

# Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial

**Background:** Sublingual treatment of grass pollen induced rhinoconjunctivitis might provide easier access to specific immunotherapy (SIT) and minimize the risk of serious adverse events (AEs) compared to subcutaneous SIT.

**Aim of the study:** To identify a safe dose range for once-daily administration of a grass allergen tablet in participants with grass pollen induced seasonal rhinoconjunctivitis.

**Methods:** A randomized, double blind, placebo-controlled Phase I trial was conducted outside the grass pollen season. Seven dosage groups [25 000, 75 000, 150 000, 300 000, 500 000, 750 000, or 1 000 000 standardized quality tablet (SQ-T)], consisting of 12 participants randomized either to active treatment or placebo (3 : 1) daily for 28 days, commenced treatment in a staggered manner at intervals of approximately 1 week to allow for intermittent safety reviews.

**Results:** The grass allergen tablet did not cause any serious, systemic or significant (leading to withdrawal) AEs. The overall incidence of AEs was 74% (1013 events); all of mild or moderate intensity and most considered treatment-related. The most frequently reported treatment-related AEs, including irritation of the throat, and itching sensations in the mouth and ears, increased with dose. These were primarily mild in intensity, started shortly after medication intake and lasted for minutes to a few hours maximum. Objective oral findings were also dose-dependent. No clinically significant observations were found in safety laboratory, vital signs and 12-lead ECG.

**Conclusions:** A sublingual grass allergen tablet in doses up to 1 000 000 SQ-T daily caused no serious or systemic AEs displaying a safety profile that allows further investigation as once-daily self-medication.

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The incidence of allergy is increasing and its significance both for the individual and the society is often underestimated (1). Current symptomatic treatment only addresses the symptoms of allergy and the majority of patients are not satisfied with their current symptomatic treatment (2). The most effective way to prevent the symptoms of allergy is to treat the underlying condition, and specific immunotherapy (SIT) is a unique treatment that is recognized as altering the natural course of the disease (3).

Specific immunotherapy with subcutaneous allergen injections (SCIT) has been successfully used to treat allergic rhinoconjunctivitis (4) and allergic asthma in selected patients (5). Sublingual applications of allergens (SLIT) might provide a better risk-benefit ratio due to less frequent severe adverse events (AEs).

The grass allergen tablet investigated in this clinical trial was developed to make SIT available to a broad group of patients suffering from IgE-mediated allergy to grass pollen. The purpose of this trial was to identify a dose range of grass allergen tablets with a safety profile that allows once-daily intake as self-medication by the

participant. Outcomes included AEs, vital signs, laboratory assessments and physical examinations.

## Materials and methods

Eighty-four participants (64 males and 20 females) were enrolled at the Parexel GmbH Institute of Clinical Pharmacology in Berlin, Germany. Main criteria for participation were: 18–65 years;  $\geq 2$  years clinical history of significant grass-pollen-induced seasonal allergic rhinoconjunctivitis; specific IgE against *Phleum pratense*; positive skin prick test against *Phleum pratense* (ALK Prick SQ<sup>®</sup>; ALK-Abelló A/S, Hørsholm, Denmark); and FEV<sub>1</sub> > 70% of predicted value.

Active treatment involved grass allergen tablets (GRAZAX<sup>®</sup>, ALK-Abelló A/S), which is an orodispersible tablet containing grass allergen extract of standardized quality (6) from *Phleum pratense*. Participants received 25 000, 75 000, 150 000, 300 000, 500 000, 750 000, 1 000 000 standardized quality tablet (SQ-T) or placebo (see Fig. 1); 100 000 SQ-T corresponds to 20  $\mu$ g major allergen (Phl p 5). The dose groups commenced treatment in a staggered manner at intervals of approximately 1 week and progression to the next higher dose was done only if the safety profile

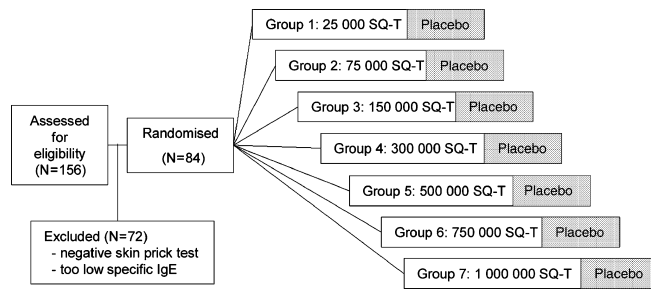


Figure 1. Subject diagram. Seven dosage groups (25 000, 75 000, 150 000, 300 000, 500 000, 750 000, or 1 000 000 SQ-T ALK Grass tablets) commenced treatment in a staggered manner at intervals of approximately 1 week. Progression to the next higher dose was done only if the safety profile after 3-day treatment with the preceding dose was considered safe and well tolerated by the safety committee. Each dosage group consisted of 12 subjects; randomized 3 : 1 to receive active treatment or placebo once daily for 28 days. All randomized subjects received intervention and all completed the trial.

after 3-day treatment with the preceding dose was considered safe and well tolerated. Tablets were administered once daily for 28 days outside the grass pollen season.

The trial included a 2 days in-house stay and 10 visits to the clinic. Participants received a telephone call on treatment days without ambulatory visits. Safety assessments during the trial were physical examination, vital signs (pulse rate, blood pressure), 12-lead ECG, routine laboratory tests on blood and urine samples, oral examination, and recording of AEs and concomitant medication.

All randomized participants were included in the full analysis set, which was used in all analyses. Participants who received placebo were pooled from all dosage groups and analyzed together as a

separate group. Adverse events were coded according to MedDRA (Version 5.1).

Results

All randomized participants completed the trial and were included in the analyses. Participant characteristics were similar between the treatment groups at baseline and the compliance was high for all treatment groups (96–100%).

Thousand and thirteen AEs were reported by 62 (74%) participants (Table 1). Of these, 53 participants (63%) were judged by the investigator as having treatment related adverse events (TAEs) with dose-dependent frequency. All AEs were of mild or moderate severity and no serious AEs were reported in any group. All AEs resolved without sequelae within the duration of the trial and no participants withdrew due to AEs.

The most commonly affected body system was the gastrointestinal tract including oropharyngeal sites, showing 832 AEs, primarily in the dosage groups from 300 000 SQ-T and up. Throat irritation and oral itching were the most frequent AEs; overall reported in 41 (49%) and 25 (30%) participants (Table 1).

Looking at oral symptoms (Fig. 2A), the number of participants reporting AEs and their reoccurrence in number of days with the AE increased significantly with 750 000 and 1 000 000 SQ-T. Other selected AEs (Fig. 2B) reoccurred more often after doses of 300 000 and 500 000 SQ-T; throat irritation being most frequent. Higher doses of 750 000 and 1 000 000 SQ-T also led to conjunctivitis and eye itching.

Table 1. Summary of adverse event

SQ-T	25 000 N (%) E	75 000 N (%) E	150 000 N (%) E	300 000 N (%) E	500 000 N (%) E	750 000 N (%) E	1 000 000 N (%) E	Placebo N (%) E
<i>n</i>	9	9	9	9	9	9	9	21
Any AE*	5 (56) 15	8 (89) 57	6 (67) 56	9 (100) 155	9 (100) 273	8 (89) 236	9 (100) 202	8 (38) 19
TAEs	2 (22) 7	6 (67) 50	6 (67) 56	9 (100) 151	9 (100) 268	8 (89) 235	9 (100) 196	4 (19) 9
Severity of AE								
Mild	5 (56) 13	8 (89) 55	3 (33) 8	9 (100) 116	9 (100) 240	8 (89) 231	9 (100) 193	7 (33) 14
Moderate	2 (22) 2	2 (22) 2	4 (44) 48	2 (22) 39	4 (44) 33	3 (33) 5	3 (33) 9	2 (9.5) 5
Most frequently reported AEs†								
Throat irritation	2 (22) 2	2 (22) 15	3 (33) 15	8 (89) 87	9 (100) 205	6 (67) 55	8 (89) 41	3 (14) 8
Oral pruritus		3 (33) 19	3 (33) 34	1 (11) 28	1 (11) 1	8 (89) 42	8 (89) 74	1 (4.8) 1
Headache	1 (11) 1	2 (22) 3		1 (11) 1	1 (11) 1	2 (22) 8	2 (22) 4	3 (14) 6
Ear pruritus		1 (11) 14		3 (33) 17	1 (11) 28	3 (33) 30	3 (33) 10	
Eye pruritus		1 (11) 11	1 (11) 1		1 (11) 1	3 (33) 5	2 (22) 2	
Conjunctivitis allergic					4 (44) 5	2 (22) 2		
Glossodynia						5 (56) 11	1 (11) 1	
Nasopharyngitis	1 (11) 1	1 (11) 1		1 (11) 1	2 (22) 2			1 (4.8) 1
Oedema mouth				1 (11) 17		2 (22) 3	3 (33) 21	
Oral discomfort						4 (44) 20	1 (11) 6	

\*There were no severe AEs, no serious AEs and no withdrawals due to AEs.

†AEs reported by >5% overall.

SQ-T, standardized quality tablet; AE, adverse event; TAE, treatment related AE, i.e. all AEs that were considered 'probably' or 'possibly' related to study medication by the investigator; N, number of subjects having an AE; %, percent of subjects having an AE; E, number of single AE occurrences.

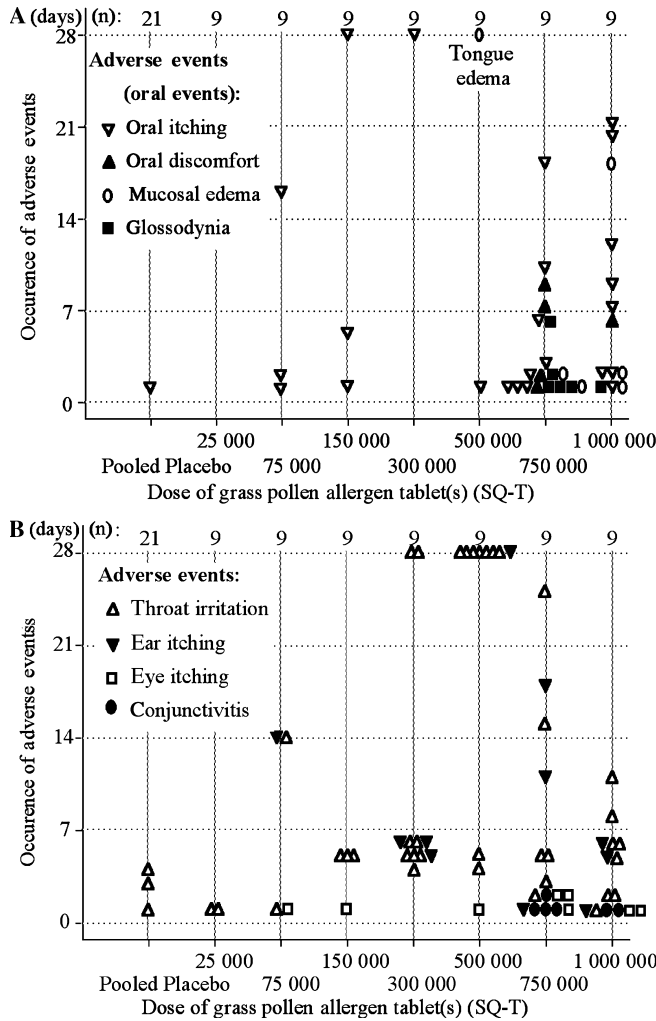


Figure 2. Number of days with reoccurring selected AEs (i.e. the most frequently reported with relation to the trial medication). Each character symbolises a single participant, the x-axis displays the doses administered and the y-axis the number of days with reoccurrence of the AEs. (A) Oral AEs, (B) other selected AEs.

The typical TAE started immediately after intake of trial medication and lasted minutes to hours. Recurrence of a TAE on all 28 treatment days were reported in the 150 000 SQ-T group (oral itching; one participant), in the 300 000 SQ-T group (throat irritation, two participants; oral itching, one participant) and in the 500 000 SQ-T group (throat irritation, seven participants; ear itching, one participant; tongue oedema, one participant) (Fig. 2). There was an indication of lighter symptoms and shorter duration for recurrent TAEs over time of treatment, but duration of single AEs were only reported for the two highest dose groups and no conclusion can be drawn. Regarding the number of TAEs, the majority occurred in the beginning of the treatment period and then the number gradually declined except in the 750 000 SQ-T group (Fig. 3).

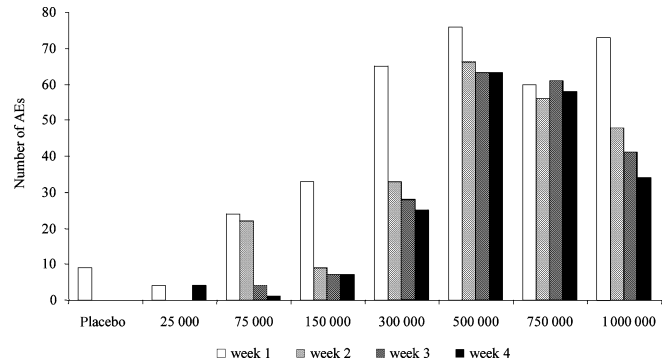


Figure 3. Occurrence of possibly/probably TAEs summarised by dose and weeks of treatment. For details of the AEs, see Table 1.

The oral examinations showed a total of 13 (15%) participants having oral findings. The findings were oedema/swelling under the tongue and/or lower lip, erythema at the soft palate, or a small ulceration (also present predose). Most findings were only present on day 1 but they occurred more frequently, lasted longer and reoccurred more often in the two highest dosage groups.

There were no changes in the other safety assessments that were considered clinically significant or classified as AEs during the trial.

**Discussion**

The grass allergen tablet was tested without any up-dosing schedule in doses from 25 000 to 1 000 000 SQ-T, and it was tolerated with no severe or serious AEs. This finding appears to be quite impressive considering the extremely high amount of sublingually applied allergen (1 000 000 SQ T equals approximately 200 µg of *Phleum pratense* major allergen; Phl p 5) without any escalation phase.

However, as expected when administering specific allergens to allergic individuals, there was a high incidence of short-lasting, local treatment-related effects. The frequency clearly increased with the dose administered. It was decided to record daily recurrent AEs as individual events, i.e. not as one recurrent AE. This is part of the reason why a relatively high number of AEs was recorded.

All AEs were mild or moderate in intensity and most were transient oral sensations, which had an onset immediately after drug intake and resolved within hours. Symptoms were not only reported in close vicinity of the oral cavity, but also more distant regions. Presumably, AEs result from local mucosal mast cell activation and subsequent release of inflammatory mediators. Local spreading of mediators like histamine, might also explain more distant symptoms such as ear and eye itching and conjunctivitis. This has also been reported in severe oral

allergy reactions after consumption of cross-reactive food allergens (7). All AEs resolved without sequelae within the duration of the trial.

The duration of the single AEs tended to decrease over time in several individuals having itching sensations on consecutive dosing days. Down-regulation of IgE-mediated signaling pathways in inflammatory cell like mast cells and basophiles (8), particularly reduced Syk protein levels (9) has been suggested to explain the quick onset of improved tolerability after repeated application of allergens. Sustained immunological mechanisms occurring after prolonged allergen application are unlikely to explain these rapid changes. Also the number of AEs reported per treatment day decreased over time. This could indicate further induction of hypo-responsiveness through IgE-mediated desensitization, i.e. that the oral sensations lasted shorter with repeated dosing.

The risk of severe systemic reactions, including anaphylaxis, has been a key concern in the development and use of SIT [3]. In addition, the inconvenience of regular visits to the allergy clinic during a period of 3–5 years has been a major reason for the search of noninvasive routes of administration. Placebo-controlled trials with sublingual immunotherapy (SLIT) using grass pollen allergens (10), and postmarketing safety surveillance data (11–12) have shown SLIT to be well tolerated in both adults and children. Recent reviews of the available literature pointed out that no severe systemic AEs (early or delayed) have been reported for SLIT in the past 15 years (13, 14)

and in agreement no severe or serious AEs were found during this trial.

Since 1998, SLIT has been included in international guidelines (3, 15) for immunotherapy, and the key messages are standardization and uniformity of high quality allergen products, and specific diagnosis to improve the treatment of allergic participants. From the published trials, it nevertheless appears that a wide range of allergen doses, formulations and dosing schedules are being used for SLIT. Thus, while the safety of SLIT is well documented there is a need for clarification on the optimal dose and dosing regimen.

### Conclusions

Overall, it can be concluded that the grass allergen tablet, given sublingually in dosages between 25 000 and 1 000 000 SQ-T daily, was tolerated with no severe or serious AEs and thus has a safety profile that allows further investigation as once-daily self-medication.

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### References

- O'Connell EJ. The burden of atopy and asthma in children. *Allergy* 2004;**59**(Suppl. 78):7–11.
- White P, Smith H, Baker N, Davis W, Frew A. Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? *Clin Exp Allergy* 1998;**28**:266–270.
- Bousquet J, Lockey RF, Malling HJ. WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;**53**(Suppl. 44):1–42.
- Malling HJ. Immunotherapy for allergic rhinoconjunctivitis. *Clin Allergy Immunol* 2004;**18**:495–509.
- Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *The Cochrane Database of Systematic Reviews* 2003, Issue 4;CD001186.
- Larsen JN, Löwenstein H. Manufacturing and standardizing allergen vaccines. In: *Immunotherapy: a practical review and guide*, Vol. 3. 2000:609–623.
- Kleine-Tebbe J, Vogel L, Crowell DN, Haustein UF, Vieths S. Severe oral allergy syndrome and anaphylactic reactions caused by a Bet v 1-related PR-10 protein in soybean, SAM22. *J Allergy Clin Immunol* 2002;**110**:797–804.
- MacGlashan D Jr. Two regions of down-regulation in the IgE-mediated signaling pathway in human basophils. *J Immunol* 2003;**170**:4914–4925.
- MacGlashan D, Miura K. Loss of syk kinase during IgE-mediated stimulation of human basophils. *J Allergy Clin Immunol* 2004;**114**:1317–1324.
- Malling HJ. Is sublingual immunotherapy clinically effective? *Curr Opin Allergy Clin Immunol* 2002;**2**:523–531.
- André C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000;**121**:229–234.
- Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients. *Allergy* 1999;**54**:1110–1113.
- Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. *J Allergy Clin Immunol* 2003;**111**:437–448.
- Wilson DR, Torres LM, Durham SR. Sublingual immunotherapy for allergic rhinitis. *The Cochrane Database of Systematic Reviews* 2003; Issue 2:CD002893.
- Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(Suppl. 5):S147–S334.