ORIGINAL ARTICLE

Tolerability During Double-Blind Randomized Phase I Trials With the House Dust Mite Allergy Immunotherapy Tablet in Adults and Children

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Abstract

Background and Objective: The orodispersible house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet (ALK, Denmark) is being developed for the treatment of HDM respiratory allergic disease. The objective of the 2 phase I trials was to investigate tolerability and the acceptable dose range of HDM SLIT-tablet treatment in adults and children with HDM respiratory allergic disease.
Patients and Methods: The trials were randomized, multiple-dose, dose-escalation, double-blind, placebo-controlled phase I trials including patients with HDM-induced asthma, with or without rhinoconjunctivitis. Both trials were registered in EudraCT (Trial 1: 2005-002151-41; Trial 2: 2007-000402-67). Trial 1 included 71 adults (18-63 years) and trial 2 included 72 children (5-14 years). Both trials included 6 dose groups that were randomized 3:1 to active treatment or placebo once daily for 28 days. Adverse events (AEs) were coded in MedDRA (version 8.1 or later). Immunological variables included specific IgE and IgE-blocking factor.
Results: No serious AEs were reported. In trial 1 (maximum dose, 32 development units [DU]), 1 patient in the 16 DU group discontinued due to AEs. The entire 32 DU group was discontinued as 1 patient had a severe adverse reaction. In trial 2 (maximum dose, 12 DU), no patients discontinued prematurely. The most frequently reported AEs were mild application-site related events. The total number of events was dose-related within each trial. HDM SLIT-tablet treatment induced changes in immunological parameters in a dose-dependent manner.
Conclusions: These trials demonstrate that doses up to 12 DU of HDM SLIT-tablet were tolerated in the selected populations, and thus are suitable for further clinical investigations in adults and children with HDM respiratory allergic disease.

Key words: Sublingual immunotherapy tablet. House dust mite. Placebo-controlled. Sublingual Immunotherapy. Phase I.

Resumen

Introducción y Objetivo: La tableta orodispersable para inmunoterapia sublingual del ácaro del polvo de casa (SLIT-tablet) se ha desarrollado para el tratamiento de la alergia respiratoria frente al ácaro. El objetivo de la fase I de estos 2 ensayos clínicos fue investigar la tolerancia y el rango de aceptación de la dosis de tratamiento en adultos y niños con alergia respiratoria al ácaro del polvo de casa. Los ensayos randomizados, con dosis múltiple escalonada, doble ciego controlados con placebo incluyeron a pacientes con asma inducida por el ácaro del polvo de casa, con o sin rinoconjuntivitis. Se registraron en EudraCT (Ensayo 1: 2005-002151-41; Ensayo 2: 2007-000402-67).
Pacientes y Métodos: El ensayo 1 incluyó a 71 pacientes adultos (18-63 años) y el ensayo 2 incluyó a 72 niños (5-14 años). Ambos ensayos clínicos incluían 6 grupos de dosis que fueron randomizados 3:1 para tratamiento activo o placebo, una vez al día durante 28 días. Las reacciones adversas (RAs) fueron codificadas en MedDRA (versión 8.1 or later). Las variables inmunológicas incluían IgE específica y factor bloqueante de la IgE. No se registraron RAs importantes. En el ensayo 1 (con la dosis máxima y 32 unidades de desarrollo [UD])

un paciente del grupo 16-UD tuvo que dejar el tratamiento por RAs. El grupo 32-UD completo abandonó el tratamiento debido a que un paciente manifestó RAs graves.
Resultados: En el ensayo 2 (dosis máxima ,12 UD) ningún paciente abandonó el tratamiento de forma prematura. Las RAs más frecuentemente registradas fueron de tipo local relacionadas con el lugar de aplicación del tratamiento. El número total de reacciones estaba relacionado con la dosis administrada en cada ensayo. Por otra parte, este tratamiento indujo cambios en los parámetros inmunológicos de forma dosis-dependiente.
Conclusiones: Estos ensayos demuestran que el aumento de dosis por encima de 12 UD se tolera bien en las poblaciones estudiadas en estos ensayos, dato a tener en cuenta para futuras investigaciones en adultos y niños con alergia respiratoria por polvo de casa.

Palabras clave: Tableta inmunoterapia sublingual. Acaro del polvo de casa. Ensayo controlado con placebo. Inmunoterapia sublingual. Fase 1.

Introduction

The increasing prevalence of respiratory allergic diseases has become a major health issue worldwide. In Western Europe more than one-fifth of the adult population has a respiratory allergic disease [1,2]. House dust mites (HDMs) are the most common indoor allergen responsible for this condition, and while outdoor allergens are perceived as a greater risk for rhinitis, HDMs are perceived as a greater risk for asthma development [3]. This is supported by data showing that the risk of developing bronchial hyperresponsiveness in patients with allergic rhinitis is higher with HDM than with pollen [4]. Allergic rhinitis and asthma often co-exist, as shown in the Copenhagen Allergy Trial, where 50% of the participants with HDM-induced rhinitis also had HDM-induced asthma and 95% of participants with HDM-induced asthma also had HDM-induced rhinitis [5].

Currently, the treatment of allergic diseases is based on allergen avoidance, symptomatic medications, and allergen-specific immunotherapy. For HDM respiratory allergic disease, allergen avoidance involves implementing extensive sanitation measures, such as the use of special mattress covers, frequent washing of bed clothing, ventilation, and frequent vacuuming. However, the effect of HDM-directed sanitation is questionable and international treatment guidelines question whether the effect on asthma outweighs the cost [6,7]. Symptomatic medications such as antihistamines, corticosteroids, and β_2-agonists are used to provide symptomatic relief, whereas allergen-specific immunotherapy addresses the underlying immunologic mechanisms responsible for allergic disease and is able to provide a sustained disease-modifying effect [8,9].

An HDM sublingual immunotherapy (SLIT)-tablet (ALK) is currently being developed for the treatment of HDM respiratory allergic disease. The aims of the 2 phase I trials reported here were to investigate tolerability and immunological changes during treatment with HDM SLIT-tablet in adults and children with HDM-induced asthma and to identify a dose range acceptable for further investigations.

Methods

Design

To investigate tolerability and dose range of HDM SLIT-tablet in adults and children, 2 randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation, phase I trials were performed. In each trial, participants were allocated to 6 dosage groups and randomized 3:1 to active or placebo (Figure 1). The investigational medicinal product (IMP) was a fast dissolving, orodispersible HDM SLIT-tablet for sublingual administration. Active and placebo were identical in appearance, smell, and taste. The HDM SLIT-tablet contains 2 drug substances: standardized allergen extracts from whole mite cultures of the HDM species *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in a 1:1 ratio. The extracts are standardized against an in-house reference based on biological activity. During development, the strength of the HDM SLIT-tablet is defined in development units (DU).

The active doses administered once daily for 28 days were up to 32 DU in adults (Trial 1; EudraCT Number: 2005-002151-41), and up to 12 DU in children (Trial 2; EudraCT Number: 2007-000402-67) (Figure 1). Trial 1 was completed before trial 2 was initiated. The inclusion of dose groups 9 and 12 DU in trial 2 was decided after initiation of the trial and warranted a protocol amendment. The first and second dose for all participants was administered under medical supervision. No adrenaline auto-injectors were provided. Treatment groups were commenced in a staggered manner with intervals of 1 or 2 weeks to allow for safety data review by a safety committee before proceeding to a higher dose group.

Written informed consent was obtained from all participants or from their parents/legal guardian before entering the trials, which were performed in accordance with the Declaration of Helsinki [10] and good clinical practice. The national ethics committees in Denmark (trial 1) and Spain (trial 2) approved the trials. The main selection criteria were a clinical history of HDM-induced mild to moderate asthma of at least 1 year prior to trial entry; use of appropriate medications for the control of asthma symptoms (in accordance with guideline [11]); positive specific IgE (≥class 2) and positive skin prick test (wheal diameter ≥3mm) to *D pteronyssinus* or *D farinae* (Soluprick, ALK, Denmark); no clinical history of severe asthma within the last 2 years; and no history of anaphylaxis.

Trial 1 was carried out at a phase I unit recruiting individuals from a pool of volunteers, whereas trial 2 was carried out in specialized allergy centers and the patients were recruited from the investigator's known pool of allergic patients.

Assessments included adverse events (AEs), lung function (forced expiratory volume in the first-second [FEV_1] and peak expiratory flow [PEF]), physical and

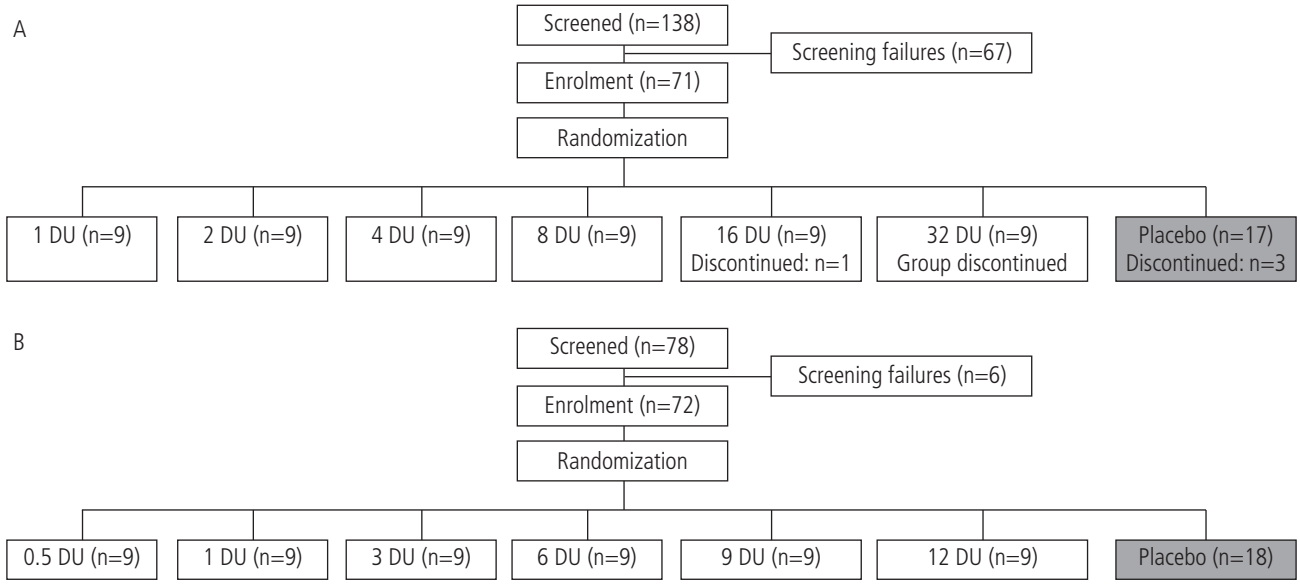

Figure 1. Trial overview for trial 1 (A) and trial 2 (B). Each trial included 6 dose groups randomized 3:1 to active treatment or placebo. Dose groups were initiated in a staggered manner at intervals of 1 week (trial 1, A) or 2 weeks (trial 2, B). DU indicates development unit.

oral examination, laboratory safety assessments, and immunological measurements.

AEs were coded according to MedDRA (version 8.1 or later). All AEs were recorded. For example, if oral pruritus occurred for some minutes after IMP intake for 5 days, this was recorded as 5 AEs. AEs were graded by the investigator as mild, moderate, or severe. Mild corresponded to transient symptoms with no interference with the individual's daily activities; moderate to marked symptoms corresponded to moderate interference with the individual's daily activities; and severe symptoms corresponded to considerable interference with the individual's daily activities and were considered unacceptable. AEs were also recorded as serious (as per ICH E2A definitions [12]) or non-serious. In addition the investigator rated the causality between an AE and the IMP as probable (good reasons and sufficient documentation to assume a causal relationship), possible (existence of a conceivable causal relationship that could not be dismissed), and unlikely (AE most likely had a cause other than the IMP).

Laboratory safety assessments (hematology, biochemistry, serology) were carried out by Pivotal Laboratories (York, UK) using standardized methods.

The immunological measurements included specific IgE antibodies and inhibitory components to IgE-allergen binding (termed IgE-blocking factor) against allergen extracts from *D pteronyssinus* and *D farinae* (for details on methodology please refer to [13]).

Statistics

The sample size for both trials followed empirical considerations. No formal sample size estimations were made, and no formal statistical comparisons of treatment groups at baseline or follow-up were performed. For both trials one analysis set (the full analysis set) was used. Data were evaluated by summary statistics, frequency tables, and graphics using statistical software from SAS (SAS Institute Inc.).

Results

For trial 1, 138 adults were screened; 71 (18-63 years of age) were enrolled from August to November 2005 and 58 (82%) completed the trial (Figure 1A). For trial 2, 78 children were screened; 72 (5-14 years of age) were enrolled from September to April 2008, and they all completed the trial (Figure 1B).

Participant characteristics from the trials are summarized in Table 1 and Table 2. Minor variations were observed between the treatment groups in each trial, but none were considered clinically important. In both trials, individuals had mild to moderate HDM-induced asthma and used medication to control their symptoms, with no significant differences between groups.

Adverse Events

No serious AEs were reported in either of the trials. One participant from the 16 DU group in trial 1 discontinued IMP treatment due to 3 AEs (2 episodes of mouth edema and 1 of throat tightness). The entire 32 DU group (9 active, 3 placebo) in trial 1 was discontinued after day 2, as 1 participant had a severe adverse reaction (vomiting immediately after intake of IMP on day 2).

The majority of AEs were mild reactions and only 7 severe AEs were reported (6 in trial 1 and 1 in trial 2). The numbers of AEs were dose-related in each trial, but tended to be lower with dose in the pediatric trial than in the adult trial. A similar

Table 1. Population Characteristics, Trial 1

Treatment	1 DU n=9	2 DU n=9	4 DU n=9	8 DU n=9	16 DU n=9	32 DU n=9	Placebo n=17
Age, y							
Mean (SD)	30.7 (10.4)	32.4 (14.1)	25.9 (5.3)	30.0 (11.2)	27.9 (6.0)	25.2 (7.6)	29.0 (9.7)
Min-max	18-51	19-63	18-32	21-50	22-39	18-42	21-55
Sex, No. (%)							
Female	6 (67)	7 (78)	6 (67)	3 (33)	5 (56)	7 (78)	9 (53)
Male	3 (33)	2 (22)	3 (33)	6 (67)	4 (44)	2 (22)	8 (47)
Height, cm							
Mean (SD)	172 (9.2)	171 (11.1)	172 (7.2)	177 (8.0)	175 (6.3)	172 (8.2)	176 (10.1)
Min-max	161-186	158-190	160-185	163-188	165-184	162-189	156-191
Weight, kg							
Mean (SD)	83.3 (19.5)	72.2 (18.4)	70.1 (7.4)	77.7 (12.0)	79.7 (19.3)	71.9 (13.8)	75.9 (14.2)
Min-max	57-115	48-97	60-82	62-97	53-108	53-92	54-114
Years with HDM-induced asthma							
Mean (SD)	13.8 (9.4)	14.8 (11.4)	13.0 (6.9)	17.1 (6.4)	16.1 (6.6)	15.8 (8.9)	14.2 (6.0)
Min-max	3-33	2-39	2-25	9-27	4-25	5-31	1-22
Baseline FEV_1 in % of predicted[a]							
Mean (SD)	84.1 (13.8)	96.2 (10.8)	91.8 (14.0)	91.6 (12.3)	95.4 (10.2)	91.5 (10.2)	93.8 (13.9)
Min-max	67.5-106.9	78.8-111.5	75.7-112.6	76.2-115.8	81.4-113.4	79.7-108.0	65.4-113.9

Abbreviations: DU, development units; HDM, house dust mite; FEV_1, forced expiratory volume in the first second; max, maximum; min, minimum.
[a]FEV_1 in % of predicted calculated post hoc.

Table 2. Population Characteristics, Trial 2

Treatment	0.5 DU n=9	1 DU N=9	3 DU n=9	6 DU n=9	9 DU n=9	12 DU n=9	Placebo n=18
Age,y							
Mean (SD)	7.9 (2.9)	8.2 (2.2)	8.6 (2.6)	9.4 (2.4)	9.1 (2.0)	10.6 (2.7)	9.6 (2.3)
Min-Max	5-13	5-12	6-12	6-13	7-13	7-14	6-14
Sex, No. (%)							
Female	4 (44)	4 (44)	2 (22)	3 (33)	3 (33)	2 (22)	4 (22)
Male	5 (56)	5 (56)	7 (78)	6 (67)	6 (67)	7 (78)	14 (78)
Height, cm							
Mean (SD)	129 (14.3)	137 (14.7)	134 (14.8)	140 (11.3)	140 (15.7)	149 (15.3)	140 (12.9)
Min-Max	117-152	113-163	117-154	121-156	123-175	127-174	123-163
Weight, kg							
Mean (SD)	28 (8.4)	38 (15.5)	37 (12.6)	36 (9.6)	39 (14.1)	41 (12.5)	40 (12.2)
Min-Max	20-42	20-65	22-60	19-50	24-66	26-65	26-64
Years with HDM-induced asthma							
Mean (SD)	2.6 (1.8)	4.7 (3.1)	3.9 (1.8)	2.9 (1.9)	5.1 (2.1)	4.8 (2.7)	4.5 (2.6)
Min-Max	1.2-6.7	1.4-9.7	1.1-6.5	1.2-6.1	3.1-8.1	2.1-10.1	1.1-9.8
Baseline FEV_1 in % of predicted							
Mean (SD)	93.7 (14.3)	91.5 (10.2)	94.7 (10.2)	93.6 (12.2)	98.5 (15.1)	100.0 (15.2)	100.0 (9.0)
Min-Max	76.0-111.4	74.2-104.7	79.3-111.0	79.5-118.7	71.8-120.8	76.0-116.9	86.0-116.0

Abbreviations: DU, development units; HDM, house dust mite; FEV_1, forced expiratory volume in the first second; max, maximum; min, minimum.

tendency was seen with IMP-related AEs (ie, AEs probably or possibly related to the IMP). The most frequently reported IMP-related AEs were oral pruritus, throat irritation, stomatitis (frequent only in trial 1), mouth edema, ear pruritus, and oral paraesthesia (reported only in trial 1) (Table 3). All these AEs were related to the administration site. The majority were graded as mild and resolved without treatment. Onset typically occurred within a few minutes of the first IMP intake. Mean duration of the most frequent IMP-related AEs varied from minutes to 4 hours after IMP intake and was not related to dose. Mean resolution (time from onset of the first AE to resolution of the last AE of the same type) was up to 3 weeks (data not shown). All participants recovered completely from IMP-related AEs.

In trial 1, 7 participants reported 9 AEs coded as asthma (eg, asthma worsening or asthma exacerbations); 5 of these were graded as mild and 4 as moderate. Four of the asthma events (2 in the 2 DU group and 2 in the 16 DU group) were assessed as being IMP-related. In trial 2, 12 participants reported 13 asthma AEs; 10 of these were graded as mild and 3 as moderate. Six of the asthma events were in the placebo group, 1 in the 0.5 DU group, 3 in the 1 DU group, 1 in the 3 DU group, and 1 in the 6 DU group. None were judged to be IMP-related.

Lung Function

No clinically significant changes were observed in FEV_1 or PEF in any of the groups.

Oral and Physical Examinations

In trial 1, there were 139 abnormal oral examination findings (110 in 30 participants in the active groups and 29 in 3 participants in the placebo group). Typical findings included blisters, redness, edema, and erythema; 96% were mild in severity. Five findings (4%) of edema (under the tongue or in the submandibular or uvula area) were considered moderate; 4 occurred in 2 participants in the 16 DU group and 1 in the 32 DU group.

In trial 2, the placebo group had no abnormal findings, whereas there were 69 abnormal findings in 25 participants in the active groups. Typical findings included aphthous tongue ulceration, edema, and erythema; 96% were mild; 1 finding (1%) of aphthous tongue ulceration in the 3 DU group and 2 findings (3%) of sublingual edema in 2 participants in the 6 DU group were assessed as moderate in severity.

Most abnormal oral findings were observed within 10 minutes of IMP intake and disappeared within 1 hour. The pattern of abnormal findings indicated a likely IMP relation.

During the physical examinations at screening and at follow-up minor abnormalities were observed across the active and the placebo groups. IMP administration was not considered to have a causal relation to the abnormalities.

Laboratory Safety Assessments

No clinically relevant changes in the laboratory safety assessments (hematology, biochemistry, serology) were observed.

Table 3. Most Common IMP-Related AEs

	Oral Pruritus	Throat Irritation	Stomatitis[a]	Mouth Edema	Ear Pruritus	Oral Paresthesia[a]
Placebo (T1)	-	1	-	-	-	2
Placebo (T2)	5	-	-	-	-	-
0.5 DU (T2)	5	-	-	-	-	-
1 DU (T1)	24	9	12	-	-	13
1 DU (T2)	5	2	-	-	2	-
2 DU (T1)	37	1	21	2	1	2
3 DU (T2)	58	21	-	8	-	-
4 DU (T1)	57	35	79	34	42	10
6 DU (T2)	75	40	3	48	5	-
8 DU (T1)	55	88	41	12	65	32
9 DU (T2)	51	51	2	4	-	-
12 DU (T2)	69	37	3	36	26	-
16 DU (T1)	100	82	41	42	38	39
32 DU (T1)[b]	4	19	1	-	4	7
Total for T1	277	235	195	90	150	105
Total for T2	268	151	8	96	33	-
Total for T1 and T2	545	386	203	186	183	105

Abbreviations: AE, adverse event; IMP, investigational medicinal product; T1, trial 1; T2, trial 2.
[a]Stomatitis and oral paraesthesia were not frequently reported in trial 2 (children).
[b]The 32 DU group (9 active, 3 placebo) was discontinued after 2 days of treatment.

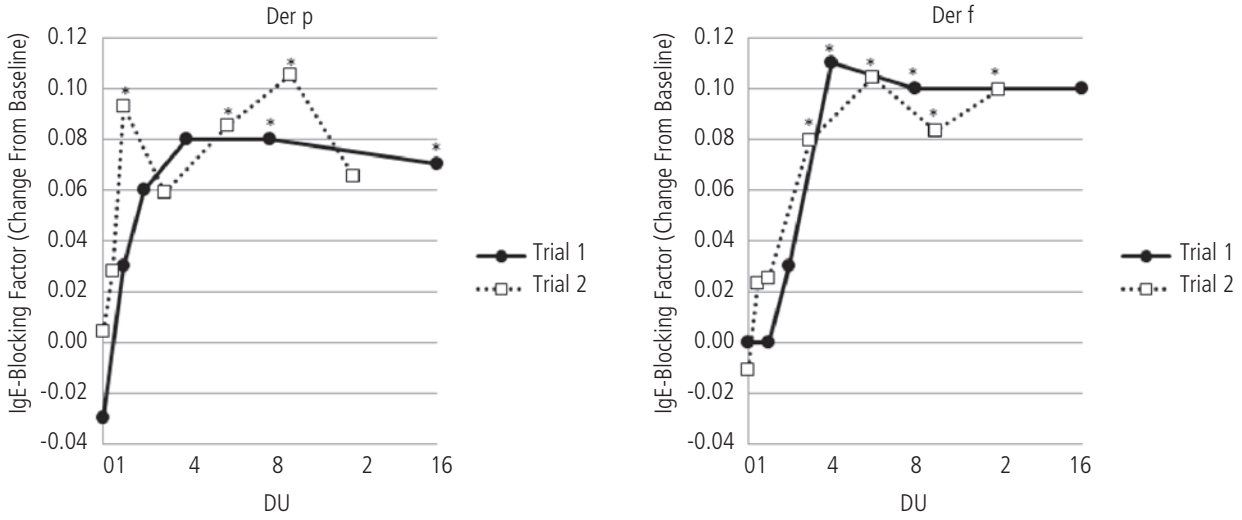

Figure 2. Change from baseline in IgE-blocking factor induced during the 28-day treatment period in each of the 2 trials, measured against allergen extracts of *Dermatophagoides pteronyssinus* (Der p) (A) and *Dermatophagoides farinae* (Der f) (B) and averaged for each dose. DU indicates development unit. 0 DU represents the placebo group. * *P* value for difference with placebo: *P*<.05.

Immunology

Specific IgE to both HDM species increased significantly from baseline to the end of treatment in all active groups in a dose-dependent manner; no changes were seen in the placebo groups (data on file).

The changes from baseline in IgE-blocking factor, measured against *D pteronyssinus* (Figure 2A) and *D farinae* (Figure 2B) for both trials also showed dose-response tendencies. At doses above 4 DU, no further increases in IgE-blocking factor were observed for the 28-day treatment period. The observed increase from baseline in IgE-blocking factor was statistically significant for most of the active groups above 4 DU (Figure 2).

Discussion

The 2 phase I trials presented here were placebo-controlled, randomized, dose-escalation trials performed in adults (trial 1) and children (trial 2) to investigate the tolerability of HDM SLIT-tablet. There were dose-response tendencies for both safety findings and immunological changes, with a plateau effect for IgE-blocking factor above 4 DU and AEs and oral findings becoming increasingly troublesome in the 16 DU and 32 DU groups. The overall conclusion is that the combined evidence suggests that HDM SLIT-tablet has an acceptable safety profile for further clinical investigations in doses up to 12 DU.

Based on phase I studies with the corresponding grass SLIT-tablet for treatment of grass allergy (Grazax) in adults and children, it was expected that treatment with HDM SLIT-tablet would induce local transient AEs, primarily mild or moderate in intensity and affecting the mouth or throat [14,15]. The results of the HDM SLIT-tablet trials confirm the similarity of both the nature of the AEs and the incidence of events. In the present trials, there seemed to be fewer AEs in children than in adults. This could imply that children tolerate immunotherapy with HDM SLIT-tablet better, but the difference could be due to random variation or different reporting patterns in children, where parents/guardians report the AEs. A pooled analysis of 8 controlled trials on sublingual immunotherapy (different allergens) involving 472 adults and 218 children found a similar occurrence of AEs in adults and children [16] and this conclusion was also drawn from the grass SLIT-tablet trials in children [13,17].

The local transient reactions observed in the mouth and throat are considered consistent with the introduction of allergens in sensitized participants. The fact that all participants in the dose groups up to 12 DU completed the trials indicates that the local AEs were not considered too bothersome. In general, most of the AEs occurred almost immediately after administration of the HDM SLIT-tablet, lasted from a few minutes up to a few hours, and stopped happening within 3 weeks. Oral pruritus and throat irritation were the most frequent AEs in both trials.

In the 16 DU group (trial 1), 1 participant discontinued IMP treatment due to 3 AEs (2 episodes of mouth edema and 1 of throat tightness), while 2 participants had 4 moderate findings in the oral examinations. The entire 32 DU group (9 active, 3 placebo) was discontinued after 2 days, as 1 participant vomited immediately after intake of the IMP on day 2 of administration. Another participant in the 32 DU group developed uvular edema 2 hours post-dose on day 2 of IMP administration that was considered severe. Together, this indicated that the maximum tolerated dose during 28 days of treatment was 16 DU. However, based on the tolerability profile for the 16 DU group it is suggested that the maximum dose for daily treatment with HDM SLIT-tablet should not exceed 12 DU.

In a trial of subcutaneous immunotherapy with common inhalant allergens including HDM, it was demonstrated that participants with asthma had a higher risk of serious systemic reactions [18]. Thus, a primary concern prior to this development program was whether HDM SLIT-tablet treatment

would trigger asthma exacerbations in participants with HDM-induced asthma. Across both trials 19 participants reported 22 AEs coded as asthma. Of these, 4 events in trial 1 (in the 2 DU and 16 DU groups) and none in trial 2 were considered to be IMP-related. All asthma AEs were mild or moderate and did not appear to be related to the administered strength of the IMP. No clinically relevant changes were observed in FEV_1 or PEF measurements. Thus, the administration of HDM SLIT-tablet did not impair asthma control or lung function in these populations. This was also the conclusion from the parallel development of the grass SLIT-tablet [19,20].

The induction of specific blocking of IgE-allergen binding over the 28-day IMP treatment showed a dose-response relationship in each trial that seemed to be comparable. However, a limitation for the direct between-trial comparison was the fact that the serum samples were not analyzed simultaneously against the same reference. Induction of allergen-specific antibodies capable of blocking IgE-allergen binding is one of the most consistent immunological findings in immunotherapy trials [21]. The levels of IgE-blocking factor induced in the present trials resemble levels consistently observed in the trials with grass SLIT-tablet after approximately 1 month of treatment (data on file; [9,13]).The level of IgE-blocking factor is expected to increase further with longer duration of treatment, as it did in the grass SLIT-tablet trials [13,22].

The parallel increases in specific IgE for the actively treated participants support the idea that HDM SLIT-tablet treatment has a pronounced effect on immune response. It was recently suggested that changes in functional allergen-specific antibodies accounted for a significant part of the clinical treatment effect after subcutaneous grass immunotherapy [23]. The clinical efficacy of HDM SLIT-tablet has been explored in 1 completed trial [24], where effect on asthma after a year of treatment was demonstrated for the 6 DU group relative to placebo by a statistically significant reduction in the use of inhaled corticosteroids. Additional efficacy is being investigated in 2 phase 3 trials (EudraCT 2010-018621-19 and 2011-002277-38).

In conclusion, the trials described in this article demonstrate that doses up to 12 DU of the HDM SLIT-tablet are suitable for further clinical investigations in adults and children with HDM respiratory allergic disease.

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Conflicts of Interest

JLCorzo, T Carrillo, CPedemonte and AM Plaza Martín have declared no potential conflicts of interest. S Martin Hurtado and E Dige are employed by ALK. MA Calderon has the following potential conflicts of interest: consultancy (ALK, Stallergenes), safety committee fees (ALK), board membership (ALK), and speakers bureaus (ALK, Stallergenes, and Merck).

Previous Presentation

The results of each of the 2 trials individually were presented at the EAACI 2009 congress. The adult trial was presented as a poster (Calderon et al, *ALK house dust mite allergen immunotherapy tablet suitable for further clinical development – results from the first phase I tolerability trial*) and the pediatric trial as an oral presentation (Carrillo et al, *ALK house dust mite allergen immunotherapy tablet suitable for further clinical development – results from a phase I tolerability trial in children*).

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