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Dose-finding study of carbamylated monomeric allergoid tablets in grass-allergic rhinoconjunctivitis patients

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Aim: To determine the optimal effective and safe dose of sublingual immunotherapy tablets containing carbamylated monomeric allergoids in patients with grass pollen-induced allergic rhinoconjunctivitis.

Methods: In this prospective, randomized, double-blind, active-controlled, multicenter, Phase II study, four different daily doses were applied preseasonally for 12 weeks. **Results:** Of 158 randomized adults, 155 subjects (safety population) received 300 units of allergy (UA)/day ($n = 36$), 600 UA/day ($n = 43$), 1000 UA/day ($n = 39$), or 2000 UA/day ($n = 37$). After treatment, 54.3, 47.6, 59.0 and 51.4% of patients, respectively, ceased to react to the highest allergen concentration in a conjunctival provocation test. Furthermore, the response threshold improved in 70.4, 62.9, 76.7 and 66.7% of patients, respectively. No serious adverse events occurred. **Conclusion:** This study found 1000 UA/day to be the optimal effective and safe dose.

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Keywords: allergic rhinoconjunctivitis • carbamylated monomeric allergoid tablets • dose-finding study • grass pollen • sublingual immunotherapy

The clinical efficacy and safety of allergen-specific immunotherapy in the treatment of seasonal allergic rhinoconjunctivitis have been proven in many clinical trials [1–6]. Subcutaneous immunotherapy significantly reduces symptoms and the need for symptomatic medication in allergic rhinitis [7], but it is used limitedly because of potential severe systemic reactions [8]. There has been considerable interest in alternative routes of administration, particularly sublingual immunotherapy (SLIT) [9]. This form of therapy is well tolerated, effective and the potential of home administration makes it especially attractive [10–12]. Furthermore, SLIT is considered a treatment of choice in children and is recommended in the recently published European Guidelines on Allergen Immunotherapy [13,14]. Adverse events (AEs) from SLIT with inhalant allergens are expected and predominantly localized at the application site [15].

Carbamylated monomeric allergoid grass tablets are one of several preparations used in SLIT for allergic rhinoconjunctivitis. Grazax[®]/Grastek[®] (ALK-Abelló, Hørsholm, Denmark) is a perennially administered tablet containing 75,000 standardized quality tablet units (SQ-T) of *Phleum pratense* 5. This tablet has been shown to be well tolerated and clinically effective for long-term use in large cohorts of North American and European adult, elderly and pediatric patients [16–21]. Oralair[®] (Stallergenes, Antony, France) consists of group 5 major allergens from five different grass species at the optimum maintenance dose of 300 index of reactivity (IR). It is a pre- and co-seasonal SLIT tablet that has been shown to be efficacious in adults for up to 2 years after they had completed treatment for three consecutive pollen seasons [22–25].

Nongrass SLIT tablets on the European market include formulations for ragweed (Ragwitek[®]; ALK-Abelló, Hørsholm, Denmark) and house dust mite (HDM) (Acarizax[®] [ALK], Actair[®] [Stallergenes]) allergy. Japanese cedar, birch and tree pollen tablets are still being investigated in late-phase clinical trials [26–28]. Acarizax with

Dermatophagoides farinae (Der f) 1–2 and *D. pteronyssinus* (Der p) 1–2 showed significant efficacy and reduction in the required inhaled corticosteroid dose for asthma control at 6 standardized quality units (SQ-E)/ml [25,29,30].

At year 1, treatment success of Actair[®], containing Der f 1 and Der p 1, was significantly greater in the 500 and 300 IR groups ($p = 0.0206$ and $p = 0.0001$, respectively) than in the placebo group [25,31]. 12-week treatment with carbamylated monomeric HDM allergoid tablets of Der f 1 and Der p 1 (Lofarma, S.p.A., Milan, Italy) significantly improved conjunctival provocation test (CPT) tolerance at a dose of 2000 units of allergy (UA)/day, but not at higher or lower doses [32].

We previously assessed the clinical efficacy and safety of carbamylated monomeric pollen allergoid sublingual tablets in a meta-analysis involving 266 patients with allergic rhinoconjunctivitis caused by grass pollen or HDM [33]. Unlike the native-allergen SLIT grass tablets marketed in Europe and North America, these monomeric allergoid SLIT tablets for pre- and coseasonal intake induce fewer local side effects and are tolerated well. They have been shown to be efficacious in the treatment of allergic rhinoconjunctivitis [33]. The sum of the allergen doses consumed in the preseasonal treatment of grass pollen allergy during all included studies ranged from 36,000 to 40,500 allergy units (AU) [33]. The purpose of the present study was to determine the optimal dose out of four different daily doses in patients suffering from grass pollen-induced allergic rhinitis and/or rhinoconjunctivitis.

Methods

Patients

A total of 158 outpatients were recruited for this study from specialized allergy centers belonging to our German Rhinitis Study Group network of investigators. Participants were included after they had given informed consent. Inclusion criteria were as follows: female or male patients 18–75 years of age; history of at least 2 years of grass pollen-induced, moderate to severe persistent allergic rhinitis and/or allergic rhinoconjunctivitis with or without seasonal controlled asthma [34,35], with the majority of clinical symptoms having appeared during the appropriate season for grass pollen; positive skin prick test for grass pollen allergen; and positive response to grass pollen allergen in the CPT. Patients with clinically relevant sensitizations to other seasonal aeroallergens not airborne during the study period, such as ragweed, tree or rye pollen, were also allowed to participate. The main exclusion criteria were: previous immunotherapy with grass pollen allergen within the last 5 years, concomitant medication (oral or topical anti-H1 antihistamines, intranasal glucocorticoids; to avoid possible interference with results from the skin prick test and CPT), existing or intended pregnancy, predominantly perennial allergic rhinitis, partly controlled or uncontrolled asthma.

Study design

The clinical trial was conducted as a prospective, randomized, double-blind, four-armed, active-controlled, multi-center, Phase II study in outpatient allergy centers in Germany. After a screening visit (V1), patients were randomized to one of four different dosage groups and received sublingual tablets on a daily basis for 12 weeks. Table 1 provides an overview of the study visits V1–V4 and the parameters checked at each visit.

Immunotherapy

The investigational medicinal product (IMP) used in this study was manufactured by Lofarma S.p.A., Milan, Italy. The active ingredients of the grass tablets are carbamylated, monomeric allergoids of grass pollen consisting of timothy grass (*P. pratense*), common meadow grass (*Poa pratensis*) and meadow soft grass (*Holcus lanatus*) in equal parts. Carbamylated allergoids are obtained when native allergens react with potassium cyanate, causing the ϵ -amino group of the lysine present on the allergen proteins to transform into ureido groups [36]. Four different doses – 300 UA/day (Group 1), 600 UA/day (Group 2), 1000 UA/day (Group 3) and 2000 UA/day (Group 4) – were applied preseasonally, amounting to cumulative doses ranging from 25,200 to 168,000 UA for the 84-day treatment period. UA is the abbreviation of ‘unit(s) of allergy’, describing the allergenic potency which corresponds to 1/40 of the mean provocation dosage of the comparable unmodified allergen determined by nasal provocation testing in patients suffering from allergic rhinitis.

Conjunctival provocation test

The CPT is a suitable instrument for assessing conjunctival susceptibility to grass pollen allergen [37]. According to Riechelmann *et al.*, the diagnostic efficacy of the CPT was 89%, regardless of whether subjects had reported nasal symptoms only or both nasal and conjunctival symptoms [38]. The test was performed at V1 (Day 0), V3

Table 1. Flowchart of study visits and check-ups.

Parameters to be checked	Planned intervals			
	V1	V2	V3	V4
	Day 0	Day 7 ± 2	Day 28 ± 7	Day 84 ± 7
Patient informed consent	X			
Demographic data	X			
General and allergological anamnesis	X			
Inclusion/exclusion criteria	X			
Randomization	X			
Physical/ENT examination	X	X	X	X
Administration of the IMP	X		X	
Distribution of rescue medication	X			
Collection of rescue medication				X
Collection of unused and empty IMP			X	X
Conjunctival provocation test	X		X	X
Skin prick test	X			
Documentation of adverse events	X	X	X	X
End-of-study form				X

ENT: Ear–nose–throat; IMP: Investigational medicinal product; V: Visit.

Table 2. Categorization of the response to allergen in the conjunctival provocation test.

Stage	Findings
0	(–) No subjective or visible reaction
I	(–) Itching, redness, foreign body sensation
II	(+) Stage I plus tearing, vasodilatation of the conjunctiva bulbi
III	(+) Stage II plus vasodilatation and erythema of the conjunctiva tarsi, blepharospasm
IV	(+) Stage III plus chemosis, lid swelling

Data taken from [38].

(28 ± 7 days) and V4 (84 ± 7 days). The solutions used in the provocation tests were produced by ALK-Abelló, Wedel, Germany. The titrated conjunctival allergen challenge was conducted with three solutions containing grass pollen allergens in increasing doses of 100, 1000 and 10,000 SQ-E/ml applied one after the other into the patient's left eye, while a control solution without allergen was applied to the patient's right eye to provide a negative control. Conjunctival symptoms of both eyes were assessed 10 min after each provocation and classified as a negative or positive reaction (right eye) and as one of five stages (left eye) according to Table 2. The CPT was considered positive if the response was Stage II or higher. As soon as a positive reaction occurred, the CPT was stopped, the eye was rinsed with water, local antihistamine solution was applied to the patient's eye and the grass pollen allergen concentration inducing the positive CPT response was recorded. If the patient showed a positive reaction in the right (control) eye, the test was considered invalid.

Objectives

The primary objective was to assess the efficacy of SLIT with allergoid tablets by comparing the proportion of patients per treatment group who showed a change in the response threshold needed to induce a positive CPT response at V1 and V4, according to the evaluation defined by Riechelmann *et al.* from 2003 [38] using the methodology and questionnaire described in detail by Dogan *et al.* [37]. For each of the four treatment groups, the changes in the threshold allergen concentration needed to induce a positive CPT response were compared. Three categories were used to describe the change in the treatment response threshold: improved (a higher allergen concentration was required to induce a positive CPT response), unchanged (the allergen concentration needed to elicit a positive CPT response stayed the same) and worse (a lower allergen concentration induced a positive CPT response). An improvement in 60% of patients after 12 weeks was considered clinically meaningful.

The secondary objectives, being the efficacy and tolerability of carbamylated monomeric allergoid tablets, were also evaluated at the end of the study (V4). On a 4-point scale from 0 to 3 (0 = worsened, 1 = unchanged, 2 = slight improvement and 3 = distinct improvement), the physician assessed, in consultation with the patient, the overall efficacy of the IMP. Similarly, the overall tolerability of treatment was classified according to one of four categories: 0 = poor, 1 = satisfactory, 2 = good and 3 = very good.

Safety assessment

The patient's AE profile and vital signs (heart rate and blood pressure) were monitored throughout the study (Table 1). Patients were asked about any AEs since their last visit and also at V1 after taking the IMP for the first time. AEs were observed, monitored and coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 15.0). At V1, all patients were also supplied with a blister of an oral antihistamine (10 mg loratadine) to be taken, if required, as rescue medication for possible local side effects such as oral pruritus and edema of the mouth, tongue or lips. Drug-related side effects occurring during SLIT were assigned to the following categories: 'local', 'gastrointestinal' and 'systemic', with the latter being subdivided into 'unspecific' (e.g., headache and abnormal fatigue), 'weak systemic' (e.g., rhinitis and mild asthma), 'non-life-threatening systemic' (e.g., urticaria, angioedema and severe asthma), and 'serious systemic' (e.g., anaphylactic shock) AEs. The participating physicians were to classify the relationship between the AE and the IMP according to the following categories: 'not related to study medication', 'unclassifiable/not assessable', 'unlikely', 'possible', 'probable/likely' and 'certain' as per specification. The term 'treatment-related adverse event' (TRAE) covered the categories mentioned except for 'not related to study medication'.

Sample size calculation

Under the assumption that 80% of the patients receiving 300 UA/day would have a positive reaction in the CPT at V4, reaction rates less than 60% in the other groups would be detected by a binominal test with a two-sided significance level of $\alpha = 5\%$ and a power of $1 - \beta = 80\%$ with 35 patients per group. Further, differences of 20 versus 55% in the reaction rates between the groups can be detected with a two-sided significance level of $\alpha = 5\%$ and a power of $1 - \beta = 80\%$ by a fourfold table test with 29 patients per group. Therefore, the number of $n = 35$ patients per group (= 140 patients altogether) was required, taking into consideration that each treatment group was likely to have a certain number of dropouts.

Blinding & randomization

This clinical trial was performed as a double-blind study. To ensure blinding of both patients and physicians, all containers and their contents were identical in shape, size, weight, color, taste and smell. Therefore, the dosage of the IMP was not recognizable. Subjects were enrolled consecutively starting on 10 January 2012; the last patient completed the trial on 9 May 2012. Subjects were allocated to the treatment groups by means of a randomization list with a random block size of 8. This list provided the randomization numbers and was computer-generated by the website *randomization.com*. A paper copy of the complete randomization list was placed in a sealed envelope and retained at the principal investigator's premises in a secure, fire-proof room with restricted access.

Statistics

Analyses were carried out using the statistical analysis program SPSS version 23.0 (IBM Corp., NY, USA). For continuous variables, the following descriptive statistics were included for each treatment group: mean, median, standard deviation, minimum and maximum. The description of dichotomous or categorical variables included numbers and percentages of each of the scores or categories for each treatment group. Scores for ordinal variables were considered as continuous. Group comparisons of continuous outcomes and factors were performed using a two-tailed *t*-test if these followed a normal distribution or a two-sided Mann–Whitney *U* test if they did not. Results with a *p*-value of 0.05 or lower were regarded as significant. The changes in the threshold allergen concentration eliciting a positive CPT response were compared after 4 and 12 weeks of treatment for each of the four treatment groups by using a two-tailed Mann–Whitney *U* test. Safety and tolerability criteria as judged by the patient and the physician, including the number and grading of AEs, were compared between the four treatment groups by means of a two-tailed Mann–Whitney *U* test. The analyses were applied to the dataset of exposed subjects.

Intention to treat

The intention-to-treat (ITT) population comprised all randomized subjects with evaluable CPT data at V1 and V3 or later.

Per protocol

The per-protocol (PP) analysis subset included all evaluable subjects who complied with the protocol in all points, delivering a complete dataset of measurements and evaluations of the primary efficacy variable. A maximum of 25% deviation from the planned intake of study medication was accepted as per-protocol drug intake. This deviation was calculated on the basis of the number of days the patients participated in the study ($\Delta V1$ and $V4$) and the total intake of study medication.

Ethical conduct of the study

The study was conducted in accordance with the Declaration of Helsinki in its revised edition (59th WMA General Assembly, Seoul, October 2008), GCP guidelines (CPMP/ICH/135/95), the requirements of German national drug and data protection laws and other applicable regulatory requirements throughout the entire process [39,40]. The study protocol and all other study documents were reviewed and approved by the independent ethics committee of the North Rhine Medical Council, Germany, and subsequent regional ethics committees on 19 September 2011 (number 2011239), and by the competent federal regulatory agency (Paul-Ehrlich-Institut) on 21 November 2011 (number 1391/01). The EudraCT number of the trial is 2011–002174–23, and the study report was published by the German regulatory agency at www.pharmnet-bund.de of the German Federal Ministry of Health. In conformity with ICH Guidelines, patients participating in the study were covered by clinical trial insurance for test subjects. Before applying any study procedures, written informed consent was obtained from all patients.

Results

Participants

Of all 158 patients randomized in this study, 3 did not receive any IMP, because they did not reach a Stage II reaction in the initial CPT at V1 (Figure 1). The safety population, for which safety analyses were performed, included all 155 randomized patients who were exposed to the study medication at least once: 36 subjects received 300 UA/day (Group 1), 43 subjects 600 UA/day (Group 2), 39 subjects 1000 UA/day (Group 3) and 37 subjects 2000 UA/day (Group 4). Four patients only had baseline assessments but no postbaseline assessment for the primary efficacy parameter (CPT). Therefore, the ITT analysis set consisted of 151 patients 18–71 years of age: 35 in Group 1, 42 in Group 2, 39 in Group 3 and 35 in Group 4. In total, 122 patients complied with the study protocol in all points, corresponding to the PP analysis set. The patients distributed among the four groups showed comparable baseline characteristics, other than the absence of asthma and the stronger predominance of male patients in Group 3 (66.7% male vs 33.3% female) compared with the other groups. The majority of patients were polysensitized: 62.9% in Group 1, 52.4% in Group 2, 59.0% in Group 3 and 62.9% in Group 4 (Table 3).

Objectives

Primary end point

Table 4 summarizes the patients' responses to different allergen concentrations used in the CPT assessed at V1, V3 and V4. Using the provocation solution with the highest allergen concentration (10,000 SQ-E/ml) at V1, a positive reaction of Stage II or III was detected in 68.6% of the patients in Group 1, 71.4% in Group 2, 59.0% in Group 3 and 65.7% in Group 4. At V4, a large percentage of subjects no longer responded to the CPT. The largest percentage was observed in Group 3, in which 59.0% of the patients did not react even to the highest allergen concentration. Regarding the threshold needed to induce a positive CPT response, improvement was observed after 4 weeks of treatment (V3) in 42.9% of the patients in Group 1, 47.6% in Group 2, 51.3% in Group 3 and in 48.6% in Group 4 (Table 5). In all treatment groups, more than 60% of patients improved in the CPT after 12 weeks of treatment (V4): 70.4% improved in Group 1, 62.9% in Group 2, 76.7% in Group 3 and 66.7% in Group 4 (Table 5). Figure 2 illustrates the mean CPT threshold improvement ($\Delta V4 - V1$) of each treatment group at V4. After 12 weeks of preseasonal therapy with carbamylated monomeric allergoid tablets, the greatest improvement was observed in Group 3 with a mean improvement of 0.744 of the tenfold threshold level. The differences in improvement were not significant between the four treatment groups.

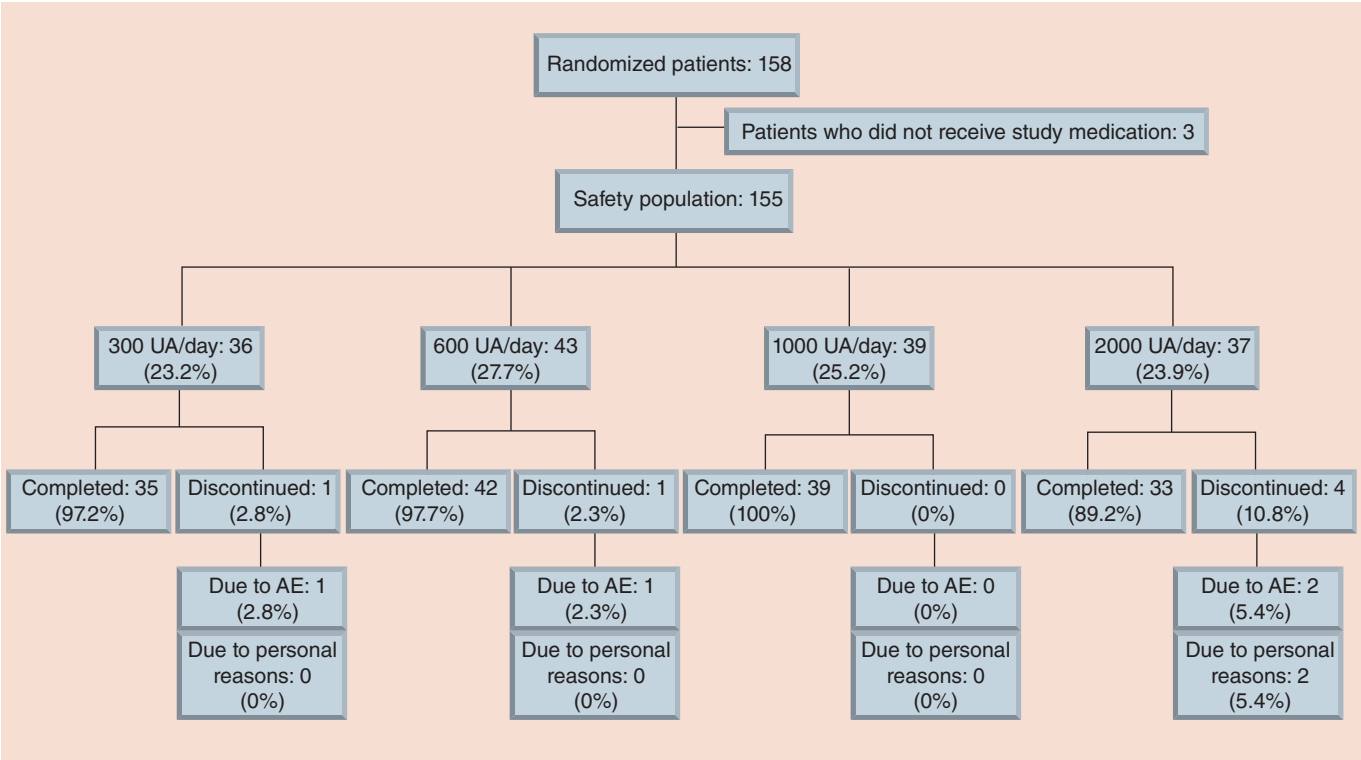


Figure 1. Participant flowchart.

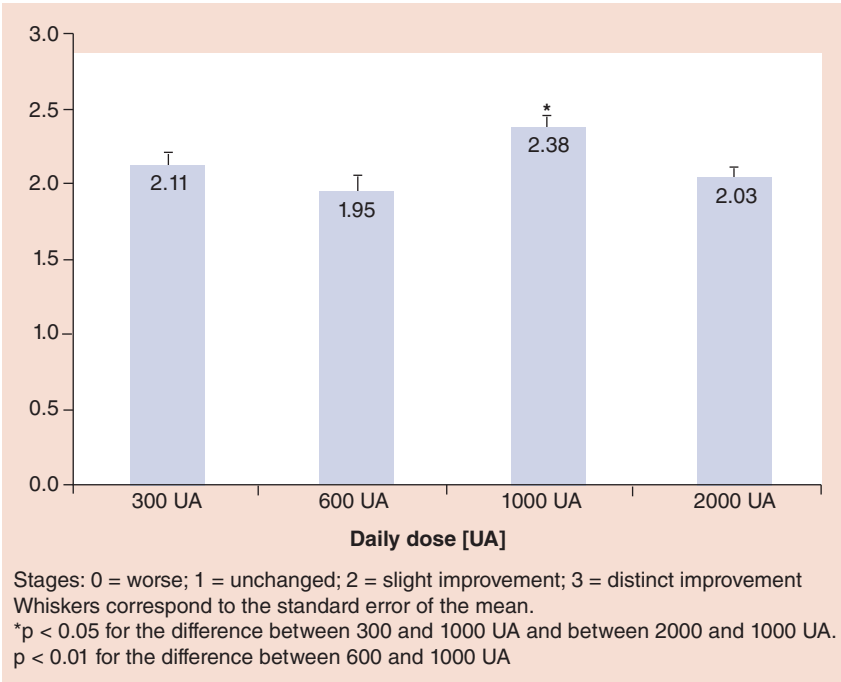


Figure 3. Mean efficacy of treatment evaluated by the physician (intention-to-treat analysis set).
UA: Unit of allergy.

Table 3. Demographic characteristics at baseline.

		300 UA/day	600 UA/day	1000 UA/day	2000 UA/day
Sex, N (%)	Female	19 (54.3%)	20 (47.6%)	13 (33.3%)	18 (51.4%)
	Male	16 (45.7%)	22 (52.4%)	26 (66.7%)	17 (48.6%)
Age, years	Mean (SD)	38.8 (14.2)	40.3 (13.7)	40.8 (13.6)	41.0 (15.9)
	Minimum	19	19	18	18
	Maximum	70	69	69	71
Height, cm	Mean (SD)	172.7 (8.0)	174.6 (10.5)	176.3 (6.5)	172.4 (8.7)
	Minimum	150	153	161	160
	Maximum	184	192	187	191
Weight, kg	Mean (SD)	72.2 (14.4)	74.6 (14.0)	77.5 (12.6)	73.0 (17.3)
	Minimum	46	48	52	45
	Maximum	115	108	109	114
Ethnic affiliation	Caucasian	34 (97.1%)	41 (97.6%)	39 (100%)	34 (97.1%)
	Asian	1 (2.9%)	1 (2.4%)	0 (0%)	1 (2.9%)
Disease, N (%)	Allergic rhinitis	35 (100%)	42 (100%)	39 (100%)	35 (100%)
	Allergic rhinoconjunctivitis	31 (88.6%)	35 (83.3%)	35 (89.7%)	28 (80.0%)
	Asthma	3 (8.6%)	5 (11.9%)	0 (0%)	4 (11.4%)
History of allergic rhinitis, years	Mean (SD)	22.7 (14.0)	21.0 (12.7)	20.9 (11.7)	19.2 (13.0)
	Minimum	4	4	3	3
	Maximum	54	51	49	58
History of allergic rhinoconjunctivitis, years	Mean (SD)	22.5 (14.2)	20.8 (12.4)	21.6 (11.8)	18.5 (12.8)
	Minimum	2	4	3	3
	Maximum	54	51	49	58
History of allergic asthma, years	Mean (SD)	5.0 (2.7)	22.6 (11.1)	-	14.5 (8.2)
	Minimum	3	2	-	7
	Maximum	8	29	-	26
Wheal diameter (grass pollen), mm	N	35	42	39	35
	Mean (SD)	7.4 (3.3)	7.9 (4.4)	7.9 (5.7)	7.9 (4.1)
	Median	6.0	6.5	6.0	8.0
Sensitization, N (%)	Grass pollen	35 (100%)	42 (100%)	39 (100%)	35 (100%)
Monosensitization, N (%)		13 (37.1%)	20 (47.6%)	16 (41.0%)	13 (37.1%)
Polysensitization, N (%)		22 (62.9%)	22 (52.4%)	23 (59.0%)	22 (62.9%)
Other sensitizations, N (%)	Alder	11 (31.4%)	9 (21.4%)	10 (25.6%)	8 (22.9%)
	Herbs	5 (14.3%)	9 (21.4%)	7 (17.9%)	9 (25.7%)
	Birch	19 (54.3%)	18 (42.9%)	16 (41.0%)	15 (42.9%)
	Food	3 (8.6%)	1 (2.4%)	2 (5.1%)	0 (0%)
	Other allergies	9 (25.7%)	5 (11.9%)	6 (15.4%)	8 (22.9%)

SD: Standard deviation; UA: Unit of allergy.

Secondary end point

The analysis of the mean efficacy of treatment per dosage group evaluated by the physician is shown in [Figure 3](#). With a mean efficacy score of 2.38 in Group 3 (1000 UA/day), the overall efficacy was rated significantly better than in the groups of comparison. In the ITT analysis set, these p-values were $p < 0.05$ for the difference between Group 1 and Group 3, $p < 0.01$ for Group 2 and Group 3 and $p < 0.05$ for Group 4 and Group 3. The mean tolerability of treatment evaluated by the physician reached a score of 2.71 in Group 1, 2.90 in Group 2, 2.85 in Group 3 and 2.74 in Group 4. Hence, the mean tolerability of treatment was assessed between ‘good’ and ‘very good’.

Table 4. Number of patients with positive response to conjunctival challenge at different allergen concentrations at V1, V3 and V4 (intention-to-treat analysis set).

Treatment Daily dose (UA)	Conjunctival challenge Allergen concentration (SQ-E/ml)	Patients					
		V1		V3		V4	
		n	%	n	%	n	%
300	100	3	8.6%	0	0%	0	0%
	1000	8	22.9%	8	22.9%	0	0%
	10,000	24	68.6%	17	48.6%	16	45.7%
	Negative response	0	0%	10	28.6%	19	54.3%
	Total	35	100%	35	100%	35	100%
600	100	2	4.8%	0	0%	1	2.4%
	1000	10	23.8%	9	21.4%	5	11.9%
	10,000	30	71.4%	17	40.5%	16	38.1%
	Negative response	0	0%	16	38.1%	20	47.6%
	Total	42	100%	42	100%	42	100%
1000	100	4	10.3%	1	2.6%	0	0%
	1000	12	30.8%	8	20.5%	2	5.1%
	10,000	23	59.0%	17	43.6%	14	35.9%
	Negative response	0	0%	13	33.3%	23	59.0%
	Total	39	100%	39	100%	39	100%
2000	100	0	0%	0	0%	0	0%
	1000	12	34.3%	7	20.0%	2	5.7%
	10,000	23	65.7%	14	40.0%	15	42.9%
	Negative response	0	0%	14	40.0%	18	51.4%
	Total	35	100%	35	100%	35	100%

SQ-E: Standardized quality unit; UA: Unit of allergy; V: Visit.

Safety assessment

No serious AEs were observed in the course of this trial, and there was no occurrence of anaphylaxis or a need to apply epinephrine. Of all 155 exposed patients, 106 subjects (68.4%) did not experience any AEs at all. In 49 patients, one or more AEs occurred, with a total of 66 AE reports. As shown in Table 6, 38 AEs were classified as treatment-related (TRAE), which corresponds to 3 AEs per 1000 tablets taken. Of total 38 TRAEs, 14 were observed in Group 1, 7 in Group 2, 7 in Group 3 and 10 in Group 4 (Table 6). The treatment Group 3 showed the lowest number of patients suffering from TRAEs: 34 (87.2%) patients without any TRAEs, 4 patients with one TRAE, and 1 patient with three TRAEs (Table 7). The most common TRAEs were diarrhea (n = 5; 3.2%), rhinoconjunctival symptoms (n = 4; 2.6%), swelling of one eye (n = 3; 1.9%), hypertension (n = 3; 1.9%), tiredness/fatigue (n = 2; 1.3%), bronchitis (n = 2; 1.3%), headache (n = 2; 1.3%) and pain in the upper abdomen (n = 2; 1.3%). A total of 6 of the 155 exposed patients dropped out of the study, 2 of whom for personal reasons (Figure 1).

Four patients discontinued the study because of AEs: one in Group 1, because of diarrhea and loss of appetite; one in Group 2 because of diarrhea; and two in Group 4 because of headache or hypertension.

Discussion

The aim of the study was to demonstrate a clinically meaningful treatment effect and to compare the effect of four different doses of carbamylated monomeric allergoid tablets, using conjunctival provocation as an instrument of measurement. EMA guidelines on clinical development for allergen-specific immunotherapy products suggest such use of provocation tests, which may show comparative effects of different doses [41].

After only 4 weeks of treatment, an improvement in the threshold needed to induce a positive CPT response was documented, ranging from 42.9% in Group 1 to 51.3% in Group 3. More than 60% of the patients in all treatment groups had improved after 12 weeks of treatment, which was predefined as being clinically meaningful: 70.4% in Group 1, 62.9% in Group 2, 76.7% in Group 3 to 66.7% in Group 4. This observation supports the hypothesis of a gradual onset of efficacy depending on time and cumulative dose. After 12 weeks of intake

Table 5. Conjunctival provocation test change of threshold at V3 and V4 compared with conjunctival provocation test at V1.

Daily dose (UA)	Change of threshold compared with CPT V1	V3		V4	
		n	%	n	%
300	Worse	2	5.7%	0	0%
	Unchanged	18	51.4%	8	29.6%
	Improved	15	42.9%	19	70.4%
	Total	35	100%	27	100%
600	Worse	2	4.8%	3	8.6%
	Unchanged	20	47.6%	10	28.6%
	Improved	20	47.6%	22	62.9%
	Total	42	100%	35	100%
1000	Worse	1	2.6%	0	0%
	Unchanged	18	46.2%	7	23.3%
	Improved	20	51.3%	23	76.7%
	Total	39	100%	30	100%
2000	Worse	0	0%	0	0%
	Unchanged	18	51.4%	10	33.3%
	Improved	17	48.6%	20	66.7%
	Total	35	100%	30	100%

CPT: Conjunctival provocation test; UA: Unit of allergy; V: Visit.

Table 6. Distribution of treatment-related adverse events.

Type of adverse event	Total	300 UA/day	600 UA/day	1000 UA/day	2000 UA/day
Local	5	1	0	2	2
Gastrointestinal	7	1	4	1	1
Mild systemic	9	4	1	1	3
Unspecific	5	1	2	1	1
Other	12	7	0	2	3
Total	38	14	7	7	10

UA: Unit of allergy.

of 1000 UA/day, it was impossible to elicit a conjunctival reaction even with the highest provocation dose of 10,000 SQ-E/ml in 59.0% of patients. The prevention of almost 60% of patients from reacting to allergens at a concentration level rarely reached during natural exposure is a remarkable finding after only 3 months of treatment. This result compares favorably with the response rate known from previous investigations with subcutaneous immunotherapy [42]. Neither the differences between the groups can be considered clinically meaningful nor are these differences statistically significant. Thus, it is surprising that the rating of efficacy as given by the blinded physicians at the end of the treatment phase clearly indicates Group 3 as being superior to all other groups ($p < 0.05$). These findings are supported by the PP analysis data, again showing the significant superiority ($p < 0.05$) of 1000 UA/day over all other dosages. This result is especially remarkable since there is no potential of unblinding, as has been discussed in trials with tablets containing natural allergens due to their high rate of local side effects [11,18,20].

While investigating grass tablet-based SLIT, Dahl *et al.* observed local TRAEs such as oral pruritus (46%), edema of the mouth (18%) and throat irritation (9%) in their patients [18]. Didier *et al.* reported the TRAEs of oral pruritus in 19.7–25.8% of subjects, edema of the mouth in 3.2–6.3% and throat irritation in 9.0–14.4% depending on the SLIT dose [11]. Compared with the previously mentioned trials, the percentage of patients experiencing any treatment-emergent local side effect (1.3%) was remarkably lower in our study. Only five patients (3.2%) reported diarrhea, the most common TRAE in our trial.

Following the CPT scheme in the study by Riechelmann *et al.* [43], we used three provocation solutions with concentrations of 100, 1000 and 10,000 SQ-E/ml. Klimek *et al.* [42] used six provocation solutions with a threefold

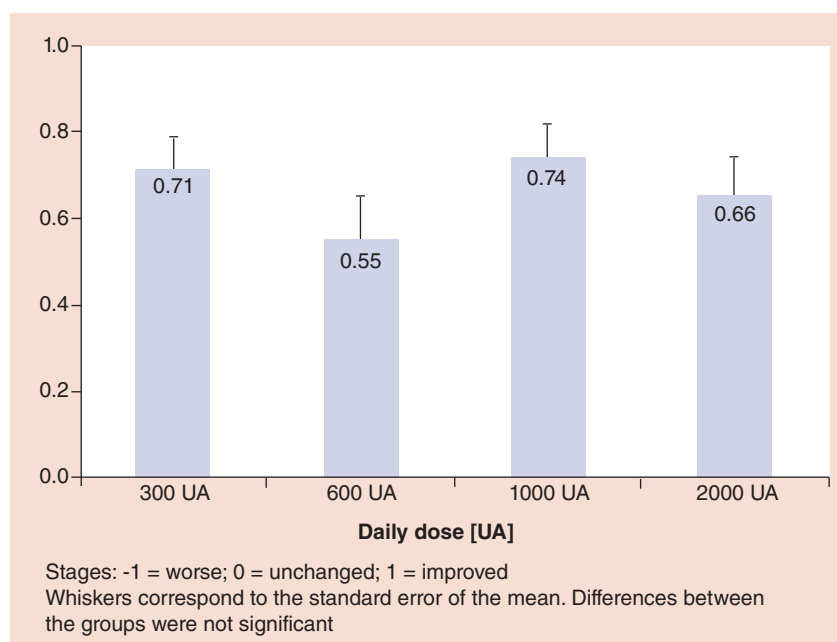


Figure 2. Mean threshold improvement at V4; $\Delta V4 - V1$ (intention-to-treat analysis set).
AE: Adverse event; UA: Unit of allergy.

increase; Riechelmann *et al.* [43] used five solutions, increasing in concentrations by a factor of 10. However, 50% of the patients in Klimek's placebo control group showed an improvement in the CPT threshold [42]. Compared with 30% of the patients showing improved CPT thresholds in Riechelmann's placebo control group [43], the gradation by a multiplication factor of 3 seems to yield more false-positive results. In conclusion, the advantages of using three provocation solutions and a gradation by a multiplication factor of 10 are: first, the lower number of false-positive results; and second, the fact that this procedure is less time-consuming.

The lack of a placebo control group may be considered by some to be a limitation of our study design. However, the study design was approved by the national regulatory agency in accordance with the EMA guidelines, which recommend using three or more dosage levels – with an optional placebo level – for the study design [44]. Four different dosage levels without placebo were applied here, based on conclusions made in previous placebo-controlled studies confirming the efficacy of the IMP [reviewed in 33]. On the one hand, patients may have been tempted to experience a placebo effect considering the subjective symptoms of the CPT challenge or even a nocebo effect with respect to AEs. This possibility should be kept in mind when considering the findings. On the other hand, the investigators expected that Group 1 would experience less protection from allergen reactions than the other groups would, which was not the case. In one recently published clinical trial, a mean improvement of one order of magnitude or more of the CPT concentration was reported in 40% of all subjects undergoing placebo injections [45]. In Group 2 of the present study, showing the lowest treatment effect overall, the rate of 63% improvement and almost 50% of patients experiencing full protection clearly distinguishes the treatment effect from a placebo effect. Even at a cumulative dose of only 25,000 UA (12 weeks of 300 UA/day), carbamylated monomeric allergoid tablets offer remarkable efficacy. This finding is in line with results from previously published studies that show an equal level of high efficacy, safety and tolerability for preseasonal cumulative doses of approximately 30,000 UA and more [33].

The US FDA stipulates that epinephrine autoinjectors be prescribed to patients participating in USA trials involving SLIT [46]. No serious AEs were documented throughout our trial with carbamylated monomeric allergoid tablets, particularly no anaphylactic reactions, so that no epinephrine injections were necessary. TRAEs were rare

Table 7. Listing of treatment-related adverse events per person (safety analysis set).

Daily dose (UA)	TRAE(s)/patient	n	%
300	0	27	75.0%
	1	5	13.9%
	2	3	8.3%
	3	1	2.8%
600	0	37	86.0%
	1	5	11.6%
	2	1	2.3%
1000	0	34	87.2%
	1	4	10.3%
	3	1	2.6%
2000	0	30	81.1%
	1	4	10.8%
	2	3	8.1%

TRAE: Treatment-related adverse event; UA: Unit of allergy.

in all dosage groups and predominantly mild in intensity. Again, 1000 UA/day displayed the most favorable safety profile, with 87% of the patients remaining free from TRAEs. Therefore, considering the patients' and physicians' overall judgements, the CPT reactions and the side effects, the outcome is widely in favor of a dose of 1000 UA/day.

Conclusion

The study results presented here for all four tested doses confirm that a 12-week course of SLIT with carbamylated monomeric allergoid tablets can prevent a large proportion of patients from reacting to grass pollen allergens. The daily dose of one tablet with 1000/UA provides the highest protection against the symptoms of grass pollen-induced allergic rhinitis and/or rhinoconjunctivitis. The safety data of this study for all four treatment groups verify that carbamylated monomeric allergoid tablets constitute a SLIT form with very few side effects. The dose of 1000 UA/day shows the most favorable safety profile. Although improvements in this clinically relevant surrogate parameter of efficacy were documented already after 12 weeks of preseasonal treatment, current guidelines recommend in the case of inhalational allergens the completion of a 3-year course of daily SLIT treatment [14,47,48] (Table 7).

Authors contributions

R Mösges was the principal investigator of the study and contributed to the protocol design together with E Compalati, C Rohdenburg and P Schmalz. A Eichel, G Zadocyan and EM Kasche critically revised the manuscript. K Shah-Hosseini performed the statistical analysis under the guidance of W Lehmacher. All authors have read and approved the final manuscript.

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Summary points

Aim

- In this prospective, randomized, double-blind, four-armed, active-controlled, multicenter, Phase II study, the optimal effective and safe dose of sublingual immunotherapy tablets containing carbamylated monomeric allergoids in patients with grass pollen-induced allergic rhinoconjunctivitis was determined.

Methods

- The LAIS[®] grass tablets used in this study contain carbamylated, monomeric allergoids of grass pollen consisting of timothy grass (*Phleum pratense*), common meadow grass (*Poa pratensis*) and meadow soft grass (*Holcus lanatus*) in equal parts.
- Four different doses were applied preseasonally, amounting to cumulative doses between 25,200 and 168,000 units of allergy (UA) for the 84-day treatment period.

Results

- Of 158 randomized adult patients, 155 subjects forming the safety population received 300 UA/day (n = 36), 600 UA/day (n = 43), 1000 UA/day (n = 39) or 2000 UA/day (n = 37).
- Primary outcome: the efficacy of the SLIT was assessed by using the conjunctival provocation test on Visit 1 and Visit 4. Conjunctival provocation test results improved after 12 weeks of treatment in more than 60% of the patients in all groups. The greatest improvement of 76.7% was achieved with a dose of 1000 UA/day.
- Secondary outcome: efficacy and tolerability of carbamylated monomeric allergoid tablets were assessed on a 4-point scale. With a mean efficacy score of 2.38 in Group 3 (1000 UA/day), the overall efficacy was rated significantly better than in the groups of comparison. The mean tolerability of the treatment was between 2 ('good') and 3 ('very good').
- Of all treatment-related adverse events, 14 were observed in Group 1 (300 UA/day), 7 in Group 2 (600 UA/day), 7 in Group 3 (1000 UA/day) and 10 in Group 4 (2000 UA/day). No events were serious.

Conclusion

- All four doses tested in this study can prevent a large proportion of patients from reacting to grass pollen allergens in a conjunctival challenge; however, the dose of one tablet per day with 1000 UA provides the highest protection with very few side effects.

ENT Section of the European Academy of Allergy, Asthma and Clinical Immunology (EAACI). E Compalati is employee of Lofarma S.p.A., sponsor of this trial and reports publication honoraria from ASIT biotech, and Takeda Pharmaceuticals outside the submitted work. Walter Lehmacher received honoraria for consultancy from ASIT biotech in this therapeutic indication but outside of the submitted work.

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