

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

Modified absorbed grass pollen/Phleum pratense

**Grass allergen for diagnosis and treatment
of Type-I allergy**

DK/W/005/pdWS/001

Rapporteur:	Denmark
Start of the procedure (day 0):	28-07-2009
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Date re-start procedure (day 90):	12-05-2010
Deadline for CMS's comments (day 115):	06-06-2010
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Alutard SQ, ALK-Abelló Aquagen SQ, ALK-Abelló Soluprick SQ, ALK-Abelló Purethal Pollen, HAL Allergy Novo-Helisen Depot, Allergopharma Novo-Helisen Oral, Allergopharma Intracutaneous Test Solution, Allergopharma Provocation Test Solution, Allergopharma Skin Prick Test Solution, Allergopharma Allergovit, Allergopharma
INN (or common name) of the active substance(s):	Grass pollen
MAH(s):	ALK-Abelló Hal Allergy Allergopharma Joachim Ganzer KG
Pharmaco-therapeutic group (ATC Code):	V01AA02
Pharmaceutical form(s) and strength(s):	Suspension for injection, 10-100000 SQ U/ml Suspension for subcutaneous injection, 500 µg/ml Suspension for subcutaneous injection, 5 TU/ml, 50 TU/ml, 500 TU/ml, 5,000 TU/ml, 1,000 TU/ml, 10, 000 TU/ml Oral solution, 1 TU/ml, 10 TU/ml, 100 TU/ml, 1,000 TU/ml Oral lyophilisate, 75000 SQ-T

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I. EXECUTIVE SUMMARY

The MAH's for approved products for diagnosis and treatment of Type-I allergy to grass pollen (ALK-Abelló, Hal allergy and Allergopharma) have submitted clinical expert statements documenting that the products used for diagnosis (Soluprick SQ, ALK-Abelló) and immunotherapy (Alutard SQ, Aquagen SQ from ALK-Abelló, Purethal from Hal Allergy and Novo-Helisen Oral, Depot and Allergovit from Allergopharma) are commonly used in children as well as adults and that the diagnostic procedure and treatment modality are identical in both children and adults. As a consequence no regulatory action is needed.

II. RECOMMENDATION

No change in approved SPCs' are needed at present as these products are commonly used for diagnosis and immunotherapy in children with asthma and seasonal allergic rhinitis due to allergy to grass pollen. However it should be added in SPC 4.2 that the posology is identical in both adults and children otherwise respecting the approved text.

Please refer to section V for final recommendation for SPC and PIL after discussion with CMS.

III. INTRODUCTION

The MAH's (ALK-Abelló, Hal Allergy and Allergopharma) have submitted clinical expert statements with international positions papers, PSUR and clinical studies.

Diagnosis and immunotherapy in general has a wide use in paediatric patients from age 5 and above, and the present products have been used in clinical practise for years. The diagnosis of allergy in children against grass pollen depends on specific allergen extracts from grasses for prick-testing. Similarly immunotherapy against grass allergy is an established treatment modality using the same allergen extracts in an up dosing schedule and maintenance dosing both in children and adults (*Malling et al. EACCI Position Paper, Allergy 1993; 14, 1 – 46, Bousquet et al. WHO Position Paper, Allergy 1998; 53: 1 – 42, Scheinmann et al. Immunotherapy in young children. Allergens and Allergen Immunotherapy 2006; 3: 567 – 83*). The approved dose regiments for immunotherapy are the same in children and adults.

No studies have been conducted to address effect and safety specifically in children.

IV. SCIENTIFIC DISCUSSION

Clinical studies

ALK – Abelló

Møller c et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002; 109: 251-6.

In this an open label study with a control group, a total of 205 paediatric patients with seasonal allergic rhinitis (6 – 14 years) were randomised to 3 years of subcutaneous immunotherapy with standardized allergen extracts (Alutard SQ or Aquagen SQ) immunotherapy or to a control group.

Of these 124 were allergic only grass pollen, 41 were allergic to both birch and grass pollen and 43 were allergic to birch. The objective was to assess whether specific immunotherapy could prevent the development of asthma and reduce the bronchial hyper reactivity. Recording bronchial hyper reactivity (BHR) the odds ratio for improvement in BHR was significantly in favour of the active group of 1 year during seasonal exposure and after 1 year and 3 years exposure outside the season indicating that the immunotherapy reduced the risk of developing asthma. No unexpected adverse events were recorded.

Niggemann B et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006; 61:855 – 9.

A total of 183 children (aged 6 – 14 years) with grass and/or birch allergy could be investigated 2 years after discontinuation of immunotherapy on no treatment (the PAT study). After 5 years the immunotherapy treated children still had significantly less asthma and experienced significant improvement in hay fever relative to the untreated control group.

Jacobsen L et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10 year follow up on the PAT Study. Allergy 2007; 62: 943 – 8.

This was an evaluation of the long-term efficacy of a 3 years immunisation regimen in children that participated in the PAT Study (see above). Seven years after stopping therapy the group of children who received active immunotherapy had significantly less asthma than the control group and the observed improvement in rhinoconjunctivitis persisted.

Lack G. A study of clinical efficacy of immunotherapy with Alutard SQ. Phleum pratense extract in children with seasonal allergic asthma: A randomised double-blind placebo-controlled trial to evaluate the efficacy and safety of specific immunotherapy in grass pollen allergic children (3 – 16 years of age) (unpublished study five, UK21).

A total of 39 children were randomised to either active immunotherapy (n = 19) or placebo (n = 17) treatment for 18 month. After stopping therapy a 50 % reduction in median symptom score and medication was observed in the Alutard SQ. However the difference to the placebo group was not statistically significant (p<0.09). No unexpected adverse events were recorded.

Lack G. Open label safety evaluation of specific immunotherapy in subjects aged 5 – 17 years, suffering from seasonal allergic rhinoconjunctivitis due to grass pollen not responding to pharmacotherapy (unpublished study, UK 23).

In this safety trial a total of 81 patients were enrolled to standard immunotherapy with Alutard SQ grass pollen extract. The dose escalation and maintenance dosing were according to SPC with a mean treatment period of 868 days corresponding to 37 injections. Due to safety alert with Alutard SQ Phleum pratense the recommended maximum maintenance dose of 100,000 SQ-U was reduced to 10,000 SQ-U by March 2004. In the up-dosing period 67 children (83 %) reached the dose of 100,000 SQ-U prior to March 2004. In general the immunotherapy was well-tolerated. A total of 10 children stopped therapy due to adverse reactions.

Assessor's comments

The MAH has submitted available clinical data on children exposed to ALK-Abelló Alutard SQ and Acquagen SQ and documented the efficacy and safety of these products in children.

Hal Allergy

Supplementary Information on Purethal pollen (Hal allergy).

The MAH has submitted an overview of the clinical experience with the use of Purethal in children referring to 6 studies (see table below).

Study	Aim	Number of children included in the study	Number of children treated with PURETHAL® Grasses	Conclusions
Zimmermann(1)	To assess clinical efficacy and tolerance of PURETHAL® Grasses compared to a semi-depot preparation with established efficacy and safety	20 (age range between 5 and 21 years)	15 (9 boys) Age range: 5 – 21 years Gender distribution was not provided	Treatment with PURETHAL® Grasses could be continued during the pollen season with same dose used pre-seasonally without an increase in adverse events
Baumgarten(2)	To investigate the side-effects and efficacy of the PURETHAL® Grasses in comparison to a semi-depot preparation, DEPOTHAL, in a perennial treatment without dosage-reduction during the flowering-time of the grasses. For this purpose a randomized open label parallel design was used	In total, 34 patients with ages ranging between 12 and 53 years were included in the study. However the total number of children is not available.	Not available	After three years of consecutive treatment it was concluded that PURETHAL® Grasses was equally effective as DEPOTHAL, with equal rate of side effects and providing a much simpler treatment scheme. No conclusions regarding patient under 18 years of age were made.
Kroon(3)	To assess the tolerability of PURETHAL® Grasses by means of Survey on the experiences with PURETHAL® Grasses in forty practices	210 children	Exact age and gender distribution is not available.	It was concluded that PURETHAL® Grasses had an excellent tolerability in children and adults, but no subgroup analysis with respect to children was performed.

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Study	Aim	Number of children included in the study	Number of children treated with PURETHAL® Grasses	Conclusions
Kroon(4)	This study was conducted as a retrospective survey on the safety and efficacy of PURETHAL	245 (aged less than 15 years)	142 (58%)	PURETHAL has high safety and efficacy and provides a high cumulative dose with a low number of injection and small injection volume. No specific conclusions regarding paediatric population were made
Brewczynski(5)	To test the efficacy and safety of PURETHAL® Grasses in a double blind placebo controlled setting	The study population included 20 patients aged between 14 and 31 years. However, the total number of children is not available.	Not available	From 20 patients included in the trial, 10 were treated with PURETHAL® Grasses. A clinical improvement matching the increases in IgG and IgG4 was observed. No specific conclusions regarding children were made

Study	Aim	Number of children included in the study	Number of children treated with PURETHAL® Grasses	Conclusions
Kleinjans(6)	To assess the efficacy and safety of PURETHAL® Grasses + Triticum in daily practice. The study was conducted following a open retrospective observational cohort study	23	23 Range 9-16 years Mean age 13 years (SD 1.9)	The treating physicians assessed the treatment as “improved” or “much improved” in 78% percent of the paediatric cases. Tolerability among the children was assessed as “good “ or “very good” in 90 % of the cases. Only 2 patients had an adverse event (9%). In conclusion PURETHAL® Grasses + Triticum was safe and effective for the treatment of IgE mediated allergic symptoms for all studied patients including the paediatric population

Reference List

1. Zimmermann Th, Beinder K, Mollet FE, et al. Therapie von Heuschnuppenfen und Pollenasthma bei Kinder mit eine neuen, modifizierten Allergenextrakt [Therapy of pollinosis and pollen asthma in children with a new modified allergenic extract (PB49391)]. Immunitat und Infektion. 1990;18:127-131.
2. Baumgarten C, Herold D, Kunkel G. Purethal: Klinische Erfahrungen aus einer randomisierten Studie mit einem neuen modifizierten Graserpollenextrakt [Purethal:Clinical experiences from a randomized study with a new modified grass-pollen extract (PB49091)]. Referate des 9 HAL Kolloquiums. 1987;43-50.
3. Kroon AM. Tolerability of PURETHAL. Survey on the experiences with PURETHAL® Grasses in forty practices. 1989.
4. Kroon AM. A post marketing survey of the safety and efficacy of PURETHAL a glutaraldehyde modified allergoid for immunotherapy (PB29991). Schweiz med Wschr. 1991;121.

5. Brewczynski PZ, Kroon AM. A double-blind placebo controlled study with the allergoid PURETHAL (PZB/hf95591+ AMK/PB46793). Allergy. 1992;47:90.
6. Kleinjans HAJ. PURETHAL® Grasses + Triticum Retrospective observational Study. (PGT/0018). 2005.
7. Kleinjans HAJ. Periodic Safety Update Report (PSUR) for PURETHAL® Pollen. 2009.

In addition the MAH presented PSUR that covered the period from 2003 to 2008 where a total of 83 adverse events referred to Purethal grasses alone or in combination with other allergens. Out of the 83 events, 34 (41 %) concerned children aged < 18 years.

Assessor's comments

The MAH has submitted available clinical data on Purethal grasses and shown that the efficacy and safety profile are identical in children and adults.

Allergopharma

Allergopharma has submitted an Expert Overview with specific reference to the use of products containing Timomothy Grass Allergens (Novo-Helisen Oral formulation and Novo-Helisen Depot and Allergovit).

An overview of published studies is presented below.

4. Studies on SCIT including children, adolescents and adults

Grass pollen

Frank conducted a multicenter study for evaluation of side-effects and efficacy of immunotherapy with seven allergoid-depot injections (ALV, grass-rye pollen). At 14 German trial centers 143 hay fever patients (age range 10-61 yrs; mean 28 years) with confirmed grass pollen sensitization received immunotherapy with depot allergoid (ALV). Seven pre-seasonal consecutive injections at a weekly interval had been given by doubling doses up to a mean cumulative dose of 11,266 Therapeutical Units (TU) \pm 21,9% cv. With the depot allergoid immediate local reactions were very rare (0,6 %) and local late phase reactions occurred after 13% of the injections. Exacerbation of typical hay fever symptoms and systemic reactions had been reported after 3.6% of the injections. During therapy there was a highly significant increase ($p < 0,001$) for the specific IgG rising to a mean value of 219%; the mean specific IgE increased up to 145 %. Results showed a subjective clinical improvement for 89% of the patients (100% for asthmatic patients); physicians reported an improvement for 83% of the patients (88% of the asthmatic group) and a reduction of medication needed for 77% of the patients (8701). Till the follow-up 3 years later, short-term and lasting clinical benefit after 3 years of immunotherapy with grass pollen depot allergoid (ALV) Aluminium adsorbed allergoid preparations have been on the market for more than 7 years with a short-course

dosage schedule. The success of this form of therapy, including patient compliance, has been investigated in a multicentre retrospective study. On the basis of data from 278 patients (age range 6-67 yrs) it was shown that 85% of the patients that had completed 3 years immunotherapy achieved a good or very good improvement. These short-term results are consistent with reports from earlier controlled clinical trials. The lasting benefit of this causal therapy conducted in 3 consecutive years was apparent in 85% of the patients an average of 3 years later. Therefore, this immunotherapy could lead to good clinical improvement and economising on both costs and time through a reduction in the need for antiallergic medication and the use of a short-term dosage schedule (9601).

Loidolt and Frank performed a 3-year hyposensitisation study with grass pollen allergic patients with modified and unmodified extracts. Immunological changes and tolerance of a specific hyposensitisation treatment with ALV and NHD were monitored over a period of 3 yrs (1983-1986). During the first treatment session 14 patients received depot allergoid and 12 patients depot allergen extract. 81% of these patients were still treated and documented until the end of the 3 yrs study. In both groups, patients' symptom scores decreased during therapy highly significantly ($p < 0.001$) in the allergoid group, whereas pollen counts did not change significantly ($p > 0.05$). The specific IgE (sIgE) only rose significantly ($p < 0.01$) during the first year of treatment, then decreased again towards the initial value. In the allergoid group the specific IgG (sIgG) increased highly significantly ($p < 0.001$) during each term of treatment; in the allergen group there was a highly significant sIgG increase during the first year and a significant one for the second year. Significant correlations were found for the allergoid group between total antigen dose and sIgE reduction as well as between decrease of symptom plus medication scores and low values of sIgE or ratio sIgG/sIgE after 3 years of therapy. After 2 and 3 years of hyposensitisation, the good results of the first year were still improved considerably, especially after allergoid treatment. High doses administered, as well as significant increase of sIgG and decrease of sIgE resulted in best improvement (9001).

Dokic et al. used the nasal provocation model, to determine whether the mediator release was altered in immunotherapy-treated patients. 17 grass pollen-allergic patients, age range: 15-37 years, were examined under controlled, reproducible conditions. Serial challenges with increasing doses of grass pollen produced increasing numbers of clinical symptoms and release of mediators such as kinins, TAME-esterase activity, and histamine. Ten patients received a semi-depot perennial grass-pollen extract for 4 years (NHD). Seven patients served as controls and did not receive immunotherapy during the observation period. Data from the group of patients receiving immunotherapy over the first year already showed a partially significant decline in the maximal mediator release after nasal allergen challenges compared to the results of pretreated challenges, whereas controls did not show any significant changes. Nasal allergen challenges after termination of 4-year-immunotherapy significantly modified the mediator release compared to pretreatment values (TAME-esterase activity $p < 0.05$, kinins $p < 0.01$, and histamine $p < 0.01$). Decrease of mediator release paralleled the symptom-medication scores and quantitative skin prick test. Finally, a significant correlation between specific IgG increase and mediator decrease in the treated group was demonstrated (9603).

Hofman and Kolasinska examined 72 patients with pollinosis (age range 5 to 38 yrs) who received immunotherapy by ALV. These vaccines had been composed individually for patients according to their spectrum of hypersensitivity to various pollen. After one year of

hyposensibilisation, 78.3% showed a very good and 20.3% showed good improvement. Among the latter, 7 patients had symptoms in the time when there had been pollen by another plant than they had been vaccinated. Only one patient did not improve because he was sensitised to many pollen, thus the vaccine was not effective because of allergen sensitisations and a challenge too large in total (9602).

The aim of the study by Hofman et al. 1997 was to compare the efficacy of the immunotherapy by ALV and Catalet. 699 patients (age 5 – 56) were desensibilised. 213 were given Allergovit: 137 in one season, 56 in two seasons and 20 in three seasons and 484 were given Catalet: 288 in one season, 151 in two seasons and 45 in three seasons. The Catalet vaccine contained 12 grasses, rye and plantain pollen, but ALV contains a group of grass pollen - 60% and rye pollen - 40%. Qualification to the desensibilisation was performed on the ground of clinics symptoms, positive skin prick tests, of specific IgE antibody, positive provocation nose test presence and symptoms connected with pollenfall checked every day in the area of Poznan, Lodz and Katowice. Estimation of the immunotherapy efficiency was assessed by patients, who noted their remarks in prepared "Patient card" using rating scores. In result of desensibilisation by ALV good and very good improvement (score 0 and 1) were achieved after one desensibilisation season in 77.3% patients, after two seasons in 85.7% and after three seasons in 90.0%, on the contrary by patients desensibilised by Catalet results good and very good were achieved in 50% after one season, after two seasons in 63.6% and after three seasons in 77.8%. Better results were achieved in patients desensibilised by ALV than Catalet (9702). In the same year, Hofman investigated immunotherapy among patients with pollen allergy using individually selected ALV. The efficacy of this treatment was compared to patients with pollinosis who didn't receive desensibilisation, because they rejected it. These results indicated that it is necessary to perform nasal provocation tests before the choice of antigens for specific immunotherapy, because the prick skin test was frequently false positive in patients which didn't have corresponding symptoms. Precise composition of the vaccine improved the course during the first season in 77.9%, in the second season in 87.5% and in third season in 91.6% (9703).

In the study conducted by Marciniak et al. 1998, serum level of ECP has been evaluated in children with allergic diseases of the respiratory system in exacerbation and remission of symptoms for purpose of monitoring of disease course. In 111 children aged 12.0 +/- 3.3 yrs with atopic bronchial asthma and/or AR ECP serum concentrations had been determined in following groups: children with grass pollen hypersensitivity (group P, n = 58), children with hypersensitivity to *D. pteronyssinus* and *D. farinae* (group D, n= 53) and controls without allergic hypersensitivity with negative prick skin tests (19 children, 16 adults). All treated children received immunotherapy with pollen or mite allergens (ALV or Novo-Helisen, Nexter, Allergopharma). ECP evaluation was performed before, during and after therapy. Serum ECP and 19E levels had been determined with CAP-system (Pharmacia) and obtained results related to clinical symptoms. In all analysed children serum total IgE had been significantly increased in relation to controls. Serum ECP levels had been increased during clinical exacerbation of symptoms in observed children and parallel with clinical score of symptoms, especially during pollen season. The authors concluded that a degree of increase of serum ECP level is parallel with clinical score of symptoms, especially during highest exposition to pollen allergens. Observed changes of serum ECP levels during immunotherapy suggested the close relationship with the allergic inflammatory reaction and indicate clinical usefulness for monitoring of this process (9801).

Hundt et al investigated the use of short-term SIT in a 3-yr RCT with grasses-rye ALV including 17 children. The complaints were assessed using a symptom and medication score, and could be reduced significantly in the treated group, but not in the untreated control group during the first trial year ($p < 0.05$). Skin prick test positive results were also decreased significantly in the treated group ($p < 0.05$). Assessment of the allergen-specific TH cell reaction was performed by stimulation of PBMCs with grass pollen extract and the main allergenic factor PhI pS, cytokines produced were measured by ELISA. After the first pre-seasonal treatment, T-cells showed a reduced cytokine synthesis compared to the synthesis before SIT. In contrast, after the 2. and 3. SIT cycle, IFN gamma/IL-4 and IFN gamma/IL-5 ratios increased. These findings indicated a TH2-cells shift to TH0/TH1 cell types. This TH reorientation is supported by the significant induction resp. increase of allergen-specific IgG4/IgE and IgG1/IgE antibody ratios ($p < 0.002$ bzw. $p < 0.045$). The control group showed no such changes. Thus, the authors could demonstrate the success of the 3-yr SIT clinically and immunologically in the lab (0203).

Gehlhar et al sought to define allergen-specific parameters that change due to treatment in correlation with the clinical outcome. A controlled study with grass pollen-allergic children (treatment group 10.82 ± 4.76 yrs; control groups similar) compared allergen-specific antibody titres before and 1 year after the onset of immunotherapy (NHD) in contrast with untreated allergic and healthy children. Two recombinant forms of the major allergen group V of *Phleum pratense* (Phl p 5) served as model allergens. No change in IgE levels and no significant reduction of skin prick test (SPT) reactivity were seen. On the other hand, a significant reduction of symptom scores in the treated group and a significant rise in allergen-specific IgG1, IgG2 and IgG4 due to the treatment could be observed, but in neither case a correlation could be established between the increasing amounts of the single antibody classes and the reduction of symptom scores. But most interestingly, when comparing the ratio of IgG4 to IgG1 with the symptom scores, significant correlations were found. Nevertheless, treated allergic patients still differ considerably from healthy controls as non-atopics had hardly any measurable allergen-specific IgG antibodies and no IgE antibodies at all. The ratio of IgG4 to IgG1 could serve as a valuable parameter that allows to assess the success of immunotherapy already 1 year after the onset. The increase of specific IgG1 in relation to IgG4 during treatment reflected a possible influence of this subclass on the induction of tolerance towards allergen (9901).

Grübl et al. performed a study using a 6 grasses and rye allergoid for hyposensitisation (ALV) in an open-labeled clinical trial to assess treatment efficacy in children. The immunological diagnostics comprised a quantitative assay of allergen-specific immunoglobulines (IgE, IgG4, IgG1) as well as as IL-5, IL-4 and interferon gamma synthesis after in-vitro synthesis of PBMCs sampled before and during the course of a 3 year pre-seasonal immunotherapy. During a pilot study including 7 children and a follow up study including 12 children an increased synthesis of interferon gamma after allergen-specific stimulation of peripheral blood lymphocytes. Concomitantly, the IL-4 and IL-5 synthesis is decreased. These results indicate a reorientation of allergen-specific TH cells from a TH2 to a TH0 resp. TH1 weighted distribution (9902).

Baumann 2002 investigated the effects of the specific immunotherapy (SIT) in pollen allergy on pollen-associated food allergy, particularly the oral allergy syndrome (OAS), in a retrospective study in pollen-allergic subjects searching for factors that could be prognostic

for the change of OAS. 72 subjects (range 14-59, mean age 32 years) allergic to pollen with a concomitant pollen-associated food allergy, namely OAS, who have been treated for an average of 2 years by SIT were interviewed using a standardised questionnaire. 40 individuals allergic against pollen and a pollen-associated food allergy (OAS) without SIT served as controls. 38 of 72 subjects (53%) treated with SIT had an improvement of their OAS. However, 23 (32%) claimed an unchangeable health status and 11 (15%) even an increase of the OAS. Of the controls, an improvement was realised in only 3 individuals (8%). 20 of them (50%) declared no change and 17 a worsening of the OAS. The results suggested that pollen-associated food allergy, specifically the OAS, can be reduced in more than half of the patients by SIT. On the other hand, in 15% of the SIT-treated collective an expansion of the spectrum of foods inducing symptoms was experienced. A successful development of the OAS by SIT seemed to occur if patients rather were older than 20 years of age, had a clinically relevant birch pollen allergy and suffered from an intensive OAS. Failure regarding OAS seemed more likely if SIT with birch pollen was combined with grass pollen extracts (0201).

Grzela et al. found a lower IL-12 production by allergic monocytes in allergy patients than in healthy controls could depend on higher IL-4 receptor alpha-chain (CD 124) expression. Since IFN-gamma production is stimulated by IL-12, which in turn is down-regulated by IL-4, the aim of the study was to analyse the influence of allergen-specific immunotherapy (AIT) on the network of these cytokines. Moreover, the possible role of CD 124 in that process was estimated. Children (mean age 11.6 ± 3.4 yrs; $n=16$) with grass pollen allergy were subjected to AIT with ALV according to standard protocol. The clinical examination and blood analyses were performed before and after AIT. Clinical improvement in course of AIT was rather weak; however, a significant increase of mean IFN- γ production by PBMC was assayed. Although the increase of mean IL-12 production by monocytes following AIT was non-significant, statistically significant decrease of monocyte sensitivity to IL-4 suppressed IL-12 production was observed. Flow cytometry analysis revealed significant decrease of CD 124 expression on monocytes after AIT. Despite unchanged mean IL-4 level the decrease of CD124 expression after AIT could explain the decreased monocyte sensitivity to IL-4 and its role in further IL-12 and IFN-gamma tuning (0202).

Eng 1994 performed a trial to investigate the safety, clinical efficacy and immunogenic effect of pre-seasonal immunotherapy with a depot allergoid extract in children with pollinosis. 14 children (7-16, mean age 10 years) with pollen allergy were prospectively treated with s.c. injections of a ALV allergoid extract, which was chosen as a combination of grasses/rye (80%/20%). In case of additional sensitisation to tree pollen, hyposensitisation using a combination of tree pollen allergens was applied concomitantly. Local and systemic reactions, variations of symptoms and total drug requirements, changes of skin reactions (Prick test) and determinations of specific IgG antibodies before and after two immunotherapies were recorded. The control group consisted of 14 pollen allergic children, who were only symptomatically treated over the same time period. After a total of 321 s.c. injections there were no systemic reactions, local reactions however were recorded in 4.7%. Allergic symptoms and drug requirement were decreased after two courses of immunotherapy. A significant decrease in skin reactions to allergens ($p < 0.01$) was observed in contrast to an increase in symptomatically treated children. Specific antibodies of all IgG-subclasses increased significantly after two immunotherapies. The pre-seasonal immunotherapy with depot allergoid extract was safe and well tolerated. Children with confirmed pollinosis

complained of fewer and less severe symptoms. There was an immunogenic effect after a second treatment course (9402, 9101).

Eng et al. carried out a follow-up study in 2002 in a group of patients previously treated (mean age 9.6; range 5-16 yrs at beginning of SIT) to see if there was still a benefit six years after discontinuation of treatment. 13 of 14 patients with previous SIT (ALV, allergoids) and 10 out of 14 patients of the control group were prospectively followed during the grass pollen season. Outcome measures were seasonal symptom scores for eyes, nose and chest, the use of symptomatic medication and visual analog scale. Objective measures included skin prick test reactivity to seasonal and perennial allergens and conjunctival provocation testing. During the 13 week observation time, scores for overall hayfever symptoms ($p < 0.004$) and individual symptoms for eyes ($p < 0.02$), nose ($p < 0.04$) and chest ($p < 0.01$) as well as combined symptom and medication scores ($p < 0.002$) remained lower in the group with previous SIT. Only 23% of patients with previous pollen-asthma who had received SIT experienced pollen-associated lower respiratory tract symptoms compared to 70% in the control group ($p < 0.05$). There was no significant difference in the use of pharmacological treatment during the pollen season except for asthma medication. The average visual analog scale was lower in the post-SIT group ($p < 0.05$). Six years after cessation of SIT the immediate skin response to grass pollen remained decreased compared to the reaction of the controls ($p < 0.01$). There was also a tendency for higher allergen concentration to provoke a conjunctival response in the post-SIT group but without reaching statistical significance. Eight years after SIT start, 61% of the initially pollen-monosensitised children had developed new sensitisation to perennial allergens compared to 100% in the control group ($p < 0.05$). A significant clinical benefit six years after discontinuation of pre-seasonal grass pollen immunotherapy in childhood was found. SIT in children with pollen-allergy reduces onsets of new sensitisation and therefore has the potential to modify the natural course of allergic disease (0205). In the next follow up 6 years later, the patients were assessed by symptom score, medication use, and combined symptom and medication score (primary end points). In addition, skin prick test reactivity, development of new sensitisations, and prevalence of seasonal asthma were evaluated. Total hay fever symptom score ($p < 0.03$), use of medication ($p < 0.05$), and combined symptom and medication score ($p < 0.03$) remained lower in patients with previous SIT when compared with the control group. Decreased immediate skin response to grass pollen returned 12 years after cessation of SIT. The percentage of new sensitisation, however, continued to be significantly smaller in patients with previous SIT (58%) compared with the controls (100%, $p < 0.05$). There was a tendency for lower prevalence of seasonal asthma in the post-SIT group ($p = 0.08$). This prospective controlled prolonged follow-up study demonstrated the ongoing clinical benefit 12 years after discontinuation of SIT. Furthermore, the reduction in onset of new sensitisation, which was found 6 years after discontinuation of SIT, is sustained 6 years later (0612).

Asero 2003 evaluated the duration of the effect of injection SIT with birch pollen extract on apple allergy in 30 birch pollen-allergic patients (mean age 42.6, range 16–60 years). The patients that showed the clinical disappearance of apple allergy and a negative SPT with fresh apple at the end of their injection SIT course were examined on follow-ups at 12-month intervals, starting 6 months after SIT was stopped. Apple tolerance as well as SPT was assessed on all occasions. 57 birch pollen-allergic subjects without apple allergy and not submitted to SIT regularly followed-up for the onset of oral allergy syndrome (OAS) were used as controls. The overall prevalence of OAS after 30 months of follow-up did not differ

between patients and controls. Although most patients became re-sensitised to apple by SPT over time, >50% of them were still able to tolerate eating the fruit at the 30-month follow-up visit. Although most patients showed a gradual propensity to apple re-sensitisation which could be a consequence of prolonged and repeated inhalation of birch pollen responsible for primary sensitisation, the clinical effects of injection SIT on food allergy seemed rather long lasting (0304).

Gawlik et al. compared the clinical efficacy of pre-seasonal and perennial immunotherapy in the seasonal allergic patients. An open comparative study was conducted in the group of 37 hay fever patients. The duration of the disease was 6 years (mean). Pre-seasonal immunotherapy was performed in a group of 22 patients (mean \pm SD: aged $24,4 \pm 13$ yrs, range 14 – 40 yrs) and perennial treatment in 15 patients (mean \pm SD: $23,2 \pm 12$ yrs, range 16 – 39 yrs). The specific diagnosis and subsequent choice of vaccine was made on the basis of a detailed clinical history, the results of skin prick tests and determination of specific IgE (Fluoro-FAST method; 3M Diagnostic System, Whittaker Bioproducts, USA). None of the patients had undergone desensitisation during the previous 3 years and none were sensitised to perennial allergens. All patients used symptom/medication diary cards to record the severity of their symptoms during the season. The active treatment was a standardised rye and grass pollen allergoid adsorbed to aluminium hydroxide (ALV). The cumulative dose for pre-seasonal AIT was 12,000 TU/year, for perennial one in the first year was 36,500 TU and in subsequent years 48,500 TU on average. Perennial AIT appeared to be more effective than seasonal AIT after three years of therapy, as confirmed in subjective evaluation by patients carrying out VAS ($p < 0.05$). Specific IgE concentration decreased after 3 years of AIT in both groups, although reduction in sIgE-g5 and sIgE-g6 were more pronounced in a group of perennially treated patients ($p < 0.038$ and $p < 0.048$, accordingly). Perennial immunotherapy was judged as a more effective therapeutic option in treatment of seasonal AR than pre-seasonal one (0404).

Keskin et al. included 35 children (mean age 12 ± 3 yrs) in the study. 27 were treated with a 7 week course of pre-seasonal grass pollen AIT and 8 were in the open control group. Both groups were allowed to take symptomatic medication. Symptom scores for eyes, nose and chest, medication scores, quality of life, and subjective-assessment questionnaire, and safety of AIT were evaluated during the first pollen season following the initiation of AIT. Methacholine (Mch) provocation was carried out during the season and during winter. ECP levels were measured in nasal fluid and in serum, and grass-specific IgE was measured in serum. Medication scores for rhinitis and total score of self assessment in the AIT group were significantly less than the control group during pollen season ($p = 0.02$ for both). The difference in asthma medication scores, and quality-of-life questionnaire score approached significance ($p = 0.08$, and $p = 0.09$, respectively). Grass-specific IgE increased [median (IQR)]1.6 times (1.2, 2.3) in the control group and 1.0 (0.9, 1.1) times in the AIT group during the grass pollen season compared to out of season ($p = 0.004$, Mann-Whitney U-test). In 11 patients who had Mch provocation during two consecutive pollen seasons (before and after AIT), Mch PD20 improved from 3.75 (0.73, 7.50) to 5.9 (1.75, 16.0) ($p = 0.051$, Wilcoxon Signed Rank Test). Post AIT seasonal Mch PD20 was higher in the AIT group 5.3 mg/ml (1.8-16.0) compared to the control group 2 mg/ml (1.75-16) but the difference did not reach statistical significance. All individuals in the study had increased nasal ECP concentrations during the pollen season compared to pre-season. However, no statistically significant difference was observed between the AIT 24.4 (4.3-62.8) μ g/l and control group

22.5 (6.2 - 311.9) $\mu\text{g/l}$ ($p > 0.05$; Mann-Whitney U-test). There was no difference in serum ECP levels between the two groups. Mild local reactions were seen in 6% and mild symptoms of rhinoconjunctivitis in 1 % of injections. The results suggested that pre-seasonal AIT is a safe and effective method for the treatment of AR. The clinical and immunological effects started early in the course of the treatment (0405).

Keskin et al 2005 aimed to study the immunological effects of AIT in children with AR due to grass pollen allergy. 53 children (mean age 12.0 ± 0.4 yrs) with AR with or without asthma were included in the study. Twenty-seven were treated with 7 preseasonal injections, followed by 1 year of maintenance AIT and 26 were followed without AIT. Grass-specific IgE, IgG, IgG1, and IgG4 were measured in serum. IL-4, IL-5, IL-10, and IFN-gamma were measured in the cell-culture supernatants before and after allergen stimulation. AIT prevented the increase in grass-specific IgE levels during grass pollen season. The ratio of seasonal/pre-seasonal grass-specific IgE was (median IQR) 2.37 (1.16, 2.88) in the control group and 1.00 (0.78, 1.69) in the AIT group ($p = 0.008$, Mann-Whitney U) (0506). In another study, they sought to investigate whether s.c. SIT injection using ALV, either during or outside the pollen season, could cause an increase in bronchial reactivity (BR) in children with pollen allergy. Twenty-two children (mean age 13.6 ± 0.7 years) with AR who were receiving maintenance SIT for 15 months were included in the study. Pre-injection BR of the patients was evaluated with Mch provocation test immediately before maintenance dose of SIT during the peak pollen season and outside the season. The post-injection test was administered 24 hours after SIT injection. There was no difference in FEV1 measures recorded during [98 (93 – 109)%] and outside [102 (96– 111)%] the pollen season. There was no significant difference between pre- [64 (7–64) mg/ml] and post-allergen injection [32 (7.5– 64) mg/ml] BR outside the pollen season ($p = 0.9$). A trend towards improvement following allergen injection [64 (5.4– 64)%] as compared to pre-allergen injection [14.6 (3.5– 64)%] was shown during the pollen season ($p = 0.053$). Although PC20 measures in the pollen season were lower than outside the season, the difference was not significant. The percentage of the patients with bronchial hyperreactivity was 62% during and 43% outside the season. SIT injections both during and outside the pollen season cause no increase in BR in children with AR. This questioned the necessity of empirical dose reduction during the pollen season (0507). A concomitant study by Tuncer in the same population confirmed the beneficial effects clinically (0508): The allergen concentration required eliciting a positive response in nasal provocation showed a 2-fold increase after 1 year of AIT in the AIT group ($p < 0.001$, Wilcoxon) but not in the control group. Similarly, skin test reactivity decreased significantly in the AIT group [11 (9, 16) vs 8.5 (6, 11)] median IQR range ($p < 0.001$, Wilcoxon) but not in the control group. Seasonal MchPC20 was 5.3 (1.8, 16) mg/ml after 7 injections of AIT; and 16 (7.7, 16) at the end of 1 year AIT ($p=0.001$, Wilcoxon). A seasonal increase in bronchial reactivity (BR) was observed in the control group [pre-seasonal: 11.7 (2.3-16) vs. seasonal: 1.8 (0.57 - 10)] ($p = 0.012$, Wilcoxon), which was totally prevented in the AIT group [pre-seasonal: 16 (11.7 - 16) vs. seasonal: 16 (7.7 - 16)] ($p > 0.05$, Wilcoxon). In addition, seasonal MchPC20 was significantly higher in the AIT group compared to the control group ($p < 0.001$, Mann-Whitney U) after 1 year of AIT. Mild local reactions were seen in 6% and mild symptoms of rhinoconjunctivitis in 1% of injections.

Dursun et al. performed a study to determine the frequency of systemic reactions (SR), and to identify their correlation with the characteristics of therapy, e.g. allergen composition and IT schedule, and diagnosis. Data of 126 patients (age range: 15-51 yrs) who received IT between

2000-2003, and suffered from respiratory allergy or hymenoptera venom anaphylaxis were analysed. IT was given by rush, clustered or conventional schedules. The standardised allergen extracts (from Allergopharma [NHD], Stallergenes, and ALK-Abellò) used were grass pollen, house dust mite and hymenoptera venom in 88, 18 and 20 patients, respectively. None of the patients received premedication. For a total of 4705 injections administered, 123 adverse events (AE) (2.6% per injection) were documented in 46 patients. 61 of them were SRs (1.3% SRs per injection) and they were seen in 28 patients. Asthmatics had more tendency to systemic reactions (SRs) ($p=0.05$). Rush (1.8%) and clustered (2.8%) IT protocols were associated with a higher rate of SRs (per injection) when compared to conventional schedule (0.9%) (rush vs. conventional; $p=0.013$, clustered vs conventional; $p=0.001$). The majority of SRs corresponded to grade 3 (49%). Forty-nine (80%) of the 61 SRs were observed during the build-up phase, and mostly with pollen extracts (75.5%). Patients showed more severe SRs during the build-up phase ($p<0.05$). Twenty-six (42.6%) of the SRs were immediate, whereas 35 (57.4%) SRs appeared within 2 hours. Delayed SRs were significantly more frequent in polysensitised patients when compared to monosensitised subjects ($p = 0.018$). The data indicated that rapid IT regimens and the presence of asthma represent a greater risk for SR development. Since the late SRs occurred as frequently as the early ones, a longer waiting period beyond 30 minutes, especially in polysensitised and asthmatic patients, was suggested (0608).

Keskin et al investigated the immunological and clinical effects of allergoid immunotherapy with ALV in children with AR due to grass pollen allergy. Children with AR were assigned to allergoid immunotherapy ($n = 27$) or control ($n = 26$, no immunotherapy) groups. Children in the immunotherapy group received seven injections of grass pollen allergoid immunotherapy before grass pollen season and continued to receive maintenance immunotherapy for 27 months. All patients were offered a pharmacotherapy regimen to be used on demand during the pollen seasons. Clinical and laboratory parameters were compared between the immunotherapy and control groups. The rhinoconjunctivitis symptom-medication score and asthma symptom score were lower in the immunotherapy group after 1 yr of maintenance immunotherapy ($p < 0.01$ for both). Skin test reactivity and nasal reactivity as determined by nasal provocation testing for grass pollen were significantly decreased after 1 yr of immunotherapy ($p < 0.001$ for both). The seasonal increase in bronchial reactivity and nasal lavage eosinophil cationic protein levels was prevented after the first year of immunotherapy ($p < 0.05$ for both). The seasonal increase in IgE decreased ($p < 0.05$) and grass-specific IgG, IgG1 and IgG4 increased significantly already at the end of the seven-injection build-up therapy ($p < 0.001$, for all). Interleukin (IL)-4 levels in the culture supernatants showed a steady decline from baseline at first and second year of immunotherapy ($p < 0.001$) but remained unchanged in the control group. Allergoid immunotherapy was appraised as an effective method in the treatment of grass pollen-induced AR in children and prevents the seasonal increase in bronchial hyper-reactivity. Changes in specific IgE and IgG levels and decreased IL-4 production in peripheral blood mononuclear cell culture supernatants may have accounted for the observed clinical effects (0609).

In 2006 Asero conducted a study to assess whether injection SIT with commercial pollen extract represents a risk factor for the de novo development of sensitisation to different pollen in monosensitised patients involving 142 subjects diagnosed as being monosensitised to a single pollen species: 64 patients who were administered a 3-years course of injection SIT and 78 controls. Subjects underwent control skin prick tests (SPT) with a series of 8 seasonal

airborne allergens at least 3 years after the first visit. Patients with 5 or more new sensitivities on SPT were considered to be de novo polysensitised. At the end of the 3-year follow-up period, the proportion of polysensitised subjects was identical in previously monosensitised patients who underwent SIT and control individuals (11% and 10%, respectively). Individuals who were polysensitised were significantly younger than those who were not (mean age \pm SD, 21.6 ± 11.0 years vs 31.6 ± 15.6 years; $p < 0.05$). Thus, SIT does not represent a risk factor for progression towards multiple pollen sensitisations in monosensitised pollen-allergic patients (0604).

In 2006, Czarnaicka-Operacz and Silny investigated 37 patients (and a drug-treated control group of 29) patients (5-44 years) with atopic dermatitis that were treated with NHD for 48 months. Grass pollen allergens 100% were used in 17 cases and grass pollen 80%/mugwort pollen 20% allergens in 6 patients. After 24 and 48 months of therapy, there was a significant difference between the two investigated groups from both the clinical (W-AZS score) and immunological standpoints after 2 and 4 years of observation, and a significant decrease of serum total IgE and as IgE (directed against airborne allergens) in the course of specific immunotherapy. In the control group, the total IgE level tended to increase. In the group of patients treated with allergy vaccines, a significant decrease of the serum sIL-2R level was observed after 48 months of therapy ($p < 0.01$). No special noticeable observations regarding the paediatric study population were made (0603, 0101). Another double-blind, placebo-controlled trial was conducted by the authors in 2006 for specific immunotherapy of atopic dermatitis in 20 patients (5 – 40 years old) over a period of 12 months in order to evaluate the efficacy of SIT in the management of a AD and monovalent sensitisation to airborne allergens (grass pollen or house dust mites). SIT was performed using NHD vaccines, administered by s.c. injection. Clinical efficacy of the treatment was assessed using the clinical score W-AZS index. Serum concentration of total IgE and sIgE were measured, as were various immunological parameters including ECP, sIL-2R, IFN-g, IL-4, IL-5 and IL-10. The mean value of W-AZS index in the SIT group before treatment was 87.6 ± 15.8 patients, and this decreased to 38.8 ± 34.4 patients after 12 months of therapy ($p < 0.01$). In the placebo group, the mean W-AZS index before treatment was 86.3 ± 15.7 and after 12 months of therapy it increased to 111.9 ± 41.7 patients. Comparative statistical analysis indicated a significant difference between the groups in favour of actively treated patients ($p < 0.01$). Serum levels of specific IgE in the SIT group showed a tendency to decrease, whilst those in the placebo group tended to increase. Serum concentrations of ECP, sIL-2R, IFN-g, IL-4, IL-5 and IL-10 were monitored before and after treatment, without showing significant differences. Allergen-specific immunotherapy appeared to be an effective method of treatment for atopic dermatitis as judged by significant improvement in clinical index in cases with well-documented IgE-mediated allergic disease (0611).

Czarnaicka-Operacz 2008 evaluated the prevalence of OAS symptoms in patients with various manifestations of pollen airborne allergy (AD, asthma, AR) treated with subcutaneous SIT. The most common patterns of cross-reactivity in OAS were analysed also, and correlations between OAS symptoms and patient age, type of sensitising pollen allergens and atopic manifestations investigated, together with the relationship between SIT duration and clinical improvement of both OAS symptoms and pollen allergy symptoms. The study included 57 patients with airborne allergy treated with NHD and ALV. AR was diagnosed in 71%, AD in 19%, AD and asthma in 4%, AR and asthma in 4%, and both AD and AR in 2% of study patients. 28% of study patients complained of overt symptoms of OAS (22% of AR and 27%

of AD patients); 69% of the subjects presenting with OAS showed polyvalent airborne allergy to pollen and 31% were sensitised to only one group of pollen allergen (mostly grass pollen, tree pollen and mugwort pollen). There was no statistically significant correlation between the presence of OAS symptoms and patient diagnosis, age or type of allergen vaccination. SIT significantly improved oral symptoms in 50% of study patients according to themselves, 44% reported no impact of SIT on OAS symptoms and 6% of patients observed worsening of OAS symptoms after unintentional ingestion of implicated food during the course of SIT. OAS was revealed as a significant problem in patients sensitised to various pollen allergens, its prevalence in atopic subjects (28%) is consistent with some literature data. A clear association between OAS and polyvalent airborne allergy (69%) was found. Cross-reactivity patterns were typical. Questionnaire analysis indicated that SCIT significantly alleviated OAS symptoms associated with ingestion of the responsible fruit and vegetables in half of study subjects (0806).

Hansen 2004 investigated 46 patients (range 11 – 71, mean 40.7 years) with regard to side effects of a Cluster regime during induction treatment with NHD. Eight treatments with tree pollen extracts were performed. 3 patients showed local reactions, 5 local reactions were observed in total. All enlarged local reactions, were grade 1, grades 2, 3, or 4 reactions did not occur. There were no differences in gender or age regarding the occurrence of side effects (all $p > 0.05$). Frequency and severity of adverse side effects in Cluster-SIT with NHD show an excellent tolerability corresponding to the occurrence of side effects with other dosage schedules (0403).

Ranibar et al performed a study on the effects of short-term SIT with allergoids on allergic asthma in children. They recruited 87 children with only pollen induced seasonal asthma (age 6-14 yrs) and divided the patients randomly in 2 groups. Group A ($n = 47$) was treated yearly pre-seasonally with 7 s.c. injections of a depot-allergoid extract for 3 years plus standard medications. Group B ($n = 40$) was treated only with standard medications. Allergen-specific IgE, IgG as well as IL-4 and IFN-gamma in serum were measured and titrated prick tests and spirometry were performed before and after SIT and during pollen season for 3 years. All patients were examined before and after SIT, during pollen season and at two extra-seasonal visits, and 3 years after discontinuation of SIT during pollen season and performed spirometry. It was possible to evaluate 42 patients in group A and 32 patients in group B. In group A clinical symptoms and drug requirement decreased significantly in the first year, compared to group B ($p < 0.01$). In the third year all patients in group A were symptom free and did not use any medications for asthma, whereas the clinical symptoms and medication intake in group B had increased, compared to the baseline. Spirometry in group A showed normal findings before and after challenge test in the third year of SIT and until 3 years after discontinuation of SIT, whereas in group B pathological findings were detected. Parallel to the clinical improvement in group A an elevation of IFN-gamma in serum ($p < 0.01$), an increase of sIgG4/sIgE ($p < 0.01$) was measured as well as a decrease of skin reaction on pollen by prick tests ($p < 0.01$), compared to group B. A new sensitisation in one patient of group A vs. 7 patients of group B three yrs. after SIT was observed. 3 years after discontinuation of SIT 2 patients of group A vs. 11 patients of group B showed new sensitisation. SIT with depot-allergoid extract was well tolerated and did not show any notable side events. The causal effect of short-term pre-seasonal SIT with depot-allergoid extract on asthmatic children with pollen allergy was demonstrated. It lasted until the end of

this study, more than 3 yrs. after discontinuation of SIT. The occurrence of new sensitisation could be prevented (0406).

Niggemann et al. investigated the long-term preventive effect (PAT study) with a follow up – 2 years after termination of a 3-year course of SIT (ALK; Alutard-/Aquagen-SQ) in children that significantly reduced the risk of developing asthma with hay fever to grass and/or birch pollen. A total of 183 children, aged 6–14 years with grass and/or birch pollen allergy could be investigated 2 years after discontinuation of SIT or no treatment. Conjunctival provocation tests (CPTs) and Mch bronchial provocation tests were carried out during the season and winter after 5 years. The development of asthma was assessed by clinical evaluation. The significant improvement in hay fever and CPT results observed after 3 years of SIT persisted at the 5-year follow-up. No difference in bronchial responsiveness to Mch was found after 5 years because of spontaneous improvement during the follow-up period in the control patients. The immunotherapy-treated children had significantly less asthma after 5 years as evaluated by clinical symptoms [odds ratio 2.68 (1.3–5.7)] in favour of SIT for prevention of development of asthma and significantly less patients reported an increase in asthma scores ($p < 0.01$). Immunotherapy for 3 years with standardised allergen extracts of grass and/or birch shows long-term clinical effect and preventive effect on development of asthma in children with seasonal rhinoconjunctivitis (0610). In the next follow-up Jacobsen et al. continued the evaluation 7-years after termination of SIT. One hundred and forty-seven subjects, aged 16 – 25 years, with grass and/or birch pollen allergy were investigated 10 years after initiation of a 3-year course of SIT with standardised allergen extracts of grass and/or birch or no SIT respectively. Conjunctival provocations were performed outside the season and Mch bronchial provocations were performed during the season and winter. Asthma was assessed by clinical evaluation. The significant improvements in rhinoconjunctivitis and conjunctival sensitivity persisted at the 10-year follow-up. Significantly less actively treated subjects had developed asthma at the 10-year follow-up as evaluated by clinical symptoms [odds ratio 2.5 (1.1–5.9)]. Patients who developed asthma among controls were 24/53 and in the SIT group 16/64. The longitudinal treatment effect when adjusted for bronchial hyper-responsiveness and asthma status at baseline including all observations at 3, 5 and 10 years follow-up (children with or without asthma at baseline, $n = 189$; 511 observations) was statistically significant ($p = 0.0075$). The odds ratio for no-asthma was 4.6 95% CI (1.5–13.7) in favour of SIT. A 3-years course of SIT with standardised allergen extracts has shown long-term clinical effects and the potential of preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after treatment (0703).

Rukhadze 2008 reported the use of three different preparations for SIT, ALV – high-dose hypoallergenic preparation (allergoid) for s.c. injections, NHD semi-depot allergens for s.c. injections, NHO – standardised allergen extracts for oral administrations. 195 patients, (range 6 – 60 years) with diagnosed asthma (52.3%), AR/AC (43.1%) and AD (4.6%) sensitised to different aeroallergens (house dust mites, grasses/cereals, weeds, trees, dog epithelia, moulds) were treated at the period of 2001–2007 by following forms of allergen extracts: NHD in 75%, NHO in 10% and ALV in 15% of the patients. 12.8% of patients were under therapy with two allergen extracts. The mean value of duration of SIT was 3 years. At least one episode of local reaction at the injection site was observed in 25.6% of treated patients and delayed systemic reactions (rhinorhea, cough and bronchospasm, itching) in 16.4%. Significant reduction of allergic symptoms and medications scores, as well as, the

improvement of QoL of patients were observed. SIT is an effective and relatively safe disease modifying treatment of asthma and ARC (0807).

Thum-Oltmer 2005 reported an open, prospective, post-marketing surveillance study. 2,047 patients including 68 % with grass and 9 % with pet allergen sensitisations, suffering from ARC, asthma and neurodermatitis were treated for at least 1 season (1 year) with an allergoid preparation adsorbed to aluminium hydroxide (ALV). Doses were given in accordance with the package insert. Efficacy was measured by physician's and patient's self-assessment on an interval scale and by the use of anti-symptomatic medication. Safety was shown in terms of local and systemic reactions and compliance by the number of drop-outs. In total, case report forms for 2,435 years of therapy were evaluated. After 1 year of therapy, 81 % of patients showed a relevant improvement in their condition. After an improvement of 3 points (median) on a 10-point interval scale at the end of the first year, the efficacy improved still further in the second and third year of therapy ($p < 0.001$). The intake of systemic antihistamines could be reduced by 36%, of local mast cell stabilisers and corticosteroids by 44% and 42%, respectively. The time of the start of SIT had no influence on the success of the therapy whereas under-dosing of the preparation resulted in lower efficacy. The response of children and patients above 50 years of age were not different compared to those of the other patients. Patients with clinically relevant sensitisations against 3 or more allergen families showed a trend ($p = 0.148$) towards less efficacy, probably because of symptoms attributable to other sensitisations. Local reactions were seen in association with 241 (1.1 %) of the injections and systemic reactions with 48 (0.3%). The systemic reactions were mainly rhinitis, conjunctivitis, difficulties in breathing and skin reactions. Severe systemic reactions were not observed. In 97% of the cases, the physicians judged the tolerance of the therapy as good. After the first 2 years of therapy, 95% of the patients wanted to continue the treatment. In total, nearly 5% of the patients dropped out. The short-term SIT with allergoids (7 injections) showed good efficacy and safety in the allergologist's practice. SIT is also suitable for children and elderly patients. Treatment should start early during the course of disease because the chance of success decreases with rising numbers of clinically manifest sensitisations. Positive results from earlier clinical trials in a large number of patients in allergologists' practices were confirmed (0502).

Brathwaite et al. evaluated the incidence and severity of adverse reactions to specific allergen immunotherapy (SIT) injections administered to children attending a paediatric allergy clinic. Data were recorded prospectively on 310 consecutive injections with standardised extracts in 14 patients (age 8-15 years at start of SIT). SIT was administered according to conventional schedules and following the guidelines of the EAACI for safety and data collection. 8 patients received conventional SIT with grass pollen extract (Alutard-SQ), 4 a pre-seasonal SIT with grass pollen extract (ALV) and 2 a wasp venoms SIT. 12 patients on grass pollen SIT had AR. Patients on conventional grass and venom SIT received weekly up-dosing injections until maintenance dose, followed by maintenance doses every 6- 8 weeks. Pre-seasonal immunotherapy consisted of 7 weekly up-dosing injections. 210/310 injections were weekly up-dosing and 100/310 maintenance doses. Early reactions (onset within 30 minutes) occurred in 85/310 doses (27.3%) and late reactions in 60/310 doses (19.4%). The majority (75.9%) occurred during the up-dosing phase. 121/145 (83.4%) of reactions were small local reactions with no change in dose schedule. There were 12 large local reactions requiring dose reduction - 4 early, 8 late (3.9% of injections), and 17 systemic reactions - 9 immediate, 8 delayed (5.5% of injections). All systemic reactions were mild or moderate and responded well to

routine treatment. Two immediate systemic reactions occurred in the maintenance phase. There were no systemic reactions in the pre-seasonal SIT group. SIT was judged safe and well tolerated. Minor local reactions are common. Systemic reactions are uncommon and are most likely to occur during up-dosing. The authors further recommend that patients should be observed for one hour after each injection (0607).

In 2007, Ullrich et al. performed a post-marketing surveillance study in which the effectiveness and overall safety of ALV was investigated. 584 questionnaires evaluated from allergic patients 5–71 (median 24) years, 27% of them children, and adolescents up to 14 years of age at the beginning of therapy, with or without asthma. 94% of patients improved after one year of SCIT. The reduced intake of anti-allergic medication was correlated with this improvement ($p < 0.001$). Higher cumulative allergen doses and an additional treatment year led to further decrease in symptoms ($p < 0.01$). In adults, underdosing of SCIT preparations reduced the beneficial effect significantly ($p < 0.01$). Children profited more from therapy than adults ($p < 0.01$). There was also a benefit for patients with asthma. 0.8% of the injections caused local reactions, 0.4% mainly mild to moderate systemic reactions, and 0.04% severe systemic reactions. Good safety and high compliance was documented. Longer treatment duration was associated with an improved outcome. Children showed a stronger improvement than adults (0708).

Martin et al. conducted a post-marketing observational safety and efficacy study on s.c. immunotherapy (SCIT) with ALV (allergoid). 221 office-based specialists participated between 2001 and 2005. 2,047 patients including 67 % with grass and 10 % with pet allergen sensitisations were included, 15.3% of patients were children (5–14 years). Efficacy and safety data of 2931 patients (3008 therapies) with IgE-mediated allergies and clinical symptoms within the relevant season, hyposensitised with a high-dose, hypoallergenic preparation, were collected via structured questionnaires. The documentation comprised case history, injections, anti-symptomatic medication, adverse events, control findings and assessments per patient for the first therapy year. Patients assessed their condition on a visual analogue scale (VAS). Additionally, doctors evaluated patients' health as well as the tolerability of the treatment. Clinically manifest sensitisations were seen in a wide allergen range. 48.5% of the subjects were sensitised to more than one allergen group. After only one injection cycle, very good efficacy in the first pollen season is shown as improvement in VAS (median: 3 scale points). In 86.3% of treatments a clinical relevant improvement of 2 or more scale points was documented. 68.7% of patients reduced their frequency of intake of anti-symptomatic medication. AEs were recorded in 8.2% of total injections (27 109), 98.9% of them were local reactions (e.g. wheal diameter ≥ 4 cm). Patients wanted to continue SCIT in 95% of therapies. SCIT was well tolerated and effective. The high numbers of patients that wished to continue therapy showed the great acceptance of this therapy in daily practice. (0901, 0505).

A post-marketing surveillance study on NHD pollen preparations conducted from October 2001 to October 2005 obtained data on the efficacy and patient tolerance of NHD pollen preparations during the first year of therapy. Data was from 295 patients between 5 and 67 years old. A considerable share of the patients (20.8%) was up to 14 years of age. Approximately 1/3 of all patients were administered pollen preparations in combination. In total, 5996 injections were recorded, 66% out of pollen season, and 34% during pollen season. 78% of the injections with adverse events occurred outside the pollen season and 22% during

pollen season. 24% of the symptoms were mild systemic (grade I according to Tryba) and 3% moderate systemic (grade II according to Tryba). No severe symptoms (grade III/IV acc. to Tryba classification) appeared. 6% of the therapies were discontinued, none because of side effects. In 5.4% of the injections (324/5996) local reactions with a diameter ≥ 4 cm occurred, in 1.5% systemic reactions were observed. 67% of the injections with AEs occurred during usage of strength 1 and 25% of the AEs occurred directly at the beginning of the therapy. 87% of the therapies improved the state of the patients' health in a clinically relevant manner. Deterioration was observed in 1.8% of the therapies. The incidence of AEs was increased for strength 1. The rate of adverse events was not enhanced during pollen season. Safety, efficacy and acceptance of ALV were confirmed (0904, 0504).

A PMS study collected data on the safety and tolerability of the NHD cluster schedule administered by doctors in private practices of 41 physicians across Germany from February 2004 through January 2005. Data was collected from 175 patients (range 5-72, median 34 years). The most commonly used products were mite preparations and a tree mixture. The study population was mainly sensitised against grasses/grains (41.1%), mites, tree pollen, pets (9%), and allergen sources such as herbs, moulds, and foods. Many patients had been sensitised to multiple allergens. AC and AR were the most frequently diagnosed symptoms. 92% of the 175 enrolled patients had rhinitis, and 72% had conjunctivitis. 34.9% of the patients had asthma, and 16.6% had skin changes. 2,485 injections were given in total, 1,806 injections did not produce local swelling. 561 injections produced an area of swelling less than 5 cm in diameter, or the size of the swelling was not reported. 4.7% of the injections resulted in a swelling greater than or equal to 5 cm in diameter. According to the treating physicians' assessment of tolerability, 81.1% of tree SITs, and 68.6% of grasses SITs were rated well-tolerated (tolerability 1 - 3 on a 10-point rating scale). A total of 15 (definitive stop in 5) cases either stopped SIT or the cluster schedule; 8 of these continued SIT on the conventional schedule. Two cases had continuation of conventional SIT planned. ADR reports analysis suggested that allergen summation potentially leading to AEs might occur on injection day 4, when the cumulative maximum dose of 1.0 ml is exceeded. Thus, it was recommended that the 0.6 ml dose should be withheld on day 4. Apart from this aspect, the available (safety) data supports the safety and utility of cluster SIT as a potential alternative to conventional schedules (0503).

The safety and efficacy was further confirmed by a post-marketing surveillance study (2007-mid 2008) investigating the safety of a modified cluster dose-escalation-regimen for NHD pollen and mite preparations. The study was performed between January 2006 and September 2007 in 5 German doctors' practices. Data of 55 patients aged between 4 and 65 years (median: 38 years) was included in the analysis. 58 therapies were performed in these 55 patients because 3 patients received two clustered preparations simultaneously. Sensitisations to grasses/cereals (56.4%) and trees were reported most often, pet allergens were also represented (8%). In total, 830 injections were applied during the course of the 58 therapies. After 461 (55.5%) injections no local reaction was observed. After 139 (16.7%) injections swelling and/or redness more than 5 cm in diameter and/or itching occurred. There were no immediate systemic adverse reactions during the cluster dose-escalation phase. All systemic adverse reactions were delayed. There were 15 single symptoms of systemic adverse reactions grade 1 or 2 in 6 patients which occurred on the third, fourth or sixth day, and no systemic reactions grade 3 or 4 (grades according to the classification of Tryba et al. (Allergo Journal 1994; 3:211-224). Treatment tolerability was patient-rated 'good' (1 to 3) in 78.9% of tree

pollen therapies. Doctors evaluated tolerability 'good' (1 to 3) in 77.3% of asthmatics and in 90.9% of non-asthmatics (0809).

Rogala et al. evaluated the side-effects of conventional s.c. allergen immunotherapy in inhalant allergy performing a retrospective analysis of early and late, local and systemic, short-term and long-term treatment. ALV was given to 47 subjects (21%), NHD to 26 subjects (12%), Catalet T to 74 subjects (33%), Catalet D to 5 subjects (2%), Alutard SQ (ALK) to 36 subjects (16%), and Alavac S to 36 subjects (16%). Side-effects of 4723 injections given to 224 patients (mean age 25.07 years, range 5-46, 127 patients with intermittent and 97 with persistent AR) included 65 systemic reactions in 48 patients (21%) after 61 injections (1.29%). Most of them were late, and included dyspnoea, rhinorrhoea, fever, fatigue and urticaria. The incidence of systemic reactions did not correlate to age or sex, but was higher in grass pollen than in house dust mite allergy and during the up-dosing phase o/treatment. Late phase intense local reactions were observed after 1.6% of injections. The authors rated allergen immunotherapy in inhalant allergy as a safe treatment (0710).

Halken et al. carried out a review in 2008 which was initiated by iPAC (international Pediatric Allergy and Asthma Consortium) on SLIT and SCIT, especially with grass and birch pollen. They found that IT is an effective treatment in children with AR and asthma when a significant part of their symptoms is caused by these allergens. A long-term effect up to 12 years after discontinuation of SCIT with timothy allergen has been shown. Efficacy and safety of SLIT in pollen AR have been demonstrated in adults. The evidence in children is a little less convincing, and more data is needed. The clinical relevance, long-term results and the size of the effect, as well as the dose, the treatment regimen and duration has been elaborated incompletely to date. It is demonstrated that SCIT has the potential for preventing the development of asthma in children with AR. Also one randomised study indicates a preventive effect of SLIT in children on the development of asthma. The authors recommended that areas with lack of evidence should be addressed in well performed prospective, randomised long-term studies both with SCIT and SLIT (0801).

Assessor's comments

The MAH has presented available efficacy and safety data on the products containing Timothy grass allergens. The efficacy and safety profile are identical in adults and in children. No specific studies were conducted in the paediatric population. However it is the opinion of the rapporteur that based on the extensive clinical data the product can be used according to the approved SPC.

Discussion on clinical aspects

The submitted clinical trials in children exposed to the various grass pollen allergens have documented both the efficacy and safety of these products in common clinical practise. Formal controlled clinical studies and dose-response studies are lacking but available information suggest that the posology is identical in children and adults. It has been suggested by CMS that the SPC should be harmonized during this procedure.

However the product in question have obtained national procedure in a number of EU member states and therefore the SPC are different in different countries and the intension for the EU work sharing project assessment of paediatric data of existing products is not to be a harmonisation process for SPC and PIL throughout Europe.

The CMS's suggest that the following modification is accepted:

“Establishing a positive skin prick test is an important tool together with the clinical history and seasonality of symptoms to confirm pollen allergy”.

In addition one MAH (ALK-Abelló) has provided a synopsis of all PSUR indication that no significant difference could be detected regarding the safety profile of ALK grass pollen products. Also the MAH has submitted reference to the use of the prick-test allergen.

The experience with the HAL allergy and Allergopharma products were not included in the Preliminary Assessment Report but is included in this Final Assessment Rapport.

ALK-Abelló Alutard SQ and Aquagen SQ are significant to document the efficacy and safety of these products in children. Hal Allergy should submit the documentation for the use of Purethal in children (reference 1 – 6 in expert report).

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall Conclusion

The products approved for diagnosis and immunotherapy of grass allergy are often used in children sensitized to grass pollen and the approved diagnostic procedure and immunotherapy dose regimen is identical in adults and children. The efficacy and safety of the various products in children have been established through extensive clinical use.

Recommendation

No further action is required. The approved SPCs' for the relevant product should therefore not be modified, apart from emphasising that the posology is identical in both children and adults.

V.1. Discussions on SmPC following circulation of Final AR

Following circulation of final assessment report, comments were received form a MS which could not accept the recommendation proposed by RMS. It was accepted by RMS to include the following texts in SPC and PIL in accordance with e.g. newly ended WS DK/W/006/PdWS/001.

SPC section 4.2:

Children under 5 years of age are normally not considered suitable candidates for hyposensitization because acceptance and cooperation problems are more likely in this age group than for adults. For children >5 years of age clinical data of efficacy are sparse and cannot prove efficacy, however data on safety do not reveal a higher risk as for adults.

Proposal for PIL:

“The product is normally not recommended for treatment of allergy in children under the age of 5 years.”

For the prick-test allergens the following statement should be implemented in the current SPC 4.2.

“Prick-testing in children is already possible after the first year of life depending on the child's constitution, but in general should not be performed before the age of 4.”

Following circulation of the opinion regarding the above recommendations, comments were received from one MS that the harmonised paediatric recommendation as proposed by the Rapporteur could not be accepted. It is the Rapporteurs opinion that agreement on a fully EU harmonised paediatric recommendation can not be achieved in this particular case, because of differences in the already approved paediatric use among MS.

The procedure will be finalised in accordance with the Rapporteur's final recommendation for paediatric use (see above) and implementation of the harmonised use in MS via appropriate regulatory procedures is recommended. However, we acknowledge that one MS is not in agreement with the proposed changes.

The Rapporteur recommends that the MAH achieve full harmonisation with regard to paediatric use through use of appropriate regulatory procedures.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Alutard SQ, ALK-Abelló
Aquagen SQ, ALK-Abelló
Soluprick SQ, ALK-Abelló
Purethal Pollen, HAL Allergy
Novo-Helisen Depot, Allergopharma
Novo-Helisen Oral, Allergopharma
Intracutaneous Test Solution, Allergopharma
Provocation Test Solution, Allergopharma
Skin Prick Test Solution, Allergopharma
Allergovit, Allergopharma