**Supplementary information**

**Table 1: Summary of study results**

| **Biomarker** | **Allergen** | **Immunologic response** | **Clinical outcome** | **Correlation** | **Tolerance** | **Number of treated patients** | **Type of study** | **Level of evidence** | **Material** | **Reference** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Domain i: IgE** |  |  |  |  |  |  |  |  |  |  |
| Total IgE | Grass | ↑ | Improved | n.r. | Not included | 472 | RDBPC | A | Serum | (145) |
|  | Grass | ↔ | Not reported | n.a. | Not included | 17 | RDBPC | A | Serum | (59) |
|  | Grass | ↑ | Improved | No correlation | Not included | 279 | Retrospective | D | Serum | (33) |
|  | Grass | ↔ | Improved | No correlation | Not included | 11 | PC | B | Serum | (42) |
|  | Grass | ↓ | Improved | n.r. | + | 22 | PC | B | Serum | (68) |
|  | Grass | ↓ | Improved | n.r. | Not included | 27 | PC | B | Serum | (146) |
|  | Grass | ↓ | Improved | n.r. | Not included | 702 | RDBPC | A | Serum | (147) |
|  | HDM | ↑Return to baseline after 3 months | Improved | No correlation | Not included | 34 | CC | C | Serum | (41) |
|  | HDM | ↔ | Improved | n.r. | Not included | 10 | RDBPC | A | Serum | (148) |
|  | HDM | ↑ | Improved | No correlation | Not included | 279 | Retrospective | D | Serum | (33) |
|  | HDM | ↑ | Improved | Correlation: decision point, 965kU/l; sensitivity, 90.7%; specificity, 54.9% | Not included | 185 | Retrospective | D | Serum | (35) |
|  | HDM | ↔ | Improved | n.r. | Not included | 32 | ROLPC | B | Serum | (36) |
|  | HDM | ↓ | Improved | n.r. | Not included | 43 | CC | C | Serum | (149) |
|  | HDM | ↔ | Improved | n.r. | Not included | 12 | RC | C | Serum | (94) |
|  | Birch | ↑ Return to baseline | Improved | No correlation | + | 30 | PC | B | Serum | (150) |
|  | Palm | ↔ | Improved | n.r. | Not included | 18 | RDBPC | A | Serum | (151) |
| sIgE | Grass | ↑ | Improved | No correlation | + | 156 | DBPC | A | Serum | (6) |
|  | Grass | ↑ | Improved | No correlation | Not included | 279 | Retrospective | D | Serum | (33) |
|  | Grass | ↑ | Improved | No correlation | Not included | 16 | RDBPC | A | Serum | (81) |
|  | Grass | ↑ | Improved | n.r. | Not included | 30 | RNBC | B | Serum | (82) |
|  | Grass | ↑ | Improved | n.r. | Not included | 18 | PC | B | Serum | (69) |
|  | Grass | ↔ | Improved | n.r. | Not included | 40 | RDBPC | A | Serum | (152) |
|  | Grass | ↑ | Stable | n.r. | Not included | 210 | RDBPC | A | Serum | (153) |
|  | Grass | ↔ | Improved | n.r. | Not included | 29 | RDBPC | A | Serum | (39) |
|  | Grass | ↔ | Improved | n.r. | Not included | 12 | RDBPC | A | Serum | (154) |
|  | Grass | ↓ | Improved | n.r. | Not included | 13 | RDBPC | A | Serum | (155) |
|  | Grass | ↔ | Improved | n.a. | Not included | 132 | RDBPC | A | Serum | (156) |
|  | Grass | ↔ | Improved | n.r. | Not included | 207 | RDBPC | A | Serum | (157) |
|  | Grass | ↔ | Improved | n.r. | Not included | 99 | RDBPC | A | Serum | (158) |
|  | Grass | ↔ | Improved | n.a. | Not included | 48 | RDBPC | A | Serum | (159) |
|  | Grass | ↔ | Improved | n.a. | Not included | 44 | RDBPC | A | Serum | (160) |
|  | Grass/ birch | ↔ | Improved | n.a. | Not included | 186 | RDBPC | A | Serum | (161) |
|  | HDM | ↔ | Improved | n.r. | Not included | 10 | RDBPC | A | Serum | (148) |
|  | HDM | ↑Return to baseline after 3 months | Improved | No correlation | Not included | 34 | CC | C | Serum | (41) |
|  | HDM | ↑ | Improved | No correlation | Not included | 279 | Retrospective | D | Serum | (33) |
|  | HDM | ↓ | Improved | n.r. | Not included | 31 | CC | C | Serum | (58) |
|  | HDM | ↑ | Improved | Correlation: decision point, 90.3kU/l; sensitivity, 70.9%; specificity, 55.8% | Not included | 185 | Retrospective | D | Serum | (35) |
|  | HDM | ↓ | Improved | n.r. | Not included | 32 | ROLPC | B | Serum | (36) |
|  | HDM | ↑ | Improved | n.r. | Not included | 42 | RDBPC | A | Serum | (162) |
|  | HDM | ↑ | Improved | n.r. | Not included | 54 | RDBPC | A | Serum | (163) |
|  | HDM | ↓ | Improved | n.r. | Not included | 20 | RDBPC | A | Serum | (164) |
|  | HDM | ↔ | Improved | n.a. | Not included | 45 | RDBPC | A | Serum | (165) |
|  | HDM | ↔ | Stable | n.a. | Not included | 16 | RDBPC | A | Serum | (166) |
|  | HDM | ↓ | Improved | n.r. | Not included | 33 | RPC | B | Serum | (167) |
|  | HDM | ↔ | Improved | n.r. | Not included | 15 | RDBPC | A | Serum | (112) |
|  | HDM | ↑ | Improved | n.r. | Not included | 55 | RDBPC | A | Serum | (168) |
|  | HDM | ↓ | Improved | n.r. | Not included | 12 | RC | C | Serum | (94) |
|  | HDM | ↔ | Improved | n.r. | Not included | 64 | RDBPC | A | Serum | (169) |
|  | HDM | ↔ | Improved | n.r. | Not included | 20 | RDBPC | A | Serum | (170) |
|  | HDM | ↔ | Improved | n.r. | Not included | 60 | RDBPC | A | Serum | (171) |
|  | Birch | ↑ Return to baseline | Improved | No correlation | + | 30 | PC | B | Serum | (150) |
|  | Birch | ↑ | Improved | n.r. | Not included | 24 | PC | B | Serum | (43) |
|  | Birch | ↔ | Improved | n.a. | Not included | 31 | RDBPC | A | Serum | (172) |
|  | Birch | ↔ | Improved | n.a. | Not included | 28 | RDBPC | A | Serum | (83) |
|  | Combined tree | ↔ | Improved | n.a. | Not included | 117 | RDBPC | A | Serum | (173) |
|  | Japanese Cedar | ↔ | Improved | No correlation | Not included | 43 | RSBPC | A | Serum | (174) |
|  | Alternaria | ↑ | Improved | n.r. | Not included | 15 | RDBPC | A | Serum | (175) |
|  | Palm | ↑ | Improved | n.r. | Not included | 18 | RDBPC | A | Serum | (151) |
|  | Cockroach | ↓ | Improved | n.r. | Not included | 50 | RDBPC | A | Serum | (176) |
| sIgE/tIgE | Grass | ↑ | Improved | Correlation: decision point, 16.2%; sensitivity, 97.2%; specificity, 88.1% | Not included | 279 | Retrospective | D | Serum | (33) |
|  | HDM | ↑ | Improved | Correlation: decision point, 16.2%; sensitivity, 97.2%; specificity, 88.1% | Not included | 279 | Retrospective | D | Serum | (33) |
|  | HDM | ↑ | Improved | Correlation: decision point, 6%; sensitivity, 82.9%; specificity, 50% | Not included | 185 | Retrospective | D | Serum | (35) |
|  | HDM | ↔ | Improved | No correlation | Not included | 32 | ROLPC | B | Serum | (36) |
| **Domain ii: IgG subtypes** |  |  |  |  |  |  |  |  |  |  |
| sIgG4 | Grass | ↑ | Improved | Correlation | + | 32 | Cross sectional | D | Serum | (84) |
|  | Grass | ↑ | Improved | n.r. | Not included | 472 | RDBPC | A | Serum | (145) |
|  | Grass | ↑ | Improved | n.r. | Not included | 189 | RDBPC | A | Serum | (177) |
|  | Grass | ↑ | Improved | n.r. | + | 282 | DBPC | A | Serum | (63) |
|  | Grass | ↑ | Not reported | n.a. | Not included | 17 | RDBPC | A | Serum | (59) |
|  | Grass | ↑ | Improved | n.r. | + | 145 | RDBPC | A | Serum | (178) |
|  | Grass | ↑ | Not reported | n.a. | Not included | 7 | Cross sectional | C | Nasal fluid | (179) |
|  | Grass | ↓ | Improved | n.r. | + | 20 | CC | C | Serum | (85) |
|  | Grass | ↑ | Improved | n.r. | Not included | 30 | RNBC | B | Serum | (82) |
|  | Grass | ↑ | Improved | Weak correlation MS  | Not included | 16 | RDBPC | A | Serum | (81) |
|  | Grass | ↑ | Improved | No correlation | + | 156 | DBPC | A | Serum | (6) |
|  | Grass | ↑ | Improved | n.r. | Not included | 28 | DBPC | A | Serum | (115) |
|  | Grass | ↑ | Improved | n.r. | + | 22 | PC | B | Serum | (68) |
|  | Grass | ↑ | Improved | Correlated with ratio sIgG4/sIgG1 | Not included | 11 | PC | B | Serum | (42) |
|  | Grass | ↑ | Improved | n.r. | Not included | 175 | RDBPC | A | Serum | (44) |
|  | Grass | ↑ | Improved | n.r. | Not included | 40 | RDBPC | A | Serum | (152) |
|  | Grass | ↑ | Stable | n.r. | Not included | 210 | RDBPC | A | Serum | (153) |
|  | Grass | ↑ | Improved | n.r. | Not included | 175 | RDBPC | A | Serum | (180) |
|  | Grass | ↑ | Improved | n.r. | Not included | 47 | RDBPC | A | Serum | (181) |
|  | Grass | ↑ | Improved | n.r. | Not included | 29 | RDBPC | A | Serum | (39) |
|  | Grass | ↓ | Improved | n.r. | Not included | 13 | RDBPC | A | Serum | (155) |
|  | Grass | ↑ | Improved | n.r.  | Not included | 132 | RDBPC | A | Serum | (156) |
|  | Grass | ↑ | Improved | n.r. | Not included | 207 | RDBPC | A | Serum | (157) |
|  | Grass | ↔temporary increase | Improved | n.r. | Not included | 99 | RDBPC | A | Serum | (158) |
|  | Grass | ↑ | Improved | n.r. | Not included | 36 | RDBPC | A | Serum | (182) |
|  | Grass | ↔ | Improved | n.a. | Not included | 48 | RDBPC | A | Serum | (159) |
|  | Grass | ↑ | Improved | n.r. | Not included | 27 | PC | B | Serum | (146) |
|  | Grass | ↑ | Improved | n.a. | Not included | 44 | RDBPC | A | Serum | (160) |
|  |  |  |  |  |  |  |  |  |  |  |
|  | Grass/ birch | ↑ | Improved | No correlation | Not included | 186 | RDBPC | A | Serum | (161) |
|  | Combined tree | ↑ | Improved | n.a. | Not included | 117 | RDBPC | A | Serum | (173) |
|  | Japanese Cedar | ↑ | Improved | No correlation | Not included | 43 | RSBPC | A | Serum | (174) |
|  | HDM | ↑ | Improved | Correlation responders/ non-responders | Not included | 34 | CC | C | Serum | (41) |
|  | HDM | ↑ | Improved | n.r. | Not included | 10 | RDBPC | A | Serum | (148) |
|  | HDM | ↔ | Improved | n.r. | Not included | 31 | CC | C | Serum | (58) |
|  | HDM | ↑ | Improved | n.r. | Not included | 42 | RDBPC | A | Serum | (162) |
|  | HDM | ↑ SCIT | Improved | n.r. | Not included | 10 | RDBPC | A | Serum | (164) |
|  | HDM | ↔ SLIT | Improved | n.r. | Not included | 10 | RDBPC | A | Serum | (164) |
|  | HDM | ↑ | Improved | Correlation | Not included | 45 | RDBPC | A | Serum | (165) |
|  | HDM | ↑ | Stable | n.a. | Not included | 16 | RDBPC | A | Serum | (166) |
|  | HDM | ↑ | Improved | n.r. | Not included | 33 | RC | C | Serum | (167) |
|  | HDM | ↑ | Improved | n.r. | Not included | 15 | RDBPC | A | Serum | (112) |
|  | HDM | ↑ | Improved | n.r. | Not included | 55 | RDBPC | A | Serum | (168) |
|  | HDM | ↔ | Improved | n.r. | Not included | 12 | RC | C | Serum | (94) |
|  | HDM | ↔ | Improved | n.r. | Not included | 20 | RDBPC | A | Serum | (170) |
|  | HDM | ↔ | Improved | n.r. | Not included | 60 | RDBPC | A | Serum | (171) |
|  |  |  |  |  |  |  |  |  |  |  |
|  | Birch | ↑ | Improved | Correlation, also with baseline sIgG4 | + | 30 | PC | B | Serum | (150) |
|  | Birch | ↑ | Improved | n.r. | Not included | 31 | RDBPC | A | Serum | (172) |
|  | Birch | ↑ | Improved | n.r | Not included | 217 | RDBPC | A | - | (131) |
|  |  |  |  |  |  |  |  |  |  |  |
|  | Birch | ↑ | Improved | n.a. | Not included | 98 | RDBPC | A | Serum | (183) |
|  | Birch | ↑ | Improved | n.a. | Not included | 28 | RDBPC | A | Serum | (83) |
|  |  |  |  |  |  |  |  |  |  |  |
|  | Alternaria | ↔ | Improved | n.r. | Not included | 15 | RDBPC | A | Serum | (175) |
|  | Palm | ↑ | Improved | n.r. | Not included | 18 | RDBPC | A | Serum | (151) |
|  | Cockroach | ↑ | Improved | Correlation sIgG4/sIgG1 | Not included | 50 | RDBPC | A | Serum | (176) |
| IgG1 | HDM | ↔ | Improved | n.r. | Not included | 31 | CC | C | Serum | (58) |
|  | HDM | ↔ | Improved | n.r. | Not included | 15 | RDBPC | A | Serum | (112) |
|  | HDM | ↑ | Improved | n.r. | Not included | 33 | RC | C | Serum | (167) |
|  | Grass | ↑ | Improved | Correlated with ratio sIgG4/sIgG1 | Not included | 11 | PC | B | Serum | (42) |
|  | Grass | ↑ | Improved | n.r. | Not included | 29 | RDBPC | A | Serum | (39) |
|  | Grass | ↑ | Improved | n.r. | Not included | 40 | RDBPC | A | Serum | (152) |
|  | Grass | ↑ | Improved | n.r. | Not included | 47 | RDBPC | A | Serum | (181) |
|  | Grass | ↑ | Improved | n.r. | Not included | 27 | PC | B | Serum | (146) |
|  | Grass | ↑ | Improved | n.r.  | Not included | 132 | RDBPC | A | Serum | (156) |
|  | Birch | ↑ | Improved | n.a. | Not included | 98 | RDBPC | A | Serum | (183) |
|  | Birch | ↑(SCIT) | Improved | n.r. | Not included | 31 | RDBPC | A | Serum | (172) |
|  | Palm | ↑ | Improved | n.r. | Not included | 18 | RDBPC | A | Serum | (151) |
|  | Cockroach | ↔ | Improved | Correlation sIgG4/sIgG1 | Not included | 50 | RDBPC | A | Serum | (176) |
| **Domain iii:** **Serum inhibitory activity for IgE** |  |  |  |  |  |  |
| IgE-BF | Grass | ↑ | Improved | Correlation | + | 156 | DBPC | A | Serum | (6) |
|  | Grass | ↑ | Improved | n.r. | Not included | 189 | RDBPC | A | Serum | (177) |
|  | Grass | ↑ | Improved | n.r. | + | 282 | DPBC | A | Serum | (63) |
|  | Grass | ↑ | Improved | n.r. | + | 145 | RDBPC | A | Serum | (178) |
|  | Grass | ↑ | Improved | n.r. | Not included | 30 | RNBC | A | Serum | (82) |
|  | Grass | ↑ | Improved | n.r. | Not included | 175 | RDBPC | A | Serum | (44) |
|  | Grass | ↑ | Improved | n.r. | Not included | 18 | PC | B | Serum | (69) |
|  | Grass | ↑ | Stable | n.r. | Not included | 210 | RDBPC | A | Serum | (153) |
|  | Grass | ↑ | Improved | n.r. | Not included | 175 | RDBPC | A | Serum | (180) |
|  | HDM | ↑ | Improved | n.r. | Not included | 54 | RDBPC | A | Serum | (163) |
| IgE-FAB | Grass | ↓ | Improved | n.r. | + | 32 | Cross sectional | C | Serum | (84) |
|  | Grass | ↓ | Improved | Correlation | + | 156 | DBPC | A | Serum | (6) |
|  | Grass | ↓ | Improved | n.r. | + | 22 | PC | B | Serum | (68) |
|  | Grass | ↓ | Improved | n.r. | Not included | 28 | DBPC | A | Serum | (115) |
|  | Grass | ↓ | Improved | n.r. | + | 282 | DPBC | A | Serum | (63) |
|  | Grass | ↓ | Improved | n.r. | Not included | 30 | RNBC | B | Serum | (82) |
|  | Grass | ↓ | Improved | n.r. | Not included | 18 | PC | B | Serum | (69) |
|  | Grass | ↓ | Improved | n.r. | Not included | 10 | RDBPC | A | Serum | (67) |
|  | Grass | ↓ | Not reported | n.a. | Not included | 7 | Cross sectional | C | Nasal fluid | (179) |
|  | Birch | ↓ | Improved | No correlation | Not included | 12 | RDBPC | A | Serum | (34) |
| **Domain iv:** **Basophil activation** |  |  |  |  |  |   |  |  |
| CD203c | Grass | ↓ | Improved | Correlation | + | 32 | Cross sectional | D | WB | (84) |
|  | Grass | ↓ | Improved | No correlation | Not included | 16 | RDBPC | A | WB | (81) |
|  | Grass | ↔ | Improved | No correlation | Not included | 45 | RDBPC | A | WB | (37) |
| ΔEC50 | Grass | ↓ | Improved | Correlation. | Not included | 18 | PC | B | WB | (69) |
| DOA | Grass | ↓ | Improved | Correlation | + | 32 | Cross sectional | D | WB | (84) |
| CD63 | Grass | ↓ | Improved | Correlation | + | 32 | Cross sectional | D | WB | (84) |
|  | Birch | ↓ | Improved | n.a. | Not included | 5 | RDBPC | A | WB | (83) |
|  | HDM | ↔ | Improved | No correlation | Not included | 34 | CC | C | WB | (41) |
| CD107a | Grass | ↓ | Improved | Correlation | + | 32 | Cross sectional | D | Serum | (84) |
|  | Grass | ↓ | Improved | n.a. | Not included | 30 | RDBPC | A | WB | (149) |
| **Domain v:****Cytokines and Chemokines** |  |  |  |  |  |  |  |
| IL-2R | Jap.Ced. | ↓ | Improved | Correlation | Not included | 22 | CC | C | Serum | (184) |
| IL-2 | HDM | ↓ | Improved  | n.r. | Not included | 15 | CC | C | Serum | (185) |
| IL-4 | HDM | ↓ | Improved | n.r. | Not included | 15 | CC | C | Serum | (185) |
|  | HDM | ↔ | Improved | n.r. | Not included | 12 | CC | C | PBMC | (94) |
|  | HDM | ↔ | Improved | n.r. | Not included | 32 | PC | B | PBMC | (36) |
|  | Grass | ↓ | Improved | Correlation | Not included | 20 | PC | B | PBMC | (186) |
|  | Grass | ↓ | Improved | No correlation | Not included | 45 | RDBPC | A | PBMC | (187) |
|  | Grass | ↓ | Improved | No correlation | Not included | 14 | PC | B | Nasal fluid | (105) |
|  | Ragweed | ↓ | Challenge Chamber  | No correlation | Not included | 18 | RDBPC | A | PBMC | (188) |
|  | Ragweed | ↓ | Improved | No correlation | Not included | 48 | CC | C | PBMC  | (126) |
|  | Jap ced. | ↓ | no symptom scores | n.r. | Not included | 22 | CC | C | PBMC  | (189) |
|  | Olea | ↔ | Improved | n.r. | Not included | 24 | CC | C | Nasal lavage; nasal biopsies;  | (111) |
|  | Dog | ↓ | Stable | n.r. | Not included | 21 | RDBPC | A | PBMC  | (190) |
| IL-4/IFNg ratio | HDM  | ↓ | Improved | Correlation | Not included | 32  | RPC | B | PBMC | (191) |
| IL-5 | Grass | ↓ | Improved | Correlation | Not included | 20 | PC | B | PBMC | (186) |
|  | Grass | ↓ | Improved | No correlation | Not included | 45 | RDBPC | A | Serum | (187) |
|  | Grass | ↔ | Improved | n.r. | Not included | 12 | RDBPC | A | PBMC | (192) |
|  | Grass | ↓ | Improved | Correlation | Not included | 9  | CC | C | PBMC | (193) |
|  | HDM | ↔ | Improved  | No correlation | Not included | 28 | RPC | B | PBMC | (194) |
|  | HDM | ↔ | Improved | n.r. | Not included | 32 | PC | B | PBMC | (36) |
|  | HDM | ↓; higher basal levels in SCIT-responders than in non-responders and AR | Improved  | Correlation | Not included | 34 | CC | C | PBMC | (41) |
|  | Ragweed | ↓ | Challenge Chamber  | No correlation | Not included | 18 | RDBPC | A | PBMC | (188) |
|  | Jap ced. | ↓ | no symptom scores | n.r. | Not included | 22 | CC | C | PBMC  | (189) |
|  | Dog | ↓ | Stable | n.r. | Not included | 21 | RDBPC | A | PBMC  | (190) |
|  | birch, alder, and hazel mix | ↓ | Improved | Correlation | Not included | 20 | RDBPC | A | PBMC | (195) |
| IL-5/IFNg ratio | HDM  | ↓ | Improved | Correlation | Not included | 32  | RPC | B | PBMC | (191) |
| IL-6 | HDM | ↓ | Improved  | n.r. | Not included | 15 | CC | C | Serum | (185) |
| IL-8 | HDM | ↓ | Improved  | n.r. | Not included | 15 | CC | C | Serum | (185) |
| IL-9 | Grass | ↓ | Improved | No correlation | Not included | 14 | PC | C | Nasal fluid | (105) |
|  | HDM | ↓; higher basal levels in SCIT-responders than in non-responders and AR | Improved  | Correlation | Not included | 34 | CC | C | PBMC | (41) |
|  | Parietaria judaica  | ↓ | Improved | No correlation | Not included | 29 | RCC | C | PBMC | (196) |
| IL-10 | HDM | ↑ | Improved | No correlation | Not included | 21 | RDBPC | A | Serum  | (164) |
|  | HDM | ↑ | Improved | Correlation | Not included | 13 | RDBPC | A | Serum  | (197) |
|  | HDM | ↑ | Improved  | n.r. | Not included | 15 | CC | C | Serum | (185) |
|  | HDM | ↑ | Improved  | Correlation | Not included | 9 | CC | C | Serum | (198) |
|  | HDM | ↑ | Improved | No correlation | Not included | 9 | CC | C | PBMC | (199) |
|  | HDM | ↑ | Improved | n.r. | Not included | 12 | CC | C | Serum | (94) |
|  | HDM | ↔ | Improved | n.r. | Not included | 32 | PC | B | PBMC | (36) |
|  | HDM | ↔ | Improved  | No correlation | Not included | 28 | RPC | B | PBMC | (194) |
|  | Grass | ↑ | Improved | No correlation | Not included | 45 | RDBPC | A | PBMC | (187) |
|  | Grass | ↑ | Improved | No correlation | Not included | 12 | RDBPC | A | PBMC | (192) |
|  | Grass | ↓↔ | Improved | Correlation | Not included | 20 | PC | B | PBMC | (186) |
|  | birch, grass, birch and grass | ↑ | Improved | Correlation | Not included | 30 | CC | C | PBMC  | (200) |
|  | birch, alder and hazel mix | ↑ | Improved  | No correlation | Not included | 20 | RDBPC | A | PBMC | (201) |
|  | Ragweed | ↑ | Improved | No correlation | Not included | 48 | CC | C | PBMC  | (126) |
|  | Jap. cedar  | ↑ | Improved | No correlation | Not included | 19 | CC | C | PBMC | (202) |
|  | birch, alder, and hazel mix | ↑ | Improved | Correlation | Not included | 20 | RDBPC | A | PBMC | (195) |
|  | Olea | ↔ | Improved | n.r. | Not included | 24 | CC | C | Nasal lavage; nasal biopsies;  | (111) |
|  | Dog | ↓ | Stable | n.r. | Not included | 21 | RDBPC | A | PBMC  | (190) |
| IL-13 | Grass | ↓ | Improved | Correlation | Not included | 20 | PC | B | PBMC | (186) |
|  | Grass | ↓ | Improved | n.r. | Not included | 14 | PC | B | Nasal fluid | (105) |
|  | HDM | ↔ | Improved  | n.r. | Not included | 28 | RPC | B | PBMC | (194) |
|  | HDM | ↓ | Improved  | Correlation | Not included | 34 | CC | C | PBMC | (41) |
|  | HDM | ↔ | Improved | n.r. | Not included | 32 | PC | B | PBMC | (36) |
|  | Ragweed | ↓ | Challenge Chamber  | No correlation | Not included | 18 | RDBPC | A | PBMC | (188) |
| IL-13/IFNg ratio | HDM  | ↓ | Improved | Correlation | Not included | 32  | RPC | B | PBMC | (191) |
| IL-17 | birch, alder and hazel mix | ↑ | Improved  | Correlation | Not included | 20 | RDBPC | A | PBMC | (201) |
| IL-18 | HDM | ↑ | Improved | Correlation | Not included | 13 | RDBPC | A | Serum  | (197) |
|  | birch, grass, birch and grass | ↑ | Improved | Correlation | Not included | 30 | CC | C | PBMC | (200) |
| IFN-y | Grass | ↑ | Improved | Correlation | Not included | 20 | PC | B | PBMC | (186) |
|  | Grass | ↔ | Improved | n.r. | Not included | 12 | RDBPC | A | PBMC | (192) |
|  | HDM  | ↑ | Improved | Correlation | Not included | 32  | RPC | B | PBMC | (191) |
|  | HDM | ↑ | Improved | No correlation | Not included | 12 | CC | C | PBMC | (94) |
|  | HDM | ↔ | Improved | n.r. | Not included | 32 | PC | B | PBMC | (36) |
|  | HDM | ↔ | Improved | n.r. | Not included | 13 | RDBPC | A | Serum  | (197) |
|  | HDM | ↔ | Improved  | n.r. | Not included | 15 | CC | C | Serum | (185) |
|  | HDM | ↔ | Improved | n.r. | Not included | 21 | RDBPC | A | Serum/ nasal  | (164) |
|  | HDM | ↔ | Improved  | Correlation | Not included | 28 | RPC | B | PBMC | (194) |
|  | Dog | ↔ | Stable | n.r. | Not included | 21 | RDBPC | A | PBMC  | (190) |
| TGF-B | HDM | ↔ | Improved | n.r. | Not included | 32 | PC | B | PBMC | (36) |
|  | HDM | ↔ | Improved  | n.r. | Not included | 28 | RPC | B | PBMC | (194) |
|  | HDM | ↔ | Improved | n.r. | Not included | 12 | CC | C | PBMC | (94) |
|  | birch, grass, birch and grass | ↔ | Improved | Correlation | Not included | 30 | CC | C | PBMC | (200) |
|   | birch, alder and hazel mix | ↑ | Improved  | No correlation | Not included | 20 | RDBPC | A | PBMC | (201) |
|  | Dog | ↑ | Stable | No correlation | Not included | 21 | RDBPC | A | PBMC  | (190) |
| TNF-a | HDM | ↓ | Improved  | n.r. | Not included | 15 | CC | C | PBMC | (185) |
| CCR3 | Birch | ↔SCIT, ↑AR | Improved | No correlation | Not included | 16 | RDBPC | A | nasal biopsies  | (97) |
| CCR3 | Birch | ↑SCIT, ↑AR | Improved | n.a. | Not included | 16 | RDBPC | A | nasal biopsies  | (97) |
| apolipoprotein A-I | Jap. cedar | ↑ | Improved | Correlation | Not included | 15 | RPC | B | Serum | (99) |
| C4a | Jap. cedar | ↑ | Improved | No correlation | Not included | 15 | RPC | B | Serum | (99) |
| Eosinophil cationic protein ECP | Jap. cedar | ↔ | n.r. | n.a. | Not included | 47 | CC | C | Serum | (104) |
| Eotaxin | Grass | ↓ | Improved | No correlation | Not included | 14 | PC | B | Nasal fluid | (105) |
| MCP-1 | HDM | ↓ | Improved  | n.r. | Not included | 15 | CC | C | Serum | (185) |
| Transthyretin | Jap. cedar | ↑ | Improved | No correlation | Not included | 15 | RPC | B | Serum | (99) |
| Tryptase | Grass | ↔ | Improved | No correlation | Not included | 14 | PC | B | Nasal fluid | (105) |
| thymus and activation-regulated chemokine (TARC) | birch | ↑ | Improved |  |  | 16 |  |  | nasal biopsies IHC | (97) |
| **Domain vi:****Cellular markers** |  |  |  |  |  |  |  |  |  |  |
| Treg(FOXP3) | HDM | ↑ | Improved | n.r. | Not included | 15 | RDBPC | A | Serum | (112) |
|  | Grass | ↑ | Improved | n.r. | Not included | 9 | CC | C | Nasal mucosa | (114) |
|  | Grass | ↑ | Improved | n.r. | Not included | 28 | DBPC | A | Sublingual biopsy | (115) |
|  | Ragweed | ↔ | Improved | No correlation | Not included | 48 | CC | C | PBMC  | (126) |
| CQ10 | Grass | ↑ | Improved | Correlation with responders | Not included | 41 | RDBPC | A | Serum | (123)  |
| **Domain vii:****In vivo biomarker** |  |  |  |  |  |  |  |  |  |
| ***Provocation tests*** |  |  |  |  |  |  |  |  |  |  |
| ICAM-1 | HDM | ↓ | Improved | n.r | Not included | 10 | RDBPC | A | Conjuntical epithelium | (128) |
| Eosinophils | HDM | ↓ | Improved | n.r | Not included | 10 | RDBPC | A | Conjuntical epithelium | (128) |
| Neutrophils | HDM | ↓ | Improved | n.r | Not included | 10 | RDBPC | A | Conjuntical epithelium | (128) |
| ***ECC*** |  |  |  |  |  |  |  |  |  |  |
| Symptom score | Grass | ↓ | Improved | n.r | Not included | 52 | RDBPC | A | - | (141) |
| Symptom score | HDM | ↓ | Improved | n.r | Not included | 118 | RDBPC | A | - | (142) |
| Symptom score | Cat | ↓ | Improved | n.r | Not included | 52 | RDBPC | A | - | (129) |
| ***TNPT*** |  |  |  |  |  |  |  |  |  |  |
| Symptom score | Grass | ↓ | Improved | n.r | Not included | 14 | RDBPC | A | - | (105) |
| Symptom score | Birch | ↓ | Improved | n.r | Not included | 217 | RDBPC | A | - | (131) |

n.r.: not reported; n.a.: not applicable

WB: Whole blood

**Table 2: Study overview**

| **Study** | **Type** | **Adult/ Child** | **Subjects\*** | **Allergen** | **Biomarkers tested** | **Clinical outcome** | **Duration** |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |
|  (82) Aasbjerg *et al 2014* | RNBC | Adults | SCIT: 15SLIT: 15SAR: 10 | SCIT: Phleum pratense; AlutardSLIT: Phleum pretense, Grazax | sIgG4sIgEIgE-FABBATIgE-BF | Nasal challenge improved | 15 months |
| (182) Amar  *et al 2009* | RDBPC | Adults | SLIT (mono): 19SLIT (multi): 17SARP: 17 |  Mono: Phl p 5Multi: Phl p5 + 9 additional pollen | sIgG4IFN-y | Symptom score improvedMedication score improved | 1 year |
| (155) Ariano *et al 1999* | RDBPC | Adults/ children | SCIT: 13SARP: 12 | SIT (Purethal) | sIgEsIgG4 | Symptom score improvedMedication score improved | 3 years |
| (58) Bahceciler *et al 2005* | CC | Children | SLIT (6 months): 17SLIT (12 months): 14NAC: 8 | D. Pteronys./ D. Farinae. Staloral | sIgG4sIgEsIgG1sIgA | Symptom score improved only in 12 months groupMedication score improved in 12 months group | 1 year |
| (185) Barberi et al, 2011 | CC | Child | SLIT+D: 15(drugs on demand)ARD: 15 | SLIT: HDM Staloral, Stallergenes | IL-4IL-10IL-2, IL-6, IL-8TNFa, MCPIFNg | VASSMS | 2 years |
| (180) Blaiss *et al 2011* | RDPBC | Adults/ children | SLIT: 142SARP: 140 | Phleum prat (Schering-Plough) | sIgG4IgE-BF | TCS (total combined score) improvedRQLQ: Improved | 23 weeks |
| (187) Bonvalet et al., 2012  | RDBPC | Adult | SLIT: 45ARP: 44 | five-grass pollenextract (Stallergenes SA) | IL-4IL-10 | TSSChallenge chamber | 2-4 months |
| (162) Bousquet *et al 1999* | RDBPC | Adults | SLIT:42AAP: 43 | Der p1, der f1 | sIgEsIgG4 | Asthma scores improvedMedcation scores improvedQoL improved | 25 months |
| (166) Bush *et al* | RDBPC | Adults | SLIT (high dose): 9SLIT (low dose): 7ARP | Der f | sIgEsIgG4 | Symptom scores and medication score stable | 18 months |
| (188) Campbell et al, 2010 | RDBPC | Adult | SCIT: 17ARP: 15 | Ragweed: Amb a 1-imm-unostimulatoryoligodeoxynucleotide conjugate | IL-4IL-5IL-13IFNg | Challenge chamber | 7 months |
| (83) Ceuppens *et al 2009* | RDBPC | Adults | SCIT: 28SARP: 30 | Birch pollen extract | sIgEsIgG4sIgGBAT-CD63 (n=5) | CIS eye en nose improved | 18 months |
| (151) Chakraborty *et al 2006* | RDBPC | Adults | SCIT: 18SARP: 17 | P Sylvestris | IgEsIgEsIgG4sIgG1 | Symptom scores improvedMedicaiton scores improved | 2 years |
| (198) Ciprandi et al, 2006 | CC | adult | SLIT HDM: 9AR: 10  | HDM: Staloral | IL-10 | FEV(25-75) | 3 years |
| (199) Ciprandi et al, 2007 | CC | adult | SLIT HDM: 9AR: 10NAC: 9 | SLIT HDM, Staloral | IL-10 | NSSRhinomanometry | 3 years |
| (196) Ciprandi et al, 2011 | RDBPC | adult | SLIT: 29, ARD: 34 | Parietaria judaica pollen allergen extract (Anallergo, Florence, Italy) | TGF-b | VASNSMS | 3 months preseasonal |
| (175) Cortellini *et al 2010* | RDBPC | Adults | SLIT: 15ARP | Alternaria (Anallergo) | sIgEsIgG4 | Symptom score improvedMedication scores improved | 10 months |
| (163) Corzo *et al 2014* | RDBPC | Adults/ children | SLIT: 54AAP | Der p, der f | sIgEgE-BF | Medicatio score improved | 2 weeks |
| (94) Cosmi *et al 2006* | RC | Adults | SLIT: 12AR: 13 | DP and D far. LAIS | IgEsIgEsIgG4IL-10IFN-y | Symptom score improvedMedication score improved | 18 months |
| (157) Cox *et al 2012* | RDBPC | Adults | SLIT: 207SARP: 223 | Dact gl, dact gl, l per, Phl prat, Poa prat | sIgEsIgG4 | Combined symptom score improvedRQLQ improve | 8 months |
| (177) Dahl *et al. 2008* | RDBPC | Adults | SLIT: 189SAR: 162 | Phleum pretense, Grazax | sIgG4IgE-BF | Symptom scores improvedRQLQ improved | 2 years |
| (33) Di Lorenzo *et al 2009* | Retrospective | Adult | SCIT: 76SLIT: 203Responders vs non-responders | Grass (P. judaica, O Europea)HDM (D. Pteronys./ D. Farinae) | IgEsIgEIgE-ratio | VAS improvedROC curve | n.a. |
| (145) Didier *et al. 2007* | RDBPC | Adults | SLIT (100 IR): 157SLIT (300 IR): 155SLIT (500 IR): 160SAR: 156 | 5 grass pollens | sIgG4IgE | RTSS improvedRescue medication lowerRQLQ improved | 6 months |
| (178) Durham *et al 2010* | RDBPC | Adults | SLIT: 145SARP: 145 | Phleum pretense, Grazax | sIgG4IgE-BF | DSS improvedMDS improvedRQLQ improved | 3 years |
| (147) Durham *et al.* | RDBPC | Adults | SLIT:702SARP: 153 | Phl. P (Grazax) | IgEIgE | Symptom score improvedMedication score stable | 18 weeks |
| (63) Durham *et al. 2012* | DBPC | Adults | SLIT: 282 – 137\*\*\*SARP: 286 - 104 | Phleum pretense, Grazax | sIgG4IgE-FABIgE-BF | DSS improvedMDS improvedRQLQ improved | 5 years |
| (36) Eifan *et al. 2010* | ROLPC | Children | SCIT 16SLIT 16ARP: 16 | SLIT and SCIT: D. Pteronys./ D. Farinae, ALK | IgEsIgEIgE-ratioIL10TGF-beta | TASS, TRSS, TSS, TMS, VAS score improved | 1 year |
| (193) Francis et al, 2007 | CC | Adult | SCIT: 9 (high dose)AR: 9NAC: 9All: 34 (blood and nasal biopsies) | High dose grass pollen SCIT | IL-4IFNg | SS | 2 years |
| (192) Francis et al, 2008 | RDBPC | Adult | SCIT: 12ARP: 6 | SCIT Alutard grass | IL-10IgG4IgA | SSProvocation | 2 years |
| (42) Gehlar *et al 1999* | PC | Children | SCIT: 11SAR: 9 | Novo-Helisen depot, allergopharma | sIgG4sIgG1sIgG2IgE | Symptom score (analogue and questionnaire) improvedVAS improved | 1 year |
| (41) Gomez *et al 2015* | CC | Adults | SCIT: 34SAR: 14 | Acaroid, Allergopharma | sIgG4sIgEIgEBAT-CD63 | 82.3% responders17.7% non responders | 1 year |
| (172) Hoiby *et al 2010* | RDBPC | Adults/ children | SCIT: 31ARP: 30 | Bet alba (depigoid) | sIgEsIgG4sIgG1IL-4,10,12,13. | Symptom score improvedMedication score improved | 2 year |
| (141) Horak *et al. 2009* | RDBPC | Adults | SLIT: 45SARP: 44 | 300-IR 5 grass | ECC | Symptom scores | 4 months |
| (174) Horichuchi *et al 2008* | RSBPC | Adult | SLIT: 43SARP: 24 | Cedar pollen extract | sIgG4sIgE | Nasal symptom scores improved | 6 months |
| (68) James *et al. 2011* | PC | Adults | SCIT only: 9 SCIT + placebo: 6 SCIT + SCIT: 7 | Phleum pratense; Alutard | sIgG4sIgEIgE-FAB | Combined symptom and medication scores improved | 2+2 years \*\* |
| (39) Jutel *et al 2005* | RDBPC | Adults | SCIT: 29SAR: 28 | Phl prat | sIgEsIgG4sIgG1 | Sympton score improvedMedication score improvedRQLQ improved | 6 months |
| (165) Keles *et al 2011* | RDBPC | Children | SCIT: 15SLIT: 15SLIT + SCIT: 15ARP | Der p, der f (ALK) | sIgEsIgG4TGF-BIFN-y | VAS improvedMedicaiton scores improved | 1 year |
| (111) Kirmaz et al, 2011 | CC | adult | SCIT Olea: 24ARD: 15 | Allergopharma Novo-Helisen Depot | IL-4IL-10IFNg | NSS | 1 years |
| (146) Keskin *et al 2006* | PC | Children | SCIT: 27SAR: 26 | Grass pollen (Allergovit) | IgEsIgG4sIgG1 | Rhinitis symptom and medication score improved | 27 months |
| (152) Klimek *et al 2012* | RDBPC | Adults | SCIT: 40SARP: 10 | rPhl p1, rPhl p2, rPhl p5a, rPhl p5b, rPhl p6 | sIgEsIgG4sIgG1 | CPT improved | 1 month |
| (190) Lent et al, 2006 | RDBPC | Adult | SCIT 21 (3 dosage groups)ARP: 7 | AP dog (cluster): (Hollister-Stier Laboratories)  | IL-4IL-5IL-10IFNgTGF-b | SSS (Bousquet) | 5 weeks |
| (35) Li *et al. 2014* | Retrospective | Children | SCIT: 185 | D. Pteronys, alutard | IgEsIgEIgE-ratio | Symptom scores improvedROC curve | n.a. |
| (148) Lue *et al 2006* | RDBPC | Children | SLIT: 10ARP: 10 | D. Pteronys./ D. Farinae. Staloral | sIgG4IgEsIgE | Symptom score improvedMedication score improvedSkin prick test showed no difference | 6 months |
| (99) Makino et al, 2010 | RPC | adult | SLIT Jap cedar: 15ARP: 9 (1 withdrawal) | Jap. cedar pollen extract, manufacturer | C4a | SMSQoL | before and during pollen season |
|  (130) Meyer *et al. 2013* | RDBPC | Adults | SCIT: 30SARP: 7 | rBET v 1-FV | ECC | Sympton scores | 10 weeks |
| (194) Moed et al, 2013 | RPC | Child | SLIT: 28ARP: 30 | HDM, Artu Biologicals Europe B.V. | IL-5IL-13IL-10TGF-b | SPTNSS, ASSEye SS | 2 years |
| (159) Mosges *et al 2007* | RDBPC | Adults | SLIT: 48SARP: 53 | Staloral | sIgEsIgG4 | Medication score improvedSymptom core improved | 9 months |
| (150) Moverare *et al 2001* | PC | Children/ Adults | SCIT: 30SAR: 16 | Birch and timothy pollen extract (ALK) | sIgG4IgEsIgEsIgG | Symptom score improvedMedication score improved | 3 year |
| (43) Moverare *et al 2002* | PC | Children/ Adults | SCIT: 24SAR: 15 | Birch pollen Aquagen | sIgE | Symptom scores improved | 3 years |
| (202) Murakami et al, 2014 | CC | Adult | OIT: 19ARD: 10 | OIT Jap cedar: Cry j 1-galactomannan conjugate (Wako Filter Technology Ltd, Ibaraki, Japan | IL-10IgG4 | NSMSEye SMS | 5 months |
| (44) Nelson *et al 2011* | RDBPC | Adults | SCIT: 175SARP: 192 | Phleum pretense: Schering-Plough | sIgG4IgE-BF | Symptom scores improvedMedication scores improvedRQLQ improved | 6 months |
| (142) Nolte *et al. 2015* | RDBPC | Adults | SLIT: 118 (2 doses)ARP: 42 | MK-8237 | ECC | Symptom scores | 24 weeks |
| (189) Nomura et al, 2013 | open-label controlled  | child and adult | SCIT Jap cedarSCIT: 22, AR: 6 | SCIT: rush followed by maintenance schedule, Japanese cedar extract (Torii Pharmaceutical,Tokyo, Japan). | IL-4IL-5 | None | n.r. |
| (112) O’Hehir *et al 2009* | RDBPC | Adults | SLIT: 15SARP: 15 | Staloral | sIgEsIgG4sIgG1sIgATreg (FOXP3) | Symptom score improvedMedication score improvedVAS improved | 2 years |
| (104) Ohashi, Nakai et al, 1997  | CC | Adult | SCIT: 47ARD: 34 | SCIT: Jap. cedar | ECP | None | 2-3 years |
| (184) Ohashi, Tanaka et al, 1997  | CC | Adult | SCIT: 47ARD: 34 | SCIT: Jap.cedar | IgEIL2R | None | 1 season |
| (158) Ott *et al. 2009* | RDBPC | Adults/ childs | SLIT: 99SARP: 46 | Phl. Prat (Staloral) | sIgEsIgG4 | Combined symptom score improved, also after cessation | 1 year |
| (37) Overtvelt *et al 2011* | RDBPC | Adults | SLIT number of patients not reported | Stallergenes | CD203c | ARTSS improved | 4 months |
| (149) Ozdemir  *et al 2007* | CC | Children | SLIT: 43AAP: 23 | Der p, der f (Stallergenes) | IgE | Medication score improved | 3 years |
| (81) Ozdemir *et al 2014* | RDBPC | Adults | SCIT: 16SARP: 15 | 6 grass pollen extract: Allergovit | sIgG4sIgEBAT-CD203c | ARTSS no differenceRescue medication score improvedACS improvedRQLQ improved | 4 months |
| (170) Pajno *et al 2000* | RDBPC | Children | SLIT: 12AAP: 12 | Der p1, der p2 (ALK) | sIgEsIgG4sIgG | Symptom score improvedMedication use decreased | 2 years |
| (128) Passalacqua *et al. 2008* | RDBPC | Adult | SLIT: 10SARP: 9 | Der P, D Far LAIS | ICAM-1EosinophilsNeutrophils | Symptom scores | 2 years |
|  (129) Patel *et al. 2013* | RDBPC | Adults | SCIT: 52ARP: 21 | Cat-PAD | ECC | Symptom scores | 1 year |
|  |  |  |  |  |  |  |  |
| (183) Pauli *et al*  | RDBPC | Adults | SCIT: 98SARP 36 | nBETv1rBETv1Birch | sIgG4, sIgG1, sIgG2 | Combined symptom en medication score improved | 2 years |
| (173) Pfaar *et al 2010* | RDBPC | Adults | SCIT: 117SARP: 40 | Co rave, aln glut, bet alba | sIgEsIgG4 | Combined symptom en medication score improved | 18 months |
| (161) Pfaar *et al* 2013 | RDBPC | Adults | SCIT: 186SARP: 99 | Bet. Ver. (50%)Dact gl, fest gl, l per, Phl prat, Poa prat (50%) | sIgEsIgG4 | Combined symtpm and medication score improvedQoL improved | 2 years |
| (131) Pfaar *et al. 2016* | RDBPC | Adults | SLIT: 217 (3 doses)SARP: 52 | SB | IgG4 | PNIFTNPTSymptom scores | 5 months |
| (168) Pham-Thi *et al 2007* | RDBPC | Children | SLIT: 55AAP: 56 | Der p, der f (Stallergenes) | sIgEsIgG4 | Medication score stableQoL improved | 18 months |
| (126) Piconi et al, 2010 | CC | adult | SLIT1 preseasonal 18SLIT seasonal: 17SLIT prologued: 13ARD: 12 | ragweed: Staloral (Stallergen SA) | IL-4IL-10IgG4PCDL-1Tregs (FOXP3) | VASSMS | 3 years |
| (97) Plewako et al, 2008 ; Follow up of (203) Arvidsson MB et al, 2002 | RDBPC | adult | SCIT (+D): (3 years after treatment): 16ARD: 12 | Birch: Alutard SQ Betula verrucosa (ALK, Hoersholm, DK) | CCR3 | NSMS | 3 years |
| (191) Potter et al, 2015 | RPC | adult | SLIT HDM 32/34 completedAR: 16/21 completed | SLIT HDM, Der.p; Staloral, Stallergenes | IL-5/IFNgIL-13/IFNgIL-4/IFNg | TSS5QoL | 2 years |
| (181) Purohit  *et al 2008* | RDBPC | Adults | SCIT: 47SARP: 37 | Bet v 1 clone | sIgG4sIgG1 | Combined symptom medication score improved | 5 months |
| (114) Radulovic *et al 2009* | CC | Adults  | SCIT: 9SAR: 13NAC: 9  | Alutard SQ | Treg (FOXP3) in nasal mucosa | Symptom scoreSkin response | 2 years |
|  |  |  |  |  |  |  |  |
| (153) Reich *et al 2011* | RDBPC | Adults | SCIT: 210SARP: 52 | Phleum pratanse Grazax | sIgEsIgG4IgE-BF | Symtpom score stable (before pollen season) | 10 weeks |
| (59) Rolinck- Werninghaus *et al 2005* | RDBPC | Children | SLIT: 17SARP: 12 | 5-grass mixture Dactylis glomerata, Festuca praten- sis, Lolium perenne, Phleum pratense and Poa pratensis; Pangramin | sIgG4IgE | Not reported | 2 years |
| (179) Saleem *et al. 2013* | Cross sectional | Adults | SLIT: 7SAR: 7NAC: 8 | Not reported | sIgG4IgE-FAB | Not reported | n.a. |
| (200)Savolainen et al, 2004 | CC | adult | SCIT birch: 18SCIT grass: 6SCIT birch+grass: 6AR: 10NAC: 10 | SCIT Alutard SQ birch, grass, or birch+grass, (ALK Abello, H**oe**rsholm, Denmark)conventional or rush | IL-10IL-18 | VASSMS | 5-15 weeks and 1-2 years after |
| (195) Savolainen et al, 2006 | RDBPC | child: A:  | SLIT (low dose): 10SLIT (high dose): 10ARP: 10 | SQ-standardized tree pollen extract: birch, alder, hazel mix | IL-5IL-10TGF-b | SMS | 2 years |
| (115) Scadding  *et al. 2010* | DBPC | Adult | SLIT: 28SARP: 28NAC: 8 | Phleum pratense; Alutard | sIgG4IgE-FabIgA2Treg (FOXP3) | Symptom score improvedDecreases LPR | 18 months |
| (105) Scadding et al, 2015 | PC | adult  | SCIT grass: 14AR: 14, NAC: 14 | SCIT Grass Phl.p; Aquagen SQ, or Grazax, ALK-Abello, Hørsholm, Denmark | IL-4IL-9EotaxinPNPT | SSPNIF | at least 6 months |
| (69) Schmid *et al. 2014* | PC | Adults | SCIT: 18SAR: 6 | Grass pollen | sIgEIgE-FABIgE-BFBAT-CD63ΔEC50 | Somptom score improvedSkin prick test improvedNasal challenge improved | 1 year |
| (186) Schulten et al, 2014 | PC | adult  | SCIT: 40AR: 40 | SCIT grass pollen extract (Phl p) | IL-4IL-5IgEIgG4 | Questionair | 1 year |
| (6) Shamji *et al. 2012* | DBPC | Adults | SCIT (l): 54SCIT (h): 112SARP: 55 | Phleum pratense; Alutard(l) 10.000 SQ-U(h) 100.000 SQ-U | sIgG4sIgEIgE-FABIgE-BF | Combined symptom and medication scores improved | 8 months |
| (84) Shamji *et al. 2015* | Cross sectional | Adults | SCIT: 14SLIT: 12SLIT-TOL: 6SAR: 24NAC: 12 | SCIT: Phleum pratense; AlutardSLIT: Grazax | sIgG4IgE-FABBAT-DOABAT-CD63BAT-CD107A | RTSS improved | n.a. |
| (160) Smith *et al 2004* | RDBPC | Adults | SLIT: 44SARP: 45 | Timothy grass (stallergenes) | sIgEsIgG4 | Symptom score improved | 2 years |
| (176) Srivastava *et al 2011* | RDBPC | Adults | SCIT: 50ARP: 50 | P. Americana (cockroach) | sIgEsIgG4sIgG1 | Symptom scores improvedMedication score improved | 2 years |
| (154) Tepas *et al 2004* | RDBPC | Adults | SLIT:12SARP: 12 | Timothy grass microbeads | sIgEsIgG | Combined symptom and medication score improved | 10 weeks |
| (67) Wachholz *et al 2003* | RDBPC | Adults | SCIT: 10ARP: 8 | Phleum pretense, ALK | IgE-FAB | Sympton scores improveMedication scores improved | 1 year |
| (156) Wahn  *et al 2012* | RDBPC | Children | SLIT: 132SARP: 47 | Dact gl, fest gl, l per, Phl prat, Poa prat | sIgEsIgG4sIgG1 | Symptom-medication score improved | 1.5 years |
| (169) Wang *et al 2006* | RDBPC | Adults | SCIT: 64AAP: 65 | D. pter (ALK) | sIgE | Peak flow improved | 1 year |
| (171) Wang *et al 2013* | RDBPC | Adults/ children | SLIT: 60ARP: 60 | D pter d far | sIgEsIgG4 | Symptom score improvedVAS improved | 24 weeks |
| (34) Wurtzen *et al 2008* | RDBPC | Adults | SCIT: 21SARP: 21 | Bet. Verrucosa, Alutard | IgE-FAB | Medication score improvedSymptom score trend | 2 years |
| (164) Yukselen *et al 2012* | RDBPC | Children | SCIT: 10SLIT: 10ARP: 10 | D. pt D f. (Novohelisen) | sIgEsIgG4IL10 | RSS ASS (symptom score) improvedRMS, AMS (medication scores) improved | 1 year |
| (197)Yukselen et al, 2013 | RDBPC | Child | SCIT (+D): 6/9 completedSLIT (+D): 7/8 completedARP (+D): 10 | SCIT and SLIT: D.p.+D.f. 50/50, NovoHelisen Depot and Oral, Allergopharma | IL-10IgG4IgE | VASNSMSASMSNasal provocation | 2 years |
| (85) Zidarn *et al 2015* | CC | Adults | SCIT: 20SAR: 13 | Purethal Mixed Grasses,HAL Allergy | sIgG4BAT-CD63 | Symptom score improvedRQLQ improved | 7 years |
| (167) Zielen  *et al 2010* | RC | Children | SCIT: 33AAP: 32 | D. pter (allergopharma) | sIgEIgG4IgG1 | Medicaiton score improved | 2 years |
|  (123) Zimmer *et al. 2012* | RDBPC | Adults | SLIT: 41SARP: 38 | n.r. | C1QSTAB1 | Symptom score | 4 months |
|  |  |  |  |  |  |  |  |

\* NAC: Nonatopic control subject, SCIT: SCIT treated patients, SLIT: SLIT treated patients, SLIT-TOL: participants who completed 3 years of SLIT treatment, SAR: untreated seasonal allergic rhinitis, SARP untreated seasonal allergic rhinitis receiving placebo, ARP untreated allergic rhinitis receiving placebo, AAP allergic asthma receiving placebo

\*\* 22 patients received SCIT for 2 years, after 2 years 13 patients continued, 6 received placebo and 7 SCIT

\*\*\* Number of patients entering the study – number of patients after 5 years

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