Original Article

Specific Immunotherapy with High Dose SQ Standardized Grass Allergen Tablets was Safe and Well Tolerated

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Abstract. *Background:* Sublingual immunotherapy with grass allergen tablets may be the future treatment for grass pollen allergy because it reduces symptoms and medication use, improves quality of life and is easy to use. Rhinoconjunctivitis and asthma co-exist and we aimed to find a safe dose range of a self-administered grass allergen tablet (ALK Abello A/S) in patients suffering from rhinoconjunctivitis and asthma.
Methods: Four doses were investigated in a randomised, double-blind, placebo-controlled, dose escalation trial. Outside the pollen season 4 groups of 12 patients commenced treatment in a staggered manner, at intervals of 1 week. For 28 days doses of 75 000 (approximately 15μg *Phleum pratense* protein 5), 150 000, 300 000, 500 000 standardised quality tablet (SQ-T) units or placebo were given once daily as sublingual tablets.
Results: Fourty three patients were randomised to receive either active treatment or placebo (3:1). Each dose group consisted of 12 patients except the 500 000 SQ-T group (5 active, 2 placebo). No asthma exacerbations were seen and no serious or severe adverse events were reported. The majority of adverse events were local reactions. The number of adverse events was dose related. No patients withdrew from the study.
Conclusions: Treatment with grass allergen tablets in doses up to 500 000 SQ-T in patients with asthma and rhinoconjunctivitis was safe and well tolerated.

Key words: Asthma. Immunotherapy. Rhinoconjunctivitis. Sublingual. Tablet.

Resumen. *Antecedentes:* La inmunoterapia sublingual con comprimidos de alérgenos de gramíneas puede ser el tratamiento del futuro para la alergia a los pólenes de estas plantas, ya que reduce los síntomas y el uso de medicamentos, mejora la calidad de vida y es fácil de administrar. La rinoconjuntivitis y el asma se presentan conjuntamente y nuestro propósito fue encontrar un rango de dosis seguro para la autoadministración de comprimidos con alérgenos de gramíneas (comprimidos ALK) para los pacientes que sufren rinoconjuntivitis y asma.
Métodos: Se estudiaron cuatro dosis distintas en un estudio aleatorizado, a doble ciego y controlado con placebo. Fuera de la estación de polinización, cuatro grupos de doce pacientes empezaron el tratamiento de forma escalonada en intervalos de una semana. Durante 28 días se administraron por vía sublingual una vez al día dosis de 75.000 (aproximadamente 15μg de proteína 5 de Phleum pratense), 150.000, 300.000 y 500.000 unidades en comprimidos de calidad estandarizada (SQ-T) o se administró un placebo.
Resultados: Se aleatorizó a 43 pacientes (3:1) en dos grupos para administrarles un tratamiento activo o un placebo. Cada grupo de dosis estaba compuesto por 12 pacientes, excepto el grupo de 500.000 SQ-T (5, tratamiento activo, y 2, placebo). No hubo exacerbaciones del asma ni se documentaron efectos secundarios de importancia o graves. La mayoría de reacciones adversas fueron reacciones locales, y la cantidad se correlacionó con la dosis. Ningún paciente abandonó el estudio.
Conclusiones: El tratamiento con comprimidos a base de alérgenos de gramíneas en dosis máximas de 500.000 SQ-T en pacientes con asma y rinoconjuntivitis fue seguro y se toleró bien.

Palabras clave: Asma. Inmunoterapia. Rinoconjuntivitis. Sublingual comprimido.

Introduction

Allergic rhinoconjunctivitis represents a global health problem affecting 10% to 25% of the population [1], and in the Western part of Europe the disease is even more pronounced [2]. Allergic rhinoconjunctivitis is one of the main reasons for visits to primary care clinics and although usually not regarded as a severe disease, it significantly limits the social life of the patient, affects school learning performance and work productivity [1].

Allergic rhinoconjunctivitis is a major risk factor for the development of asthma, and rhinoconjunctivitis and asthma are part of the same allergic condition and co-exist in up to 80% of patients [3-5]. Several controlled trials have documented the efficacy of specific immunotherapy in treating allergic diseases [6-10], and also in preventing the further progression of the allergic disease into asthma [3, 11, 12].

Specific immunotherapy is most often administered as subcutaneous injections by specialists and requires an up-dosing phase followed by a maintenance phase of 3 to 5 years. This treatment modality is well known and has been carried out during the past century in several European countries as well as in the United States of America. Sublingual immunotherapy (SLIT) given as drops of allergen extracts is also a widespread application but mainly in Southern Europe [13]. SLIT has been developed to circumvent the risk of severe systemic side effects linked to injection based immunotherapy and to provide an alternative which can be administered at home by patients themselves instead of at clinics. Side effects related to SLIT are mainly mild events related to the oral cavity and upper airways.

A grass allergen tablet (ALK Grass tablet, ALK-Abelló A/S, Hørsholm, Denmark) for once daily sublingual administration has been developed, and this treatment may be the future treatment for grass pollen allergy. ALK Grass tablet is easy to use and reduces rhinoconjunctivitis symptoms and usage of symptom-preventing medication by addressing the allergic condition [10]. As exposure to large quantities of airborne grass pollen is known to trigger asthma crises in grass pollen allergic asthmatics, it would be of clinical interest to establish a safety margin for the recommended dose, ALK Grass tablet 75 000 SQ-T (GRAZAX®).

The purpose of this trial was to identify a safe dose range of the ALK Grass tablet allowing once daily intake as self-medication by patients with grass pollen-induced rhinoconjunctivitis and asthma.

Materials and Methods

Design

The trial had a randomised, double-blind, placebo-controlled, multiple dose, dose-escalation design and was conducted outside the grass pollen season. The patients were randomised to 1 of 4 dosage groups. Each dosage group was planned to consist of 12 patients randomised to either active treatment or placebo (3:1) (Figure).

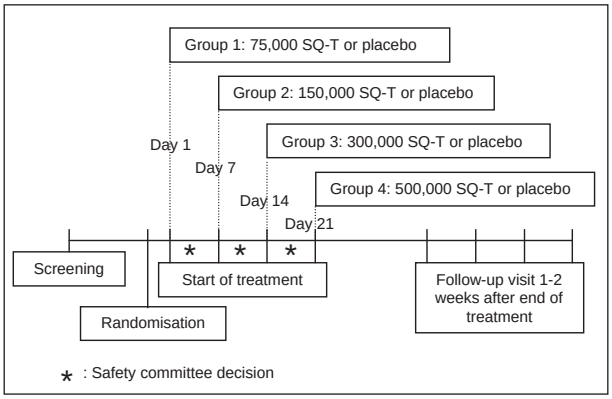

Figure. Study design

The dosage groups commenced treatment with ALK Grass tablet in a staggered manner. Intervals between groups were approximately 1 week allowing a safety committee to review the initial safety data in each group before dosing began at the next (higher) level. The safety committee included in addition to the principal investigator, an expert in allergy, the trial manager and a medical expert from ALK-Abelló. The safety committee reviewed available blinded data on adverse events for each dosage group before deciding if the next dosing group was to be initiated. The treatment was a fast dissolving grass allergen tablet. The doses administered were 75 000 (approximately 15μg *Phleum pratense* major allergen (Phl p 5), 150 000, 300 000, 500 000 SQ-T or placebo, given once daily sublingually for 28 days.

The trial visits included a screening visit, an in-house visit (48 hours), 8 ambulatory visits (days 3 – 7, 14, 21 and 28), and an ambulatory follow-up visit (between days 35 and 42). Examination of the oral cavity was performed by the investigator on all visits in the treatment period. At the first in-house visit in the treatment period, oral examination was made before medication intake and 10 minutes, 30 minutes, 1 hour, 2 hours, 6 hours and 12 hours after medication intake. At the ambulatory visits oral examinations were performed before medication intake and 10 minutes after medication intake.

Forced expiratory volume in 1 second (FEV1) was measured at all visits (prior to medication intake). Additionally, 3 peak expiratory flow rate (PEF) recordings were performed each day in the morning and in the evening (prior to medication intake). Patients were instructed to use a Mini-Wright® peak flow meter and to note triple determinations of PEF in a diary.

In addition to the visits, the trial included daily telephone contacts on all other days during the treatment period. During the telephone contact, the patients reported any adverse events and any changes in concomitant medication since last contact, confirmed that the daily PEF

measurement had been made, and confirmed that the trial medication had been taken.

All adverse events were reported daily in the diary. Severity of the events was graded by the investigator according to the following definitions: mild (transient symptoms, no interference with the patient's daily activities); moderate (marked symptoms, moderate interference with the patient's daily activities); and, severe (considerable interference with the patient's daily activities, unacceptable). In addition the investigator assessed the causality as: probable (good reasons and sufficient documentation to assume a causal relationship); possible (a causal relationship is conceivable and cannot be dismissed); and, unlikely (the event is most likely related to an etiology other than the Grazax®).

Written informed consent was obtained before participants entered the trial and the trial was performed in accordance with the Declaration of Helsinki [14] and Good Clinical Practise. The Research Ethics Committee, Queen's University, Belfast, Northern Ireland approved the study (Application Id. 105/04).

The main inclusion criteria were: Age 18 to 65; a clinical history of significant grass pollen-induced allergic rhinoconjunctivitis and mild to moderate grass pollen-induced asthma of 2 years or more; well controlled seasonal asthma in accordance with the British Thoracic Society criteria[15]; a positive skin prick test (Soluprick® SQ, ALK-Abelló; wheal diameter ≥3mm) and specific IgE (≥CAP allergy Class 2) to *P. pratense*.

The main exclusion criteria were: Significant asthma outside the grass pollen season; FEV_1<70% of predicted value; significant allergic rhinitis (requiring medication) caused by allergens other than grass pollen during the planned treatment period; conjunctivitis, rhinitis or asthma at the screening or randomisation visits; history of anaphylaxis; immunosuppressive treatment; hypersensitivity to the excipients of the trial medication or rescue medication; having received immunotherapy with grass-pollen allergen within the previous 10 years or any other allergen within the previous 5 years; pregnancy or lactation.

The sample size for this phase I trial followed empirical considerations. No formal sample size estimation was made, and no formal statistical comparison of treatment groups at baseline or follow-up was performed.

In addition to the recording of all adverse events, a subset of selected adverse events were further investigated by specifically analyzing details of duration and resolution. The terms were selected according to relevance and frequency at a blinded review.

Results

A total of 116 patients were initially screened and 43 patients were enrolled from February to April 2004. All patients completed the trial. Patient demographics and characteristics were similar between treatment groups (Table 1).

On average, the actively treated patients had a history of 15.6 years with rhinoconjunctivitis due to grass pollen and 17.3 years with asthma in the grass pollen season while patients receiving placebo had a history of 13.7 years with

Table 1. Patient demographics

Treatment Dose (SQ-T) N		Active 75 000 9	Active 150 000 9	Active 300 000 9	Active 500 000 5	Active all 32	Placebo 11
Age (years)	Mean (SD) Range	22.1 (3.2) 20-29	23.2 (2.8) 18-28	28.0 (9.5) 19-42	25.8 (5.5) 21-35	24.7 (6.2) 18-42	24.5 (5.5) 21-40
Height (cm)	Mean (SD) Range	175 (11.1) 157-192	170 (10.3) 151-185	172 (8.5) 160-192	174 (7.3) 166-180	173 (9.4) 151-192	172 (6.5) 164-183
Weight (kg)	Mean (SD) Range	70.9 (13.3) 53-99	77.6 (18.7) 48-110	80.4 (22.0) 58-112	84.4 (19.6) 68-109	77.6 (18.2) 48-112	83.6 (14.3) 54-105
Years with Rhino-conjunctivitis	Mean (SD) Range	13.7 (6.3) 4-25	8.8 (6.1) 4-20	21.1 (10.7) 7-42	21.4 (10.1) 10-36	15.6 (9.6) 4-42	13.7 (9.2) 3-29
Years with asthma	Mean (SD) Range	12.9 (4.5) 5-18	15.7 (5.3) 7-20	22.2 (10.2) 9-42	19.4 (11.0) 8-36	17.3 (8.3) 5-42	15.4 (7.2) 2-27
Gender	Female % Male (%)	3 (33) 6 (67)	3 (33) 6 (67)	3 (33) 6 (67)	2 (40) 3 (60)	11 (34) 21 (66)	5 (45) 6 (55)

N = number of patients; Active = grass allergen tablet; SD = standard deviation

Table 2. Overview of adverse events

Treatment Dose (SQ-T) N	Active 75 000 9 N (%) E	Active 150 000 9 N (%) E	Active 300 000 9 N (%) E	Active 500 000 5 N (%) E	Placebo 11 N (%) E
All adverse events	9 (100%) 58	9 (100%) 131	9 (100%) 279	5 (100%) 140	10 (91%) 60
Severity					
Mild	9 (100%) 58	9 (100%) 130	9 (100%) 272	5 (100%) 138	10 (91%) 57
Moderate	0	1 (11%) 1	4 (44%) 7	2 (40%) 2	2 (18%) 3
Action taken					
None	9 (100%) 39	9 (100%) 95	9 (100%) 244	5 (100%) 122	10 (91%) 30
Therapy	6 (67%) 19	9 (100%) 36	6 (67%) 35	4 (80%) 18	6 (55%) 30
Relation to trial medication					
Missing	0	0	0	0	1 (9%) 1
Possible	6 (67%) 13	7 (78%) 28	8 (89%) 50	4 (80%) 14	4 (36%) 7
Probable	7 (78%) 22	9 (100%) 66	8 (89%) 191	5 (100%) 106	5 (45%) 7
Unlikely	8 (89%) 23	8 (89%) 37	6 (67%) 38	4 (80%) 20	9 (82%) 45

N = number of patients; E = number of events; Active = grass allergen tablet; % = percent of patients

Table 3. Therapy used due to an adverse event

Treatment Dose (SQ-T) N	Active 75 000 9 N (%) E	Active 150 000 9 N (%) E	Active 300 000 9 N (%) E	Active 500 000 5 N (%) E	Placebo 11 N (%) E
All	7 (78%) 46	9 (100%) 40	6 (67%) 46	4 (80%) 17	7 (64%) 32
Acetylsalicylic acid	0	0	0	0	1 (9%) 1
Acyclovir	1 (11%) 1	0	0	0	0
Anacin	1 (11%) 12	0	0	0	1 (9%) 1
Antiseptics	0	0	1 (11%) 6	1 (20%) 1	
Beclometasone	1 (11%) 1	0	0	0	1 (9%) 1
Campho-phenique	0	0	1 (11%) 1	0	0
Famcilorvir	0	0	0	1 (20%)	0
Ibuprofen	0	0	1 (11%) 2	0	0
Lemsip	2 (22%) 2	0	1 (11%) 1	0	0
Panadeine co	0	1 (11%) 1	0	0	0
Paracetamol	1 (11%) 17	1 (11%) 1	3 (33%) 18	3 (60%) 6	1 (9%) 1
Pseudoephedrine hydrochloride	0	0	0	0	1 (9%) 1
Salbutamol	4 (44%) 10	7 (78%) 37	4 (44%) 18	2 (40%) 8	5 (45%) 24
Terbutaline sulphate	0	0	0	0	1 (9%) 3
Thomapyrin	0	1 (11%) 1	0	1 (20%) 1	0

N = number of patients; E = number of events; Active = grass allergen tablet; % = percent of patients

rhinoconjunctivitis due to grass pollen and 15.4 years with asthma in the grass pollen season. Overall, the patients suffered from mild to moderate grass pollen induced asthma and significant grass pollen-induced rhinoconjunctivitis.

No serious adverse events were reported, and no patients withdrew from the trial due to adverse events. All adverse events were mild or moderate in severity with frequency related to the dose (Table 2). The majority of the adverse events were local reactions in the mouth or throat.

All patients recovered from their adverse events and in only 18% of cases was therapy required. The most frequently used therapy was asthma medication (salbutamol) and pain killers (paracetamol, acetyl salicylic

acid). In accordance with the higher adverse event frequency in patients receiving active treatment, use of therapy was more frequent in these patients (81%) compared to placebo (64%) (Table 3).

Eighty-one percent (490 of 608 events) of the adverse events in the groups receiving active treatment were considered to be possibly or probably related to Grazax. However, in the 75 000 SQ-T group only 60% (35 of 58 events) of the adverse events were considered to be related to Grazax®. In the placebo group 23% (14 of 60 events) of the adverse events were considered related (Table 2).

Oral pruritus was by far the most frequent treatment related adverse event. Eighty-eight percent (28 of the 32) of the actively treated patients reported oral pruritus compared to 36% (4 of the 11) of the placebo treated patients. Headache and pharyngitis appeared as second and third most frequently reported treatment related adverse events, when sorted by number of patients. Forty-four percent (14 of 32) of the actively treated patients, but none of the placebo treated patients reported headache, while 22% (7 of 32) of actively treated and 9% (1 of 11) of placebo treated patients reported pharyngitis.

Ear pruritus and oral hypoesthesia appeared as second and third most frequent treatment related adverse events. There were 72 adverse events of ear pruritus, and of these 61 were reported by 3 patients in the 300 000 SQ-T dose group. Only a single event of ear pruritus was reported by a placebo treated patient. Four patients reported in total 15 events of oral hypoesthesia and they all received active treatment.

In Table 4 treatment related adverse events in concern are listed. Notably, only 6 patients (19%), who received active treatment, reported in total 14 treatment related adverse events that could indicate change in asthma status (chest discomfort, chest tightness, hoarseness, dyspnoea, cough and wheezing). Of these events 5 required concomitant medication. One patient treated with placebo reported aggravated asthma, and 1 reported wheezing.

The duration of the adverse events varied in time from minutes to days but the duration was only partly related to the dose given. The mean daily duration of oral pruritus, ear pruritus and oral hypoesthesia was less than 1 hour, while the mean duration of pharyngitis was approximately 3 days. Notably, the median duration of oral pruritus was only 10 minutes for patients treated with Grazax®.

In Table 5 resolution of the most frequent treatment related adverse events is presented. The resolution was defined as days from first medication intake until the adverse event no longer occurred again. Last occurrence of oral pruritus in the 75 000 SQ-T group ended on average 6.3 days after first medication intake but resolution increased with the dose to 18.6 days in the 500 000 SQ-T group. The average resolution for the placebo treated patients was 0.5 day.

Fourteen abnormal findings appeared at the oral examinations, 12 in active treatment patients and 2 in placebo treated patients. The findings were described by the investigator as e.g. “white, swollen raw area”, “broken mucosa”, “small white area”, “specks of blood”, “small blister”, “small ulcer”, “white speckled dots”. There was no dose relationship or difference between active and placebo groups. The oral findings occurred on random

Table 4. Concerned treatment related adverse events

Treatment Dose (SQ-T) N Preferred term	Active 75 000 9 N (%) E	Active 150 000 9 N (%) E	Active 300 000 9 N (%) E	Active 500 000 5 N (%) E	Placebo 11 N (%) E
All related AEs	8 (89%) 35	9 (100%) 94	9 (100%) 241	5 (100%) 120	7 (64%) 14
Asthma aggravated	0	0	0	0	1 (9%) 1
Chest discomfort	0	0	1 (11%) 1	1 (20%) 1	0
Chest tightness	1 (11%) 1	0	1 (11%) 1	0	0
Cough	0	0	2 (22%) 4	0	0
Dry throat	2 (22%) 4	0	0	1 (20%) 1	0
Dysphagia	0	0	1 (11%) 2	0	0
Dyspnoea NOS	1 (11%) 1	0	1 (11%) 1	0	0
Hoarseness	0	0	1 (11%) 1	0	0
Oral hypoaesthesia	0	0	1 (11%) 4	3 (60%) 11	0
Odynophapia	0	0	1 (11%) 1	0	0
Oedema mouth	3 (33%) 3	1 (11%) 1	2 (22%) 4	0	0
Oral pruritus	6 (67%) 13	9 (100%) 49	8 (89%) 96	5 (100%) 77	4 (36%) 5
Pharyngitis	3 (33%) 3	0	4 (44%) 9	0	1 (9%) 1
Swollen tongue	1 (11%) 1	0	1 (11%) 1	1 (20%) 1	0
Throat irritation	0	0	1 (11%) 1	1 (20%) 1	0
Throat tightness	0	0	0	0	1 (9%) 1
Wheezing	0	1 (11%) 1	1 (11%) 2	0	1 (9%) 1

N = number of patients; E = number of events; Active = grass allergen tablet; % = percent of entire treatment group; NOS = not otherwise specified.

Table 5. Resolution (in days) of the most frequent treatment-related adverse events

Treatment Dose (SQ-T) N Preferred term	Active 75 000 9	Active 150 000 9	Active 300 000 9	Active 500 000 5	Active all 32	Placebo 11
Oral Hypoaesthesia						
N	0	0	1	3	4	0
Mean	0	0	6.0 (0)	10.3 (14.5)	9.3 (12.0)	0
Median	0	0	6.0	3.0	4.5	0
P25%-P75%	0	0	6.0-6.0	1.0-27.0	2.0-16.5	0
Min-Max	0	0	6.0-6.0	1.0-27.0	1.0-27.0	0
Ear pruritus						
N	0	2	3	1	6	1
Mean (SD)	0	4.5 (6.4)	26.3 (0.6)	10.0 (-)	16.3 (11.5)	2.0 (-)
Median	0	4.5	26.0	10.0	18.0	2.0
P25%-P75%	0	0-9.0	26.0-27.0	10.0-10.0	9.0-26.0	2.0-2.0
Min-Max	0	0-9.0	26.0-27.0	10.0-10.0	0.0-27.0	2.0-2.0
Oral pruritus						
N	6	9	8	5	28	4
Mean (SD)	6.3 (10.1)	9.0 (6.0)	17.4 (11.5)	18.6 (10.2)	12.5 (10.3)	0.5 (0.6)
Median	0.5	10.0	22.0	24.0	11.5	0.5
P25%-P75%	0.0-13.0	4.0-15.0	7.5-26.5	8.0-27.0	1.5-24.0	0.0-1.0
Min-Max	0.0-24.0	0.0-16.0	0.0-27.0	7.0-27.0	0.0-27.0	0.0-1.0
Pharyngitis						
N	3	0	4	0	7	2
Mean (SD)	9.7 (8.5)	0	19.5 (4.0)	0	15.3 (4.0	5.5 (2.1)
Median	13.0	0	20.5	0	16.0	5.5
P25%-P75%	0.0-16.0	0	16.5-22.5	0	13.0-22.0	4.0-7.0
Min-Max	0.0-16.0	0	14.0-23.0	0	0.0-23.0	4.0-7.0

N = number of patients; SD = standard deviation; Active = grass allergen tablet; Resolution on the same day as first medication dose was defined as 0 days

days in the trial period and all adverse events observed in the oral cavity resolved within the trial period.

No clinically significant changes were observed in FEV_1 or PEF values during the trial period.

Discussion

All randomised patients completed the trial, and the majority of adverse events were mild local reactions related to the oral administration of Grazax®. In addition no asthma exacerbations or serious adverse events were reported.

Based on previous trials with SLIT and with the ALK Grass tablet, it was expected that the patients would experience local transient adverse events [10, 16]. The type and frequency of adverse events probably caused by ALK Grass tablet were comparable to what has previously been found in allergic patients with or without asthma [10, 16]. The fact that all patients completed the trial indicates that the patients did not consider the events bothersome. This is supported by the low use of therapy for treatment related adverse events.

Trials on subcutaneous immunotherapy have shown that patients with asthma have a higher risk of adverse systemic reactions [17]. In this trial very few patients reported adverse events indicating worsening of asthma and there was no obvious difference between placebo and active treatment. The only patient reporting aggravated asthma received placebo. Thus, the sublingual administration of ALK Grass tablet did not impair asthma control.

Oral pruritus was by far the most frequent adverse event. However, it was mild and momentary, caused no dropouts and thus raised no safety concerns. Ear pruritus, oral hyperesthesia and oral pruritus for most patients lasted for less than 30 minutes spread over several days. The number of adverse events was dose related, and this study confirms that the profile of adverse events is directly linked to the major allergen content in SLIT [18]. In general few adverse events are reported in SLIT trials, but trials investigating multiple doses are rare [19-21]. Both high and low doses of SLIT have been shown efficacious [20] and as adverse events are dose related optimal treatment of the allergic patient does not solely depend on a high content of major allergen.

This study was performed outside the grass pollen season and exposure in the grass pollen season needs to be investigated to complete the safety profile. Additionally, the patients included were strictly selected according to the inclusion criteria. Based on the presented safety profile, it seems plausible to initiate safety studies with the ALK Grass tablet in more severe asthmatics, children and the elderly. A minor limitation of this trial concerns the reduced number of patients in the highest dosage group (500 000 SQ-T). Due to recruitment difficulties the group included 7 patients instead of 12.

Overall, this trial adds supportive safety information concerning daily intake of ALK Grass tablet in high doses as self medication in patients with grass pollen-induced rhinoconjunctivitis and asthma. Based on this trial, a safety window has been established in asthmatic patients. A dose as high as 500 000 SQ-T was safe and well tolerated.

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