Pfaar, 2011, Germany | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  |  |  |  | X |  | 2 y | Depigmented and glutaraldehyde-polymerized grass pollen mix adsorbed onto aluminum hydroxide / Depiquick® (Laboratorios LETI) | X | X | X |  |  |  | X | X |
| Powell, 2007, UKPrimary study Frew, 2006 | X |  |  |  |  |  |  |  | X |  | X |  | X |  |  | X | X |  |  |  |  | 14m | Standardized depot preparations of grass pollen extract / Alutard® SQ grass pollen (ALK-Abello´) |  |  |  |  |  |  |  | X |
| Radcliffe , 2003, UK | X | X | X | X | X | X | X | X |  | X | X |  |  | X |  |  |  |  |  |  |  | 2-3 m | Enzyme potentiated mixed inhaled allergen extract (pollen mixes for trees, grasses, and weeds; allergenic fungal spores; cat and dog danders; dust and storage mites) / NR | X |  |  |  |  |  | X | X |
| Rak, 2001, Sweden  |  | X |  |  |  |  |  |  | X |  |  | X |  | X |  |  |  | X |  |  |  | 1 y | Birch pollen extract adsorbed onto aluminum / Alutard® (ALK-Abelló) | X | X |  |  |  |  |  |  |
| Riechelmann, 2010, Germany & Austria  |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 1 y | Single-strength glutaraldehyde-modified aluminum hydroxide–adsorbed extract / HDM PURETHAL Mites ® (HAL-Allergy) | X | X |  |  |  |  | X | X |
| Tabar, 2005, Spain |  |  |  |  | X |  |  |  | X |  |  |  | X |  |  |  | X | X |  |  |  | 1 y | Biologically standardized HDM depot extract adsorbed on aluminum hydroxide / Pangramin Depot UM D pteronysinus® (ALK-Abello´) | X | X |  |  |  |  | X |  |
| Tabar, 2008, Spain |  |  |  | X |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 18 m | Metabolic extract of *Alternaria alternata* / Allergovac® depot | X | X |  |  |  |  | X | X |
| Tari, 1997, Italy |  |  | X |  |  |  |  |  | X |  | X |  |  |  |  | X | X |  |  |  |  | 2 y | Alum-adsorbed *Parietaria judaica* pollen allergoid/ Allergovit® (Allergopharma) | X | X |  |  |  |  | X |  |
| Tworek, 2013, Poland | X |  | X |  |  |  |  |  |  | X |  |  | X | X |  | X | X |  |  |  |  | 3 y | Allergoid preparation consisting of 80% grass pollen and 20% rye pollen extracts / Allergovit® (Allergopharma) | X | X | X |  |  |  | X |  |
| Varney, 1991, UK |  | X |  |  |  |  |  |  | X |  | X |  |  | X | X |  | X |  |  |  |  | 8 m | Partially purified and standardised extract of *Phleum pratense* adsorbed onto aluminium / Alutard SQ® (ALK-Abelló) | X | X |  |  |  |  | X |  |
| Varney, 2003, UK  |  |  |  |  | X |  |  |  | X |  |  |  |  |  |  | X | X |  |  |  |  | 1 y | Intact HDM extract vaccine adsorbed onto aluminum hydroxide/ Alutard SQ® (ALK-Abelló) | X | X |  |  |  |  | X |  |
| Walker, 2001, UK | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  | X |  | X |  |  |  | 2 y | Alutard SQ (ALK Abelló, Horshølm,Denmark), a standardized extract of Phleum pratense (timothygrass pollen),7 aluminum adsorbed for slow release | X | X |  |  |  |  | X | X |
| Weyer, 1981, France | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  |  | 8 m | Crude 4 grass pollen extract / NR | X | X | X |  |  |  | X |  |
| Zenner, 1997, Germany  | X |  | X |  |  |  |  |  | X |  | X |  |  |  | X |  | X |  |  |  |  | 4 m | Partially purified and standardized extracts of 6 grasses (50%, *Dactylis glomerata, Lolium perenne, Arena elatior, Phleum pratense, Poa pratensis, and Fetuca pratensis*) and rye, (50%, *Secale cereale*) adsorbed onto aluminum hydroxide / NR (manufactured by ALK A/S ) | X | X |  |  |  |  | X |  |

***AIT****, allergen specific immunotherapy;* ***m,*** *month;* ***NBS****, not better specified;* ***NR****, not reported;* ***Rx,*** *treatment;* ***SCIT****,* subcutaneous immunotherapy; ***SLIT****, sublingual immunotherapy;* ***UR,*** *unclear reporting* ***w,*** *week;* ***y****, y.*

*\*environmental exposure chamber*

**Table 1b: Characteristics of SLIT studies (n=71 studies, reported in 75 papers)**

| **udy****(First author, y, country)** | **Allergen(s) type** | **Allergen no.** | **Comparator** | **AIT Protocol** | **Short term effectiveness** | **Long term effectiveness** | **Safety** | **Quality of life** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Grass pollen(s)** | **Tree pollen(s)** | **Weed(s)** | **Mold(s)** | **House dust mite** | **Cat** | **Dog** | **Other(s)** | **Single** | **Multiple** | **Placebo** | **Routine care** | **Active** |  |  |  |
| **Pre-seasonal** | **Co-seasonal** | **Continuous** | **Conventional** | **Cluster** | **Semi-rush** | **Rush** | **Ultra-rush** | **Rx duration** | **Product type/****Name (manifacturer)** | **Symptom score** | **Medication score** | **Combined score** | **Symptom score** | **Medication score** | **Combined score** |
| Ahmadiafshar, 2012, Iran | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  | X | 6 m | 10, 100, and 300 IR rye grass spray (Staloral 638) | X | X |  |  |  |  | X |  |
| Alvarez-Cuesta, 2007, Spain |  |  |  |  |  | X |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 12 m | Aqueous solution of cat dander extract with NaCl 0.9%, phenol 0.4% and glycerol 50% (protocol supplied by Laboratorios LETI, S.L. | X |  |  |  |  |  | X |  |
| Amar, 2009, US | X |  |  |  |  |  |  |  |  | X | X |  | X |  |  | X |  |  |  |  |  | 10 m | Monotherapy group: timothy extractMultiple allergen group: same amount of timothy plus 1 mL each ofan additional 9 unstandardized extracts 1:20 wt/vol in 50% glycerin: maple,ash, juniper, American elm, cottonwood, Kochia, ragweed, sagebrush, andRussian thistle (ALK-Abello´). | X | X |  |  |  |  | X |  |
| André, 2003, France |  |  | X |  |  |  |  |  | X |  | X |  |  |  | X |  |  |  |  |  |  | 6.5 m | standardized ragweed extract (Stallergènes SA, Antony, France)  | X | X |  |  |  |  | X |  |
| Ariano, 2001, Italy & France |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  | X |  |  |  |  |  | 12 m | Aqueous solution of an allergic fraction of *Cupressus arizonica* partially purified through dialyis in a phyiological solutionwith 15% glycerin. | X | X |  |  |  |  | X |  |
| Aydogan, 2013, Turkey, UK & Cyprus. |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 12 m | 1:1 mixture of *D. pteronysinus and D. farinae* (STALORAL, Stallergenes SA, Antony, France)  | X | X |  |  |  |  |  |  |
| Bahçeciler, 2007, Turkey |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 6 m | *D. pteronysinus and D. farinea* 50/50 extract. | X |  |  |  |  |  |  |  |
| Bergmann, 2013, Germany, France, the Netherlands & Spain |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 2 y | Oral tablets of 1:1 mixture of *D pteronysinus and D farinae* (28 mg and 120 mg respectively for the 500 IR tablet, 16 mg and 68 mg respectively for the 300 IR tablet)  | X |  |  | X |  |  | X |  |
| Blaiss, 2010, US & Canada | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 18 m | f 2,800 bioequivalent allergen units of grass AIT treatment (oral lyophilisate, *Phleum pratense*, 75,000 standardized quality tablet, containing approximately 15 mg of Phl p 5; Schering-Plough Corp, a division of Merck & Co, Kenilworth, NJ)  | X | X | X |  |  |  | X | X |
| Bowen, 2004, Canada |  |  | X |  |  |  |  |  | X |  | X |  |  | X |  |  |  |  |  |  |  | 4 m | Ragweed allergen extract  | X | X |  |  |  |  | X |  |
| Bozek, 2012, Poland |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 3 y | Oral Staloral 300 SR Der p and Der f (1:1)  | X | X |  |  |  |  | X |  |
| Bozek, 2014, Poland | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 3 y | Oral Staloral 300 SR 5 grass pollen solution *of P. pratense, D. glomerata, A. odoratum, L. perenne, and P. pratensis* (Stallergenes) | X | X |  |  |  |  | X |  |
| Bufe, 2004, Germany | X |  |  |  |  |  |  |  | X |  | X |  |  |  | X |  |  |  |  |  |  | 3 y | Grass pollen extracts (Sublivac B.E.S.T.TM, HAL-Allergy, Haarlem, the Netherland) |  |  |  |  |  |  |  |  |
| Bufe, 2009, Germany | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 8-23 w | Orodispersible, fast-dissolving, SQ-standardized grass allergen tablet (Grazax; ALK, Hørsholm, Denmark; 75,000 SQ-T/2800 bioequivalent allergen units, approximately 15 mg Phl p 5, Phleum pratense major allergen 5) | X | X |  |  |  |  | X |  |
| Caffarelli, 2000, Italy | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  |  |  |  |  |  | 3 m | Mixture of monomeric grass-pollen allergens (33% *Holcus lanatus*, 33% *Phleum pratense*, and 33% *Poa pratensis*) in tablets (LAIS, Lofarma S.p.A, Milan, Italy)  | X | X |  |  |  |  | X |  |
| Clavel, 1998, France | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 7 m | Mixture of five major grass pollens (orchard grass, meadow grass, ryegrass, sweet vernal grass, and timothy grass | X | X |  |  |  |  | X |  |
| Cortellini, 2010, Italy |  |  |  | X |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 10 m | Glycerinated *Alternaria alternata* extract in droplets (Anallergo, Firenze, Italy) | X | X |  |  |  |  | X |  |
| Cox, 2012, US | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 6 m | 300IR SLIT tablets containing a standardized 5-grass pollen allergen obtained by means of extraction of a mixture of 5 grass pollens in equal amounts (orchard grass, *Dactylis glomerata*; Kentucky bluegrass, *Poa pratensis*; perennial rye grass, *Lolium perenne*; sweet vernal grass, *Anthoxanthum odoratum*; and timothy grass, *Phleum pratense*) | X | X | X |  |  |  | X | X |
| Creticos, 2013, US |  |  | X |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 20 m | Short ragweed tablets (1.5, 6, or 12 units of *Ambrosia artemisiifolia* major allergen 1 [Amb a 1-U])  | X | X | X |  |  |  | X |  |
| Creticos, 2013, Canada |  |  | X |  |  |  |  |  | X |  | X |  |  |  | X |  |  |  |  |  |  | 12 w  | ragweed SAIL (RW-SAIL) Standardized glycerinated short ragweed  | X |  | X |  |  |  | X |  |
| Dahl, 2006, Denmark, Germany, Italy, the Netherlands, Sweden, Austria, Spain & UK | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 1 y | Grass pollen allergen tablet (GRAZAX) (75,000 SQ-T; 15 mg major allergen *Phleum p* 5)  | X | X |  |  |  |  | X |  |
| Dahl, 2006, Denmark & Sweden | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  |  | Orodispersible grass allergen tablet (GRAZAX; approximately 15 mg major allergen *Phleum pretense* (75 000 SQ-T)  | X | X |  |  |  |  | X |  |
| de Blay, 2007, France | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 12 m | 3-grass pollen extract (33.3% *Dactylis glomerata* [orchard grass], 33.3% *Phleum pretense* timothy grass], and 33.3% *Lolium perenne* [rye grass]) Allerbio, Varennes-en-Argonne, France) in 50% glycerin | X | X |  |  |  |  | X | X |
| De Bot, 2011, The Netherlands |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 2 years | aqueous extract of house dust mites (*D pter*,) in a glycerinated isotonic phosphate-buffered solution (Oralgen Mijten) / placebo treatment consisting of the glycerol-containing solvent | X | X |  |  |  |  | X | X |
| Demoly, 2015, Europe |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 1 y | 1:1 mixture of two species of house dust mite allergens (*D. pteronysinus and D. farinae*) (1:1:1:1 ratio of the major allergens *Der p 1, Der f 1, Der p 2*, and *Der f 2*)  | X | X |  |  |  |  | X | X |
| Didier, 2007, Europe | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 6 m | Mixture of 5 grass pollens (orchard, meadow, perennial rye, sweet vernal, and timothy grasses)  | X |  |  |  |  |  | X | X |
| Didler, 2009, France, Germany & Spain | X |  |  |  |  |  |  |  | X |  | X |  | X | X | X |  |  |  |  |  |  | 6 m | Lyophilized vaccines of ﬁve grass pollens (orchard or cocksfoot (*Dactylis glomerata*), meadow ( *Poa pratensis*), perennial rye (*Lolium perenne*), sweet vernal (*Anthoxanthum odoratum*) and timothy (*Phleum pratense))*  | X |  |  |  |  |  | X |  |
| Didier, 2013, Denmark, Austria, France, Canada & Germany | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 4 y | 300IR tablets containing mixture of 5 grasses [cocksfoot (*Dactylis glomerata*), meadow (*Poa pratensis*), rye (*Lolium perenne*), sweet vernal (*Anthoxanthum odoratum*) and timothy (*Phleum pretense)*  | X |  |  |  |  |  | X | X |
| Durham, 2005, Canada, Denmark & Sweden | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 2 y | Fast-dissolving grass allergen tablet (ALK-Abello A/S) containing timothy grass extract (*Phleum pratense)*  | X | X |  |  |  |  | X | X |
| Durham, 2007, UKPrimary study: Dahl, 2006 | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 16 w | Grass allergen tablet (Grazax) |  |  |  |  |  |  |  |  |
| Durham, 2009, UKResults after 1 y follow-up of Dahl, 2006 study | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 3 y | Grass allergen tablet with *Phleum pratense* 75,000 SQ-T/2,800 BAU (ALK-Abello´, Hørsholm, Denmark) (Grazax)  |  |  |  |  |  |  |  |  |
| Durham, 2011, UKResults of 2 y follow-up of Dahl 2006 trial  | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  | X | 2 y | SQ-standardized grass allergy tablet (*Phleum* *pratense* 75 000 SQ-T/2,800 BAU, ALK, Denmark) (Grazax)  |   |  |  |  |  | X |  |  |
| Durham., 2012, UK, Austria, Germany, the Netherlands, Sweden & Denmark Results of 2 y follow-up of Dahl 2006 trial | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 3 y | SQ-standardized grass allergy tablet (Grazax)  |  |  |  | X |  |  | X |  |
| Drachenberg, 2002, Germany  | X | X |  |  |  |  |  |  |  | X | X |  |  |  |  |  | X |  |  |  |  |  | Grass, rye or birch pollens | X | X | X |  |  |  |  |  |
| Feliziani, 1995, Italy | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  | X |  |  | Grass pollen extracts (5 x 1 drop of 0.04 BU/ml, up until 5 x 1 drop of 100 BU/ml)  | X | X |  |  |  |  | X |  |
| Frølund, 2010, Austria, Denmark & UK | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 4 y | SQ-standardized grass allergy immunotherapy tablet (AIT), Grazax (*Phleum pratense* 75,000 SQ-T/2800 BAU; ALK, Denmark).  |  |  |  |  |  |  |  | X |
| Guez, 2000, France |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 24 m | *D. pteronysinus and D. farinae* 50/50 extract | X | X |  |  |  |  | X |  |
| Halken, 2010, Germany, Denmark, Poland, France & Spain | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 10 m | five-grass pollen 300IR tablets (Stallergènes SA, France)  | X |  |  |  |  |  | X |  |
| Hirsch, 1997, Germany |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 12 m | Purified *D. pteronysinus* extract in 50% aqueous glycerol (cumulative dose 570 jag) (Allergopharma J. Ganzer KG, Reinhek, FRG)  | X | X |  |  |  |  |  |  |
| Horak, 1998, Austria |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 4m | Biologically standardized *Betula Alba* Alergia e Immunologia Abello SA | X |  |  |  |  |  | X |  |
| Horak, 2009, Austria | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 4m | 300-IR 5 grass pollen tablet (orchard, meadow, perennial rye, sweet vernal, timothy) | X |  |  |  |  |  | X |  |
| Hordijk, 1998, the Netherlands | X |  |  |  |  |  |  |  | X |  | X |  |  |  | X |  |  |  |  |  |  | 10 m | Glycerinated (50% w/v) five-grass pollen extract (*Anthoxanthum odoratum* (Sweet vernal grass), *Cynodon dactylon* (Bermuda grass), *Dactylis glomerata* (Orchard grass), *Holcus lanatus* (Velvet grass) and *Phleum pratense* (Timothy grass)) (9,500 BU/ml) (Oralgen) (ARTU Biologicals Europe B.V., Lelytad, The Netherlands)  | X |  |  |  |  |  | X |  |
| Ibanez, 2007, Spain & Germany | X |  |  |  |  |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  | 28 d | Orodispersible grass allergen tablet (75,000 SQ-T; 15 Ig *P. pratense* major allergen (Phl p 5)) (Grazax) ALK-Abello A/S, Horsholm, Denmark)  |  |  |  |  |  |  | X |  |
| Ippoliti, 2003, Italy |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 6 m | *D. pteronysinus* extract  | X |  |  |  |  |  |  |  |
| Kaluzinska-Parzyzek , 2011, Poland (Polish, translated) | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  | X |  |  |  | 2 y | Staloral 300 IR (Stallergenes)  |  |  |  |  |  |  |  |  |
| La Rosa, 1999, Italy & France |  |  | X |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 2 y | *P judaica* extract (Stallergènes, Antony, France) in drops  | X | X |  |  |  |  | X |  |
| Marcucci, 2003, Italy |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 1 y | house dust mite allergens (1 ml of the top-dose vial 1000 STU/ml/4 lg of the major mite allergen Group 1 and 2 lg of the major mite allergen Group 2) |  |  |  |  |  |  |  |  |
| Moreno-Ancillo, 2007, Spain | X |  |  |  |  |  |  |  |  | X | X |  |  | X | X |  |  |  |  |  |  | 10 m | 2 μg of grass Group 5 and 3 μg of Olive europaea Ole e 1 (daily)  | X | X | X |  |  |  | X | X |
| Mosbech., 2014, Denmark, Italy, Germany & France |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 1 y | Oral lyophilisates containing *D. pteronysinus* and *D. farinae* in a 1:1 ratio . Three active strengths were investigated: 1, 3, and 6 SQ-HDM. |  |  | X |  |  |  | X | X |
| Mosges, 2007, Germany | X |  |  |  |  |  |  |  |  | X | X |  |  |  |  |  |  |  |  |  |  | 9 m | Grass and rye pollen extract mixture solution(Staloral(r) (Stallergenes, Antony, France)) and a tablet (freeze-dried pollen extract) |  | X | X |  |  |  | X |  |
| Okubo, 2008, Japan |  | X |  |  |  |  |  |  | X |  | X |  |  | X | X |  | X |  |  |  |  | 7 m | Diluted cedar antigen extract (2 to 2000 JAU/ml)  |  | X |  |  |  |  | X | X |
| Ott, 2009, Germany | X |  |  |  |  |  |  |  | X |  | X |  |  |  | X |  |  |  |  |  | X | 3 y | Pollen extract mixture of five grasses (cocksfoot or orchard, meadow, perennialrye, sweet vernal and timothy grasses; Staloral, Stallergenes SA,France) (300 IR/ml, equivalent to 21 lg/ml of Phleum pratense major allergen)  | X | X | X | X | X | X | X |  |
| Nelson, 1993, US |  |  |  |  |  | X |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 105 d | Cat dander extract (total dose: 4.5 AU) | X |  |  |  |  |  | X |  |
| Pajno, 2003, Italy |  |  | X |  |  |  |  |  | X |  | X | X | X | X | X |  |  |  |  |  |  | 14 m | *P. judaica*, fluticasone | X | X |  |  |  |  |  |  |
| Palma-Carlos, 2006, Italy | X |  |  |  |  |  |  |  | X |  | X |  | X | X |  |  |  |  |  |  |  | 2 y | Mixture of carbamylated grass pollens (*Holcus lanatus* 33%, *Phleum pratense* 33%, and *Poa pratensis* 33%) in tablets | X |  |  |  |  |  | X |  |
| Panzner, 2008, Czech Republic  | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  |  |  |  |  |  | 1 y | Mixture of six grass pollen species extracts (oat grass (*Arrhenatherum elatius*), orchard grass (*Dactylis glomerata*), fescue (*Festuca sp*.), rye grass (*Lolium sp*.), timothy grass (*Phleum pratense*) and rye (*Secale cereale)*) (H-Al per os) (Sevapharma A.S., Prague, Czech Republic)  |  X | X |  |  |  |  | X |  |
| Passalacqua, 1996, Italy |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 2 y | Monomeric allergoid tablets with *Dermatophagoides pteronysinus and D farina* | X |  |  |  |  |  | X |  |
| Passalacqua, 1999, Italy | X |  |  |  |  |  |  |  | X |  | X |  |  | X |  |  |  |  |  | X |  | 7 m | ALK-Abello (major allergen Par j) (0.016, 0.08, 0.4, 2, and 10 BU/mL)  | X | X |  |  |  |  | X |  |
| Passalacqua, 2006, Italy |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  | X |  |  |  |  |  | 2 y | Monomeric carbamylated grass pollen allergen (Lais) | X | X |  |  |  |  | X | X |
| Pfaar, 2008, Germany, Poland & Macedonia | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 2 y | Six-grass pollen mixture (high-dose) | X |  |  |  |  |  | X |  |
| Pradalier, 1999, France | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 4.5 m | Five-grass-pollen extracts (orchard grass, meadow grass, ryegrass, sweet vernal grass, and timothy grass) (Stallerge Ánes SA, Antony, France) | X | X |  |  |  |  | X |  |
| Purello-D'Ambrosio, 1999, Italy |  |  | X |  |  |  |  |  | X |  | X |  |  | X |  |  |  |  |  | X |  | 6 m  | *P. judaica* extract (five 3-ml vials: 0.016 BU/ml (vial 0), 0.08 (#1), 0.04 (#2), 2.00 (#3), and 10.00 (#4) in phyiologic saline with 50% v/v of glycerol & 0.4% w/v of phenol) (maximum concentration of major allergen Par j 1: 0.6 mg/ml)  | X | X |  |  |  |  | X |  |
| Qeuiros, 2013, Brazil & US |  |  |  |  | X |  |  |  | X |  | X |  | X |  |  |  |  |  |  |  |  | 18 m | SLIT 1:*D. pteronysinus* extract (FDA Allergenic Ltda, Rio de Janeiro, Brazil) SLIT 2: *Dpt plus* mixed respiratory bacterial (MRB) (FDA Allergenic Ltda) |  |  | X |  |  |  | X |  |
| Rak, 2006, UK | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 174 d | Grass pollen allergen tablets (2,500, 25,000, and 75,000 SQ-T)  |  |  |  |  |  |  |  | X |
| Roder, 2007, The Netherlands | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  | X |  |  |  |  |  | 2 years | Aqueous extracts of 5 grass pollen (*Lollium perenne, Phleu*m pratense, Dactylis glomeratein, Anthoxantum odoratum, Holcus lanatus) Oralgen grass pollen, Artu Biologicals | X | X |  |  |  |  | X | X |
| Rolinck-Werninghaus, 2004, Germany | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  | XX |  |  |  |  |  | 32 m | Pangramin (0.5 lg major allergens) (ALK-SCHERAX) three times weekly  | X | X |  |  |  |  | X |  |
| Sabbah, 1994, France | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 4 m | Five-grass pollen extracts in glycerol-saline diluent (from 1 drop of 1 IR/ml up to 20 drops of 100 IR/ml)  | X | X |  |  |  |  | X |  |
| Stelmach, 2011, Poland | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 2 y | Staloral 300 IR with five grass pollen (*Dactylis glomerata, Anthoxanthum odoratum, Lolium perenne, Poa pratensis and Phleum pretense*)  | X | X |  |  |  |  | X |  |
| Tari, 1990, Italy |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 18 m | Graded courses of aqueous mite extract with 0.4% phenol  | X |  |  |  |  |  | X |  |
| Valovirta, 2006, Finland |  | X |  |  |  |  |  |  | X |  | X |  | X |  |  |  |  |  |  |  |  | 19m | Intervention arm #1: *Betula verrucosa, Corylus avellana and Alnus glutinosa* (weekly dose: 24 000 SQ-U); intervention arm #2: *Betula verrucosa, Corylus avellana and Alnus glutinosa* (weekly dose: 200,000 SQ-U)  | X | X |  |  |  |  | X |  |
| Van Niekerk, 1987, South Africa | X |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 24 m | Mixture of aqueous extracts of twelve grass pollens (B2 grasses) (Bencard, UK), plus Bermuda grass pollen and maize pollen in phosphate buffered phyiological saline with 0 5% w/v phenol identical to Bencard SDV® vaccine (Beechams, UK)  | X |  |  |  |  |  | X |  |
| Vourdas, 1998, Greece & France |  | X |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 2 y | Olive pollen extract (major allergen Ole e 1 13.5 jig/ml (100 IR/ml)) (four concentrations: 1, 10, 100, and 300 IR/ml) (Stallergenes SA)  | X | X |  |  |  |  | X |  |
| Wang, 2013, China |  |  |  |  | X |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  |  | 6 m | Mixture of *D. pteronysinus and D. farinae* in 50% glycerol solution (Zhejiang Wolwo BioPharmaceutical Co., Ltd., China) (five treatment dosages with different concentrations: 0.75 lg/ml, 7.5 lg/ml, 75 lg/ml, 250 lg/ml, and 750 lg/ml)  | X | X |  |  |  |  | X |  |
| Wahn, 2012, Germany & Poland | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | 8m | Aqueous grass pollen preparation containing 6 species (*Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense, and Poa pratensis*) in a water/glycerol solution with phosphate-buffered saline (40 μg per maintenance dose) Allergopharma Joachim Ganzer KG, Reinbek,German  |  |  | X |  |  |  | x |  |
| Wahn, 2009, Denmark & France | X |  |  |  |  |  |  |  | X |  | X |  |  | X | X |  |  |  |  |  |  | Approx 5-6 m | Aqueous mixture of 5 grass pollen extracts (orchard, meadow, perennial rye, sweet vernal, and timothy; Stallergenes SA, Antony, France) (300 IR)  | X | X |  |  |  |  | X |  |

**Table 1c.** Characteristics of ILIT studies (n = 2)

| **Study****(First author, year, country)** | **Allergen(s) type** | **Allergen number** | **Route AIT** | **Comparator** | **AIT Protocol** | **Short term effectiveness** | **Long term effectiveness** | **SAFETY** | **Quality of life** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Grass pollen's** | **Tree pollens** | **Weeds** | **Moulds** | **House dust mite** | **cat** | **dog** | **other (s)** | **single** | **Multiple** | **SCIT** | **SLIT** | **ILIT** | **placebo** | **routine care** | **active** |  |  |  |  |  |
| **Pre-seasonal** | Co-seasonal | **Continuous** | **Conventional** | **Cluster** | **Semi-rush** | **Rush** | **Ultra rush** | **Duration of Rx** | **Product type/****Name (manifacturer)** | **Symptom score** | **Medication score** | **Combined score** | **Symptom score** | **Meidication score** | **Combined score** |  |
| Hylander et al, 2016, Spain | X | X |  |  |  |  |  |  | X |  |  |  | X | X |  |  | X |  |  |  | X |  |  |  | 2 mos | aluminium hydroxide adsorbed, depot birch- or grass-pollen vaccine / Alutard (ALK Abéllo) | X | X |  |  |  |  | X |  |
| Senti, et al , 2012, Switzerland |  |  |  |  |  | X |  |  | X |  |  |  | X | X |  |  |  |  | X |  | X |  |  |  | 2 mos | recombinant major cat dander allergen Fel d 1 fused to a modular antigen transporter (MAT) vaccine (MAT–Fel d 1)/ NR (extract purchased from Stallergenes) | X\* |  |  |  |  |  | X | X |

*\* assessment after 300 days of discontinuation of ILIT*

***AIT****, allergen specific immunotherapy;* ***mo,*** *month;* ***NR****, not reported;* ***Rx,*** *treatment;* ***SCIT****,* subcutaneous immunotherapy; ***SLIT****, sublingual immunotherapy,* ; ***ILIT****, intralymphatic immunotherapy.*

**Figure 1: PRISMA Diagram**

Records identified through database searching
N = 5944

Additional records identified through other sources
N = 16

## Identification

Records after duplicates removed
N = 4392

## Screening

Records screened
N = 4392

Records excluded
N = 4055

Full-text articles excluded, with reasons
N = 183

Full-text articles assessed for eligibility
N = 337

## Eligibility

Studies included in qualitative synthesis
N = 160

## Included

Studies included in quantitative synthesis (meta-analysis)
N = 62

**Figure 2: Meta-analysis of double-blind RCTs comparing symptom scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)**



**Heterogeneity: τ2 = 0.090; χ2 = 173.586, df = 57 (P<0.0001); I2 = 67%;**

**Test for overall effect: Z = -9.992 (P<0.0001)**

*\*denotes SCIT studies*

**Figure 3: Meta-analysis of double-blind RCTs comparing symptom scores between (a) SCIT and placebo groups and (b) SLIT and placebo group (random-effects models)**

**a)**



**Heterogeneity: τ2 = 0.106; χ2 = 39.357, df = 15 (P<0.001); I2 = 62%;**

**Test for overall effect: Z = -5.875 (P<0.0001)**

*\*denotes SCIT studies*

**b)**

**Heterogeneity: τ2 = 0.088; χ2 = 129.171, df = 40 (P<0.0001); I2 = 69%;**

**Test for overall effect: Z = -7.855 (P<0.0001)**

*\*denotes SCIT studies*

**Figure 4: Meta-analysis of double-blind RCTs comparing symptom scores between AIT (SCIT or SLIT) and placebo group in (a) those <18 years old and (b) those≥18 years old (random-effects models)**

**a)**



**Heterogeneity: τ2 = 0.059; χ2 = 24.209, df = 11 (P<0.012); I2 = 54%;**

**Test for overall effect: Z = -2.423 (P<0.015)**

**b)**



**Heterogeneity: τ2 = 0.057; χ2 = 57.748 df = 22 (P<0.0001); I2 = 62%;**

**Test for overall effect: Z = -7.969 (P<0.0001)**

*\*denotes SCIT studies*

**Figure 5: Meta-analysis of double-blind RCTs studies comparing medication scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)**



**Heterogeneity: τ2 = 0.074; χ2 = 110.337, df = 44 (P<0.0001); I2 = 60%;**

**Test for overall effect: Z = -6.502 (P<0.0001)**

*\*denotes SCIT studies*

**Figure 6: Meta-analysis of double-blind RCTs comparing medication scores between (a) SCIT and placebo groups and (b) SLIT and placebo groups (random-effects models)**

**a)**



**Heterogeneity: τ2 = 0.126; χ2 = 42.241, df = 15 (P<0.0001); I2 = 64%;**

**Test for overall effect: Z = -4.399 (P<0.0001)**

*\*denotes SCIT studies*

**b)**



**Heterogeneity: τ2 = 0.057; χ2 = 64.535, df = 28 (P<0.0001); I2 = 57%;**

**Test for overall effect: Z = -4.805 (P<0.0001)**

**Figure 7: Meta-analysis of double-blind RCTs studies comparing combined symptom and medication scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)**



**Heterogeneity: τ2 = 0.071; χ2 = 33.631, df = 14 (P<0.002); I2 = 58%;**

**Test for overall effect: Z = -4.997 (P<0.001)**

*\*denotes SCIT studies*

**Figure 8: Meta-analysis of double-blind RCTs comparing combined symptom and medication scores between (a) SCIT and placebo groups and (b) SLIT and placebo groups (random-effects models)**

**a)**



**Heterogeneity: τ2 = 0.096; χ2 = 23.777, df = 10 (P<0.008); I2 = 58%;**

**Test for overall effect: Z = -3.984 (P<0.0001)**

*\*denotes SCIT studies*

**b)**



**Heterogeneity: τ2 = 0.070; χ2 = 8.584, df = 3 (P<0.035); I2 = 65%;**

**Test for overall effect: Z = -2.648 (P<0.008)**

**Figure 9: Meta-analysis of double-blind RCTs comparing quality of life scores between SCIT and placebo groups (random-effects models)**



**Heterogeneity: τ2 = 0.186; χ2 = 28.432, df = 5 (P<0.0001); I2 = 82%;**

**Test for overall effect: Z = -1.764 (P<0.078)**