

# Successful specific subcutaneous immunotherapy (SCIT) with non-modified semi-depot pollen and mite preparations

## Results of a post-marketing surveillance study

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### Summary

**Background:** The efficacy of the semi-depot preparation Novo-Helisen<sup>®</sup> Depot is well established in the SCIT market. Here, data of a post-marketing surveillance study concerning effectiveness and overall safety is presented.

**Methods:** A total of 584 questionnaires on therapy with pollen or mite allergen extracts in allergic patients with or without asthma were available. The subjective course of treatment was assessed by visual analogue scale (VAS) and intake of anti-allergic medication. Safety aspects were assessed by monitoring local and systemic adverse reactions. Compliance was thought to be correlated with the number of dropouts.

**Results:** There was a large subjective benefit for patients of all ages. 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 fur-

ther 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: asthmatic symptoms improved in 48% and intake of medication could be reduced in 49% of asthmatic patients. 0.8% of the injections caused local reactions, 0.4% mainly mild to moderate systemic reactions, and 0.04% severe systemic reactions.

**Conclusion:** The present study provides evidence of the effectiveness of SCIT with a non-modified aluminum-adsorbed semi-depot preparation (pollen and mite allergens) in the control of allergic diseases in “everyday” medical treatment. Additionally, good safety and high compliance was documented. Longer treatment duration was associated with an improved outcome. Children showed a stronger improvement than adults.

**Erfolgreiche spezifische subkutane Immuntherapie (SCIT) mit unmodifizierten Semidepot-Pollen- und -Milbenpräparaten: Ergebnisse einer Anwendungsbeobachtung**

### Key words

Specific subcutaneous immunotherapy – semi-depot preparation – post-marketing surveillance study – effectiveness – safety – compliance

### Zusammenfassung

**Hintergrund:** Die Wirksamkeit („efficacy“) des Semidepotpräparats Novo-Helisen<sup>®</sup> Depot ist dokumentiert. In der vorliegenden Anwendungsbeobachtung werden Daten zur Wirkung und Sicherheit der SCIT präsentiert.

**Methoden:** Insgesamt wurden 584 Beobachtungsbögen zur SCIT mit Milben- oder Pollenallergenextrakten bei allergischen Patienten mit oder ohne Asthma ausgewertet. Der Verlauf der Therapie wurde mittels visueller Analogskala (VAS) und anhand der Einnahme antiallergischer Medikamente beurteilt. Zur Beurteilung der Sicherheit wurden lokale und systemische Nebenreaktionen erfasst. Therapieabbrüche wurden als ein Maß für die Compliance angesehen.

**Ergebnisse:** Es zeigte sich ein deutlicher therapeutischer Nutzen für Patienten aller Altersstufen. Bei

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**Schlüsselwörter**  
 Spezifische sub-  
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 depot-Präparat  
 – Anwendungs-  
 beobachtung –  
 Wirkung –  
 Sicherheit –  
 Compliance

94% der Patienten verbesserte sich das Befinden bereits nach dem ersten Therapiejahr, was mit einer reduzierten Einnahme antiallergischer Medikamente korrelierte ( $p < 0,001$ ). Eine höhere kumulative Allergendosis sowie ein zusätzliches Therapiejahr führten zu weiter signifikant abnehmender Symptomatik ( $p < 0,01$ ). Eine Unterdosierung der SCIT-Präparate bewirkte bei Erwachsenen eine signifikante Abnahme der oben beschriebenen Effekte ( $p < 0,01$ ). Kinder profitierten in höherem Maße von der SCIT als Erwachsene ( $p < 0,01$ ). Es ergab sich auch ein Nutzen für Patienten mit Asthma: Die asthmatischen Beschwerden verbesserten sich bei 48% der Asthmatiker, 49% der Patienten konnten die Anwendung von An-

tiasthmatica reduzieren. Nach 0,8% der Injektionen traten Lokalreaktionen, nach 0,4% milde bis mäßige systemische Nebenreaktionen und nach 0,04% schwerwiegende systemische Reaktionen auf.

**Schlussfolgerung:** Die vorliegende Studie dokumentiert, dass die Behandlung allergischer Erkrankungen mittels SCIT mit einem unmodifizierten, aluminiumadsorbierten Semidepotpräparat (Pollen und Milben) wirkungsvoll und effizient erfolgen kann. Die Therapie war sicher und die Patienten zeigten eine gute Compliance. Eine längere Therapiedauer bewirkte eine weitere Verbesserung der Allergiesymptome. Kinder profitierten stärker von der Durchführung der SCIT als Erwachsene.

## Introduction

Allergen immunotherapy involves the administration of gradually increasing quantities of allergen(s) to an allergic patient to ameliorate symptoms associated with subsequent exposure to the causative allergen. Efficacy of subcutaneous specific immunotherapy (SCIT) has been demonstrated for pollen and house dust mite allergens in numerous studies [4, 9, 10]. Various studies investigated the course of treatment [2, 10, 15], and the immunogenic effect [6] of the semi-depot preparation on hand. The aim of the present study is to sum up the results of a post-marketing surveillance study investigating the effectiveness, safety and compliance in a large number of patients in “everyday” allergists’ practices after 1 to 2 years of SCIT.

## Methods

### Patients

Patients’ characteristics are shown in Table 1. Diagnosis of allergic diseases was made by skin tests in

468 patients (89%), by provocation tests in 121 patients (21%), and by serologic tests of specific IgE in 296 patients (56%). Skin tests were combined with provocation tests in 94 patients (18%), and with serologic tests in 227 patients (43%). In 66 patients (13%) diagnosis was based on all three methods.

In total, 63% of patients were monosensitized to one allergen group (e.g., trees, grasses, house dust mites), and 37% were polysensitized.

### Preparations

The present study of SCIT was conducted in Germany as a prospective, open, multicenter, observational cohort study in 255 medical practices between September 1998 and October 2001. Registered pollen and mite preparations of the non-modified semi-depot preparation Novo-Helisen<sup>®</sup> Depot (Allergopharma Joachim Ganzer KG, Reinbek, Germany) were used. All patients were treated with at least one pollen or mite preparation according to the generally accepted therapy criteria for SCIT [10]. Pollen preparations were applied either preseasonally (25% of therapies) or perennially (75%).

According to the patients’ history and the diagnostic results the most frequently administered preparations are shown in Table 2.

### Evaluation of therapy effectiveness, safety, and compliance

Outcome parameters were patients’ subjective impression of their own state of health before SCIT and the changes after 1 or 2 years of treatment. The patients assessed their state of health on a ten-point visual analogue scale (VAS) from 1 (very good) to 10 (very poor). Additional monitoring of symptomatic medication and adverse drug reactions (immediate and late local reactions of at least 5 cm in diameter and systemic reactions) was performed.

**Table 1. Characterization of patients**

Patients (n)	523
Age (years)	5–71 (median 24) (27% children [up to 14 years of age at the beginning of therapy])
Gender (n)	289 female (55%) 211 male (40%) 23 without gender designation
History (% of patients)	90 rhinitis and/or 61 conjunctivitis and/or 34 asthma
Use of medication before SCIT (% of patients)	77 antihistamines 32 glucocorticoids 16 $\beta_2$ -mimetics 28 mast cell stabilizers

Compliance was thought to be indicated by drop-outs.

A total of 584 questionnaires were submitted. For details see Figure 1.

### Statistics

Analysis of data was performed using the software SPSS for Windows, Version 13.0. Figure 2 was drawn with SigmaPlot 9.0 (SYSTAT Software GmbH, Erkrath, Germany).

### Results

#### Clinical outcome (effectiveness)

Before immunotherapy, patients rated their state of health at a median value of 8 (VAS). After the first year of therapy, patients' assessment improved to a median 5 points and to 4 points after the second year.

In detail, in the present SCIT study in 94% of the therapies an improvement – according to the self-evaluated state of health – was observed (relevant improvement by at least 2 scale points in 87%), in 5% no change was reported, and in 1% the state of health had deteriorated. There was a positive correlation of allergy health improvement and therapy duration ( $p < 0.001$ ; Spearman rho = 0.180).

#### Influence of cumulative dose and age of patients

To investigate the influence of dose on therapy outcome, the cumulative dose for one year of SCIT was subdivided into “low dose”, “standard dose”, and “high dose”. According to this grading, adults and children were allocated separately (see Tab. 3).

In total, for all subjects included in the three „dose groups“ after the first year children showed an amelioration in median VAS from 8 to 3 and adults from 8 to 4, respectively ( $p < 0.01$ ). Effectiveness in adults under “low dose” regimen was statistically significantly lower than in the “standard” and “high dose” groups (Mann-Whitney U-test;  $p < 0.01$ ) (Fig. 2). There were no differences in therapy outcome between patients with pollen or with mite SCIT.

#### Therapy outcome in patients with allergic asthma

106 patients showed asthmatic symptoms before the start of immunotherapy. After SCIT, asthmatic symptoms improved in 51 patients (48%), remained unchanged in 54 patients (51%), and deteriorated in one patients (1%). These findings went well with a reduced intake of anti-asthmatic medication in 52 patients (49%); the intake was not affected in 44 patients (42%), and increased in ten patients (9%).

**Table 2. Allergen preparations administered**

	Therapies
Grasses/grass mixtures (timothy grass, velvet grass, rye grass, Kentucky blue grass, meadow fescue, orchard grass, rye)	217
Trees (birch, alder, hazel, beech)	100
Other pollens	7
House dust mites ( <i>Dermatophagoides pteronyssinus</i> , <i>D. farinae</i> )	260
<b>Total</b>	<b>584</b>

**Table 3. Allocation of patients (n = 357) to different dose groups\***

	Low dose	Standard dose	High dose
Pollen preseasonal	< 6,325 TU	> 16,325 TU	Not classified
Pollen perennial	< 16,325 TU	26,325–45,325 TU	> 55,825 TU
Mites perennial	< 16,325 TU	26,325–57,825 TU	> 67,825 TU
Adults (n)	96	134	31
Children (n)	30	61	5

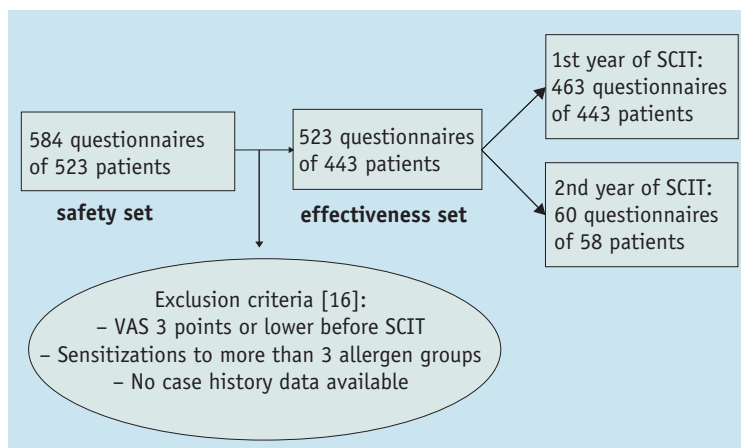
\*166 questionnaires of 86 patients who received doses between “low”, “standard” and “high” dose were not included into this calculation. TU, Therapeutic Unit

#### Compliance and safety

35 patients (6%) discontinued SCIT due to the following reasons: absence (21 patients), adverse reactions (2), lack of effectiveness (1). No information was available in 11 cases.

In 95% of all cases (584 therapies), physicians evaluated the therapy to be “very well” (62%) or “well” (33%) tolerated. Table 4 shows the incidence of side effects.

In 327 therapies of all included patients at least one new maintenance treatment set was started, ei-



**Figure 1. Flow chart showing the number of patients and questionnaires evaluated for safety and effectiveness. In 73 patients more than one questionnaire was available because they were treated with different allergen solutions at the same time.**

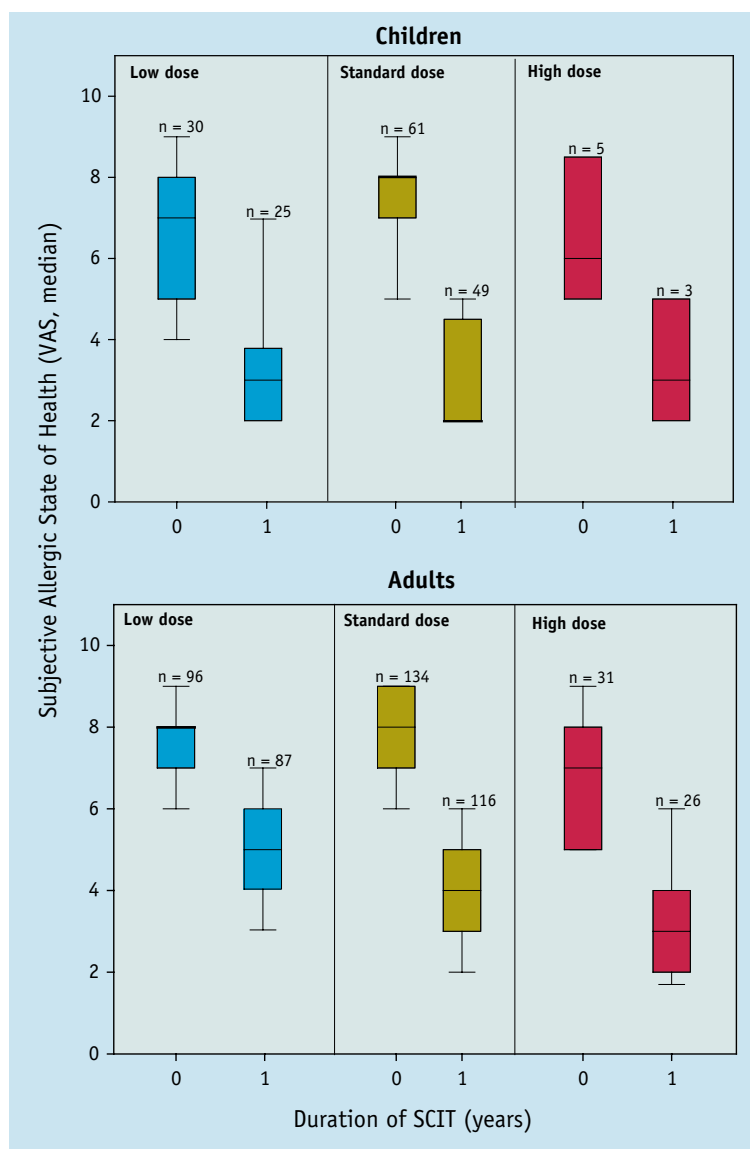


Figure 2. Subjective allergic health status (VAS scores) at the beginning (0) and after 12 months SCIT (1). Top: children (n = 96) up to 14 years; bottom: adults (n = 261). Median values with 25<sup>th</sup>, 75<sup>th</sup> (boxes), 5<sup>th</sup>, and 95<sup>th</sup> (error bars) percentiles.

ther with dose reduction of the first injection from the new vial (195 cases) or without (132 cases). The rate of adverse events was not affected by the different procedures. The same held true for low or high pollen exposure during the observation period (1998–2001) and the injection of two preparations on the same day.

### Discussion

Results of the present study indicate the effectiveness of SCIT under everyday conditions. Thus, in 94% of therapies the patients regarded their state

of health as improved (87% with a relevant improvement by 2 scale points or more). This is in accordance with another study using the same preparation [5]. Medication scores and patients' self-evaluation by VAS were significantly correlated ( $p < 0.001$ ; Spearman  $\rho = 0.359$ ). Low cumulative allergen doses resulted in less improvement of allergic symptoms as indicated by VAS which was also shown for other native allergen preparations [8] and hypoallergenic allergen preparations (allergoids) [16]. We could not show any difference between patients treated with "standard" or "high dose" immunotherapy, probably due to the small number of patients receiving "high dose" immunotherapy (n = 36).

There was a significant difference in clinical outcome between children and adults in favor of the children which is in accordance with the literature [4, 10].

The therapeutic use of SCIT in asthma is discussed controversially. A meta-analysis proved the efficacy and safety of SCIT in asthma [1], and recently asthma grades GINA I and II were recommended to be indications for SCIT [10]. In the observational study on hand a beneficial effect for asthmatic patients was seen as well, although the effects were lower compared with those for allergic rhinitis and conjunctivitis.

The application of this non-modified semi-depot preparation was tolerated very well. The incidence of local reactions  $\geq 5$  cm in diameter was remarkably low (0.8% of injections). Other studies revealed an incidence of 2.8% [5] for the same preparation or 1.9–2.7% for other non-modified allergen extracts [3, 13].

In 0.4% of injections, systemic side effects occurred, most of them being mild to moderate. In the four patients who developed severe systemic reactions, no risk factors (e.g. asthma) could be identified, though all side effects occurred during application of an injection out of the vial with the highest concentration. All these patients continued SCIT. Moreover, there was no difference in systemic reactions between the initial dose-escalation and the maintenance phase. This is in contrast to the observation that systemic reactions occur more frequently during the dose-escalation phase [2, 12].

Patients' compliance is very important in long-term therapies like SCIT, because poor adherence severely compromises the effectiveness of treatment with respect to quality of life and health economics [18]. In the case of atopic diseases, only SCIT is able to prevent the so-called allergic march and to reduce the onset of new sensitizations [4]. There is an economic loss if patients discontinue SCIT, especially due to the proven economic benefit of SCIT in comparison to symptomatic treatment [7, 14]. In the

post-marketing surveillance study on hand, the number of dropouts was small (n = 35 therapies), which was interpreted as showing a good compliance (94%) and acceptance of therapy.

Controlled, randomized studies are needed to confirm the efficacy of therapeutic options, but results cannot directly be transferred to the situation in everyday practice because these studies are usually performed in homogeneous patient groups resulting from very strict exclusion and inclusion criteria in specialized clinics instead of physicians' practices. Therefore, the findings have to be supplemented by results of observational studies reflecting everyday medical work [17]. The prospective, open, uncontrolled, observational design of this study has some methodological limitations when compared to placebo-controlled clinical trials, i.e., the so called placebo effect cannot be determined. It might reach up to 30% in SCIT studies [11]. Nevertheless, post-marketing surveillance studies are necessary and useful because they describe "real life situations" (e.g., polysensitized patients, dose modifications, patients of different ages, adverse events which appear in standard practice routines), and data of large numbers of patients (here, n = 523) can be obtained. This is the reason why authorities demand post-marketing surveillance studies (§ 67, 6 German Drug Law) or sometimes grant registrations only on condition that those studies are conducted. Since in this study the observed level of improvement in VAS and medication intake shows a distinct correlation with the applied cumulative allergen dose, a pure placebo effect is unlikely.

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**Table 4. Incidence of side effects\***

Side effects	Injections (n)	Incidence (% of injections)
<b>Local reactions (swelling, redness, pruritus)</b>		0.8%
5–10 cm diameter	41	
> 10 cm diameter	40	
Movement restriction of the upper arm	1	
<b>Mild to moderate systemic reactions</b>	45	0.4%
e.g., rhinitis, conjunctivitis, cough, sneezing, facial erythema, urticaria, pruritus and heat sensation, headache, vertigo, nausea, ague, numb feeling at the neck		
<b>Severe systemic reactions</b>		0.04%
Cough, dyspnea, and drop in blood pressure	1	
Dyspnea	3	

\*Total number of injections: 10,610. In five patients more than one symptom appeared.

## Conclusion

In addition to well-known studies concerning efficacy, the present study documents effectiveness of SCIT under "everyday" conditions. Thus, SCIT with a non-modified semi-depot preparation leads to a decrease in allergic symptoms which is paralleled by decreased drug intake even after only one year of therapy. This therapy shows a good safety and compliance in a large number of patients in allergists' practices. Children profited to a greater degree from SCIT. A further year of therapy is able to augment the good treatment outcome. Underdosing with regard to the manufacturer's recommendations reduced the beneficial effect.

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