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House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma

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Abstract

Background: The efficacy and safety of sublingual immunotherapy in house dust mite–induced asthma have yet to be firmly established. We report the results of a double-blind, placebo-controlled, randomized clinical trial performed in mainland China.

Methods: After a three-month baseline period, 484 asthmatic adults were randomized 2 : 1 to 12 months of daily treatment with either an aqueous, standardized, 300 index of reactivity mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extracts or a placebo. The primary efficacy criterion was well-controlled asthma for at least 16 of the last 20 weeks of treatment.

Results: In the active (n = 308) and placebo (n = 157) groups, well-controlled asthma was achieved by 85.4% and 81.5% of the patients, respectively (P = 0.244). A subsequent post hoc analysis by asthma severity revealed significant clinical benefits in actively treated subjects with moderate, persistent asthma at baseline [401–800 μg budesonide/day (n = 175)], with greater achievement of well-controlled asthma (80.5% and 66.1% for the active treatment and placebo groups, respectively; P = 0.021) and totally controlled asthma (54.0% and 33.9%, respectively, P = 0.008), a higher percentage of patients with an asthma control questionnaire score < 0.75 (56.6% and 40.0%, respectively; P = 0.039) and a greater mean reduction in inhaled corticosteroid use (218.5 μg and 126.2 μg, respectively; P = 0.004). The active *vs* placebo differences in disease control and corticosteroid use were not significant for mild, persistent asthma. No treatment-related serious adverse events were reported.

Conclusions: Sublingual mite allergen immunotherapy was well tolerated in adult asthmatics and effectively controlled disease in patients with moderate (but not mild) persistent asthma (ClinicalTrials.gov: NCT00660452).

The causal role of house dust mites (HDMs) in allergic asthma is well established (1). The use of allergen immunotherapy (AIT) in allergic respiratory disease has long been acknowledged (2). Recent meta-analyses and systematic reviews (3–6) suggest that although SLIT may be beneficial in allergic asthma, the effect size has been small and highly variable. Most studies involved fewer than 100 subjects and were performed in children rather than adults. Lastly, the majority of the efficacy analyses were based on symptom scores, rescue medication use, peak expiratory flow or bronchial hyper-responsiveness rather than the asthma control parameters recommended in the Global Initiative for Asthma (GINA) (7–10). In China, asthma affects 20 million people (prevalence: 2.1%) (11), and HDMs are the most prevalent allergens in this context (12). We assessed the efficacy and safety of HDM SLIT in a cohort of Chinese adult patients with mild-to-moderate, persistent allergic asthma using well-controlled asthma (WCA) as the primary efficacy criterion (7).

Material and methods

Study subjects

This was a randomized, double-blind, placebo-controlled (DBPC) parallel-group study performed at 14 centres in the

Chinese cities of Beijing, Shanghai, Hangzhou, Wuhan, Chengdu, Chongqing, Nanjing and X'ian, over a 18-month period (ClinicalTrials.gov identifier: NCT00660452). The study population consisted of adult patients (aged 16–50) having suffered from mild or moderate, persistent, HDM-induced asthma for at least previous 12 months. Asthma was diagnosed with a bronchial reversibility test ($\geq$12% after inhalation of β_2-agonist) or a positive methacholine challenge within the previous year or at screening (V1). Sixty per cent of the patients were being treated with inhaled corticosteroids (ICSs) at V1, and the remainder were started on budesonide (from 200 μg to 1000 μg/day) at that time. Sensitization to *Dermatophagoides pteronyssinus* (*D. pt*) and *Dermatophagoides farinae* (*D. far*) allergens was confirmed by skin prick tests (wheal diameter: $\geq$4 mm) and specific serum IgE ($\geq$0.70 kU/l).

The main exclusion criteria were previous AIT, severe asthma, cosensitization to confounding aero-allergens and a smoking history of more than 10 pack-years. The study was approved by the local institutional review boards. Written informed consent was obtained from all patients.

Study design

The study consisted of a screening phase, a 12-week baseline phase and a 12-month treatment phase (Fig. 1). In compliance with international guidelines on the minimum clinically effective dose of ICS (7), a budesonide dose step-down was initiated at V3 and again at V4 if the patient had WCA (as defined in GINA) in the 4 weeks preceding the visit, an Asthma Control Questionnaire (ACQ) score at 1.50 (13) and a $FEV_1 \geq 80\%$ of the predicted value. At V5, patients were randomized 2 : 1 to active treatment or placebo. After 24 weeks of treatment, a second, 16-week budesonide step-down phase was initiated to identify a possible steroid-sparing effect of AIT. Patients filled out a daily record card.

Sample size calculation

Based on the GOAL trial (10) (the only available data when our study was designed), we expected a WCA rate of 43% in the placebo group and so powered our study to detect an intergroup difference of 14%, that is, 57% of well-controlled patients in the SLIT group. Using a randomization ratio of 2 : 1, a sample size of 300 patients in the active treatment group and 150 patients in the placebo group would yield a power of 80% for detecting the expected difference at a 5% two-sided significance level. A lower than expected dropout rate yielded 465 patients in the full analysis set (FAS), that is, more than the planned 450 (Fig. 2).

Immunotherapy and medications

The aqueous STALORAL® SLIT solution (Stallergenes, Antony, France) contained equal proportions of *D. pt.* and *D. far* extracts. The daily 300 index of reactivity (IR) maintenance dose corresponds to approximately 28 μg Der p 1 and 50 μg Der f 1. The only authorized medications were budesonide dry powder 100 μg (controller), salbutamol, prednisolone (for asthma exacerbations) and loratadine (for allergic rhinitis).

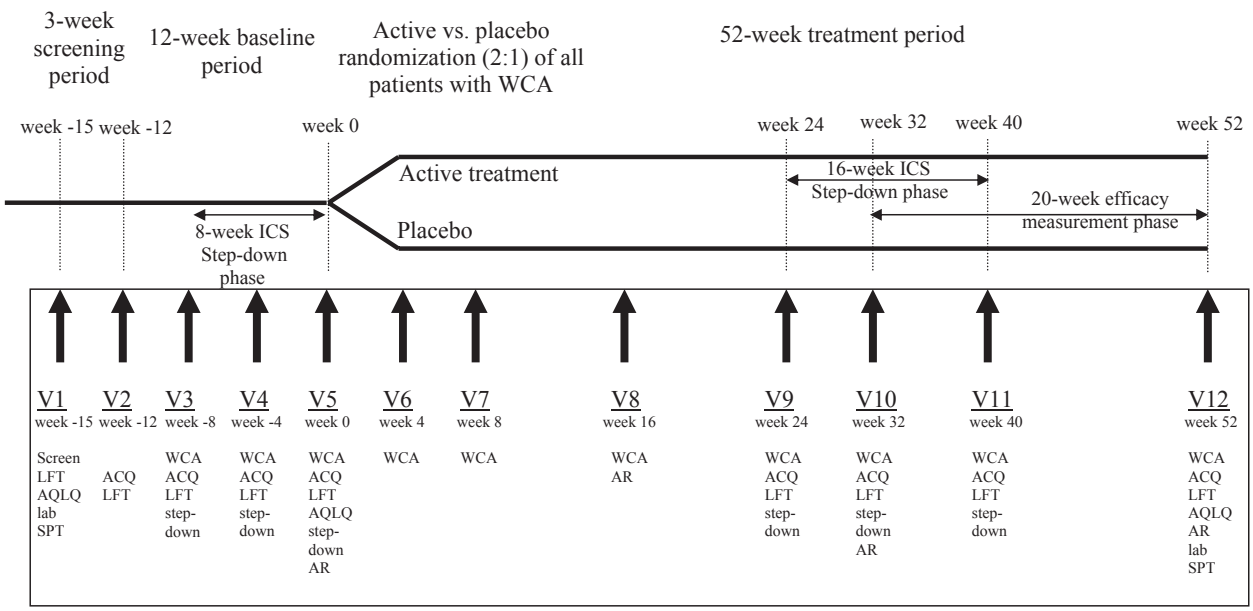

Figure 1 Study design. WCA, well-controlled asthma; wk, week; ICS, inhaled corticosteroid; LFT, lung function test; AQLQ, Asthma Quality of Life Questionnaire; lab, laboratory tests for safety assessment; SPT, skin prick test; ACQ, Asthma Control Questionnaire; WCA, well-controlled asthma assessment; AR, overall allergic rhinitis assessment.

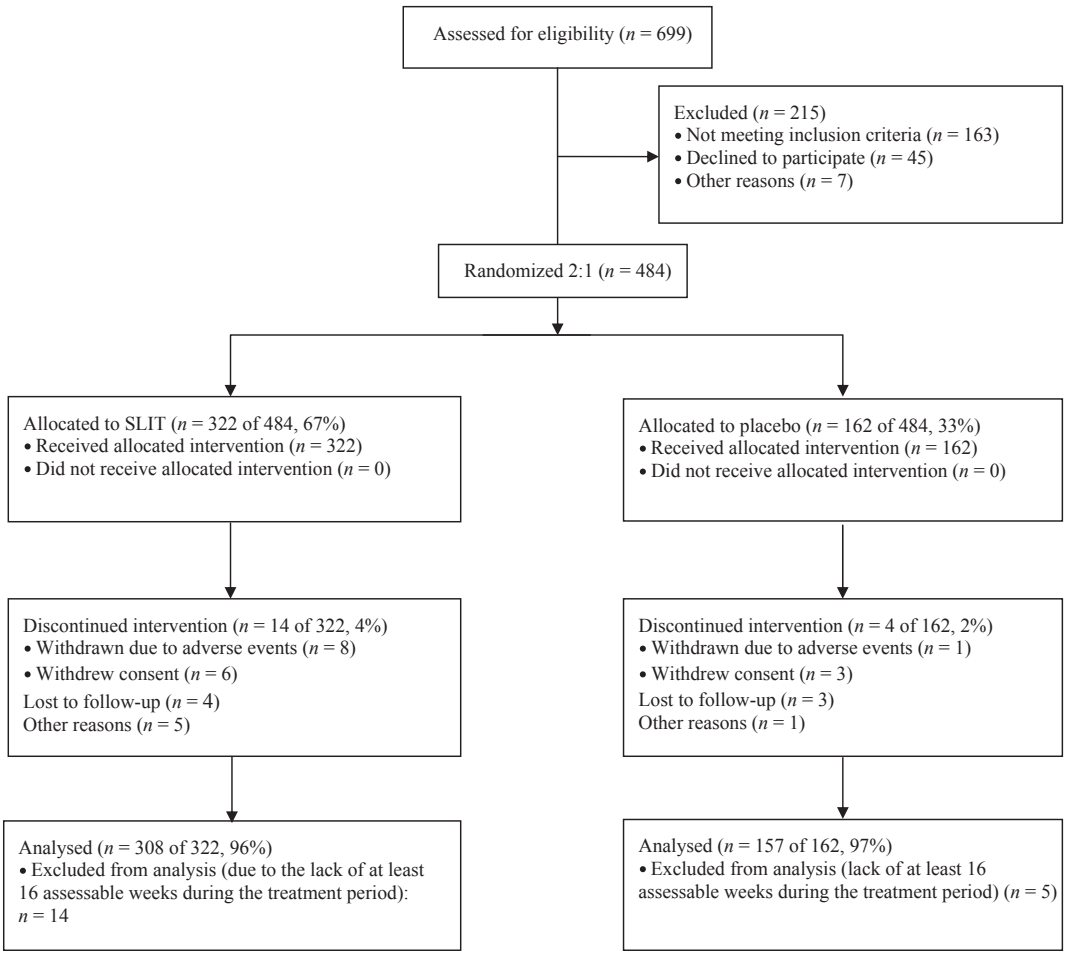

Figure 2 Patient disposition.

Efficacy, immunological and safety endpoints

The study's primary efficacy criterion was WCA (7, 10) for at least 16 of the last 20 weeks of treatment (weeks 32–52). Totally controlled asthma (TCA) (10) was assessed as a secondary efficacy criterion. The seven-item ACQ (13) was administered at every visit during the baseline period and at each of the four visits during the last 6 months of treatment (Fig. 1). The 32-item Asthma Quality of Life Questionnaire (AQLQ) (14) was administered at V1 (screening), V5 (randomization) and V12 (study completion).

Statistical analysis

Statistical analysis was performed using SAS® software (version 9.1.3, SAS Inc., Cary, NC, USA). The primary efficacy analysis was performed on the FAS (randomized patients having received at least one dose of study medication and with at least 16 assessable treatment weeks). The WCA and TCA success/failure rates were analysed in a logistic regression model including treatment group, pooled centre, gender, age and FEV_1 (L) at randomization as independent variables. The number and proportion of successes/failures in each treatment group and the corresponding odds ratio, 95% confidence interval and the *P*-value in a Wald test (15) were calculated. The absolute and relative changes in ICS use from baseline to study end in each treatment group were compared in a Wilcoxon two-sample test. Changes in FEV_1 from baseline to study end in each treatment group were compared in an analysis of covariance (ANCOVA), with treatment group and pooled centre as main factors and gender, age and baseline FEV_1 as covariates. Because the characteristics at randomization were well balanced when comparing patients taking 200–400 μg budesonide per day at randomization (i.e. mild asthma) and those taking 401–800 μg per day (i.e. moderate asthma) (Table 1), post hoc analyses of WCA, TCA, ACQ score and the change in ICS dose were performed within these two subgroups. Supporting analyses on the corresponding per-protocol (PP) populations and *post hoc* sensitivity analyses on subgroups of patients receiving a baseline ICS dose below or over 400 μg budesonide were also performed. The ACQ and AQLQ scores and skin wheal diameters were compared in an ANCOVA.

Table 1 Baseline characteristics of the patients in the full analysis set

	Active			Placebo		
	Entire group	Mild asthmatics†	Moderate asthmatics†	Entire group	Mild asthmatics†	Moderate asthmatics†
n	308	161	113	157	76	62
Age [years, mean (SD)]	31.2 (9.0)	29.5 (8.3)	33.4 (9.1)	31.3 (8.2)	29.3 (7.9)	33.5 (8.1)
range	14–50	16–49	14–50	16–49	16–45	17–49
Gender [*n* females, (%)]	164 (53.2)	88 (54.7)	57 (50.4)	92 (58.6)	40 (52.6)	41 (66.1)
BMI (kg/m^2) [mean (SD)]	22.6 (3.5)	22.0 (2.8)	23.3 (4.2)	23.0 (3.4)	22.6 (3.1)	23.1 (4.0)
Time since onset of asthma	12.8 (9.9)	12.2 (9.9)	13.5 (9.5)	13.7 (10.0)	12.4 (9.6)	15.2 (10.6)
[mean (SD) years]	1–45	1–44	2–41	2–43	2–43	2–40
Range						
Asthma exacerbations requiring oral corticoids in the previous year (% patients):	16.6	14.9	21.2	20.4	11.8	29.0
FEV_1 (% predicted) at inclusion (V2) [mean (SD)]	79.5 (13.3)	81.0 (11.7)	74.8 (13.0)	81.2 (12.7)	84.1 (12.1)	76.9 (12.0)
AQLQ at screening (V1) [mean (SD)]	4.6 (1.0)	4.7 (1.0)	4.3 (1.1)	4.5 (1.1)	4.7 (1.1)	4.1 (1.1)
ACQ at inclusion (V2) [mean (SD)]	1.41 (0.83)	1.21 (0.72)	1.81 (0.88)	1.41 (0.86)	1.19 (0.73)	1.78 (0.90)
FEV_1 (% predicted) at randomization (V5) [mean (SD)]	85.2 (11.3)	86.4 (10.1)	81.9 (10.5)	84.6 (11.3)	87.4 (11.4)	80.1 (9.6)
ACQ at V5 [mean (SD)]	0.68 (0.52)	0.62 (0.50)	0.79 (0.56)	0.74 (0.58)	0.64 (0.49)	0.92 (0.67)
[ACQ < 0.75 (%)]	66.3	68.4	60.7	61.5	65.2	52.5
AQLQ at V5 [mean (SD)]	6.0 (0.9)	6.1 (0.8)	5.8 (1.1)	5.9 (0.9)	6.0 (0.9)	5.7 (1.0)
ICS dose at V5 (randomization) [mean (SD)]	431.7 (221.8)	313.7 (95.8)	661.1 (112.1)	453.5 (240.9)	297.4 (96.6)	677.4 (104.7)
Patients with perennial, allergic rhinoconjunctivitis (*n*, %)	237 (76.9)	123 (76.4)	81 (71.7)	123 (78.3)	64 (84.2)	42 (67.7)
Skin wheal diameter (mm)						
Dermatophagoides pteronyssinus	8.9 (5.4)	9.0 (6.2)	8.8 (4.7)	9.1 (5.5)	9.7 (6.5)	8.5 (4.7)
Dermatophagoides farinae	8.5 (4.9)	8.6 (5.9)	8.2 (3.7)	9.0 (5.9)	10.2 (7.1)	8.1 (4.7)
Specific IgE (kU/l)*						
Anti-*Dermatophagoides*	28.7	31.4	26.7	30.3	29.5	33.0
pteronyssinus	[24.7; 33.4]	[25.3; 39.1]	[21.1; 34.0]	[24.7; 37.3]	[21.2; 40.9]	[24.5; 44.4]
Anti-*Dermatophagoides farinae*	26.4	27.6	25.0	26.3 [21.3; 32.4]	25.1	28.4
	[22.7; 30.6]	[22.3; 34.2]	[19.8; 31.6]		[18.0; 34.8]	[20.8; 38.9]

N, number of patients in the FAS. Results describing continuous variables are expressed as the mean (SD). Results describing categorical variables are expressed as *n* (number of patients) and as a percentage of the FAS population.

FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; IgE, immunoglobulin E; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; V, visit.

*Geometric mean with the 95% confidence interval.

†Mild and moderate asthmatics are defined as those taking 200–400 μg and 401–800 μg budesonide per day at randomization, respectively.

Results

In all, 699 patients were screened and 484 were randomized to active treatment ($n = 322$) or placebo ($n = 162$) (Fig. 2). There were no significant differences between the active and placebo groups in terms of demographic characteristics, time since onset of asthma, asthma exacerbations in the previous year, ICS dose, asthma medication prior to study enrolment, the ACQ score and the AQLQ score (Table 1). At least two thirds of the patients had WCA for each of the 4 weeks prior to randomization.

The proportions of patients achieving WCA or TCA by the study end were slightly but not significantly greater in the active treatment group than in the placebo group (Tables 2 and 3). For patients with moderate asthma ($n = 175$), the WCA success rate was greater in the active treatment group than in the placebo group (80.5% and 66.1%, respectively; $P = 0.021$) (Fig. 3). There was no significant difference for patients with mild asthma ($n = 237$). However, in the subgroup of patients with moderate asthma, the percentage of patients achieving TCA was higher ($P = 0.008$) in the active treatment group when compared with the placebo group

Table 2 Well-controlled asthma: proportion of patients in the full analysis set (FAS) achieving success or failure at study end

			Comparison between treatment group*		
	Active	Placebo	OR	95% CI	*P*
FAS					
N	308	157			
WCA success *n* (%)	263 (85.4)	128 (81.5)	1.37	[0.81; 2.33]	0.244
WCA failure *n* (%)	45 (14.6)	29 (18.5)			
Subgroup analysis (at randomization, ICS stratum)					
Budesonide [200–400] μg at randomization					
N†	161	76			
WCA success *n* (%)	140 (87.0)	69 (90.8)	0.88	[0.33; 2.33]	0.793
WCA failure *n* (%)	21 (13.0)	7 (9.2)			
Budesonide [401–800] μg at randomization					
N†	113	62			
WCA success *n* (%)	91 (80.5)	41 (66.1)	2.42	[1.14; 5.13]	0.021
WCA failure *n* (%)	22 (19.5)	21 (33.9)			

N, number of patients in the FAS population; *n,* number of patients achieving success or failure; %, percentage of patients achieving success or failure relative to number of patients in the FAS. ICS: inhaled corticosteroid.

*Active *vs* placebo; OR: odds ratio; CI: confidence interval; *P*-value from the Wald test.

†Forty three patients had an ICS dose <200 μg and 10 patients had an ICS dose >800 μg at randomization and thus were not included in the subgroup analysis.

Table 3 Totally controlled asthma: proportion of patients achieving success or failure at study end

			Comparison between treatment groups*		
	Active	Placebo	OR	95% CI	*P*
FAS overall group					
N	308	157			
Success *n* (%)	188 (61.0)	83 (52.9)	1.41	[0.95; 2.09]	0.085
Failure *n* (%)	120 (39.0)	74 (47.1)			
Subgroup analysis (at randomization, ICS stratum)					
Budesonide [200–400] μg at randomization					
N†	161	76			
Success *n* (%)	107 (66.5)	53 (69.7)	0.89	[0.49; 1.61]	0.699
Failure *n* (%)	54 (33.5)	23 (30.3)			
At randomization, ICS budesonide [401–800] μg					
N†	113	62			
Success *n* (%)	61 (54.0)	21 (33.9)	2.47	[1.27; 4.83]	0.008
Failure *n* (%)	52 (46.0)	41 (66.1)			

N, number of patients in FAS population; *n,* number of patients achieving success or failure; %, percentage of patients achieving success or failure relative to number of patients in study population. ICS: inhaled corticosteroid.

*Active *vs* placebo; OR: odds ratio; CI: confidence interval; *P*-value from the Wald test.

†Forty three patients had an ICS dose <200 μg and 10 patients had an ICS dose >800 μg at randomization and thus were not included in the subgroup analysis.

(54.0% and 33.9%, respectively) (Fig. 3). Similar analyses of treatment success in the PP populations gave similar results: in the sub-group of patients with moderate asthma, the WCA rates were 81.7% in the active treatment group and 67.2% in the placebo group ($P = 0.015$; odds ratio: 2.73), and the TCA rates were 56.7% in the active treatment group and 34.5% in the placebo group ($P = 0.0035$, odds ratio 2.85). These statistically significant findings were confirmed by sensitivity analyses of WCA and TCA in the subgroups of patients receiving a baseline ICS dose below or over 400 μg of budesonide.

The ACQ score improved markedly during the baseline period (Table 1), and over 80% of patients had an ACQ score <1.5 at randomization. In moderate (but not mild) asthma, the percentage of individuals with ACQ < 0.75 was higher in the active treatment group than in the placebo

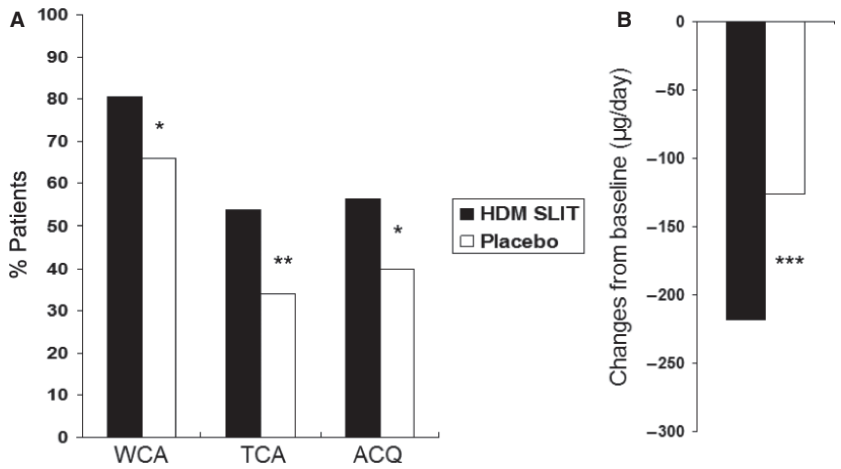

Figure 3 (A) The proportion of patients with moderate, persistent asthma achieving well-controlled asthma (WCA) or totally controlled asthma (TCA) during the last 16 weeks of the study and an ACQ score < 0.75 at study end. (B) Absolute changes from baseline in the budesonide daily dose at study end, in patients with moderate, persistent asthma. *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$.

group (56.6% and 40.0%, respectively; $P = 0.039$) (Fig. 3). In patients with moderate (but not mild) asthma, mean absolute decrease in budesonide dose was significantly greater in the active treatment group than in the placebo group (218.5 µg and 126.2 µg, respectively; $P = 0.004$) (Fig. 3).

Overall, the mean FEV_1% predicted remained above 80% during the treatment period in both the active treatment and placebo groups. The study end *vs* baseline changes were non-significant in both groups. The AQLQ overall scores in both groups improved considerably during the baseline period, from a mean value of 4.5 (1.08) at screening to 5.9 (0.91) at randomization.

At study end, the mean (SD) changes in the skin prick test wheal size for *D. pt* and *D. far* in the active treatment group were −2.8 (5.4) mm and −2.9 (4.7) mm, respectively, and were significantly greater ($P < 0.0001$) than the values of −1.4 (5.4) mm and −1.8 (6.3) mm in the placebo group. In the active treatment group, *D. pt*-specific serum immunoglobulins increased markedly over the study, with a 1.58 geometric mean fold-change (95% CI: 1.44, 1.74) in specific IgE levels and a 1.99 (95% CI: 1.81, 2.18) for IgG4. There were no significant changes in the placebo group.

Compliance (based on the number of unused SLIT packs) was 90.9% and 93.0% in the active treatment and placebo groups, respectively.

All 484 subjects were included in the safety analysis. The most common treatment-emergent adverse events (recorded in ≥5% of the patients) were more frequent in the active treatment group than in the placebo group, with (generally mild) abdominal pain, swollen tongue, oral pruritus, glossitis, cheilitis and mouth oedema. The active and placebo groups did not differ greatly in terms of the incidence of rhinitis, upper respiratory tract infections, nasopharyngitis and asthma events. Six serious adverse events (knee fracture, Arnold–Chiari syndrome, contact dermatitis, ovarian cyst ruptured/pneumonia and traumatic brain injury) were reported in four patients in the active treatment group (1.2%) and one in the placebo group (0.6%). None were causally related to the study treatment. No deaths or anaphylactic reactions were reported.

Discussion

With 484 subjects randomized, this was probably the largest DBPC study of SLIT to have been performed to date in adult patients with HDM-induced asthma. The study's quality was confirmed by the low dropout rate (7.1% and 4.9% in the active treatment and placebo groups, respectively) and high treatment compliance (>90%) over a rigorous, 12-month period of daily dosing. The trial was broadly consistent with Casale et al.'s 2009 recommendations on producing high-quality evidence of efficacy in SLIT studies (16), that is, a DBPC superiority study with relatively high doses and screening for clinically relevant sensitizations in essentially AIT-naïve patients. This was the first SLIT study to measure WCA (7, 10), as opposed to single outcome measures.

The primary efficacy criterion was not met because of a higher than expected WCA rate at randomization in both placebo and active groups. A post hoc analysis revealed a significant active *vs* placebo difference in both WCA and TCA in patients with moderate (but not mild) persistent asthma. A significant active *vs* placebo difference was also observed for the percentage of moderate asthma patients with an ACQ score < 0.75 (13). Moreover, for moderate asthmatics, the ICS dose reduction in the active group was twice that in the placebo group. These results in patients with moderate asthma are probably due to the fact that they had a lower level of asthma control and a higher ICS dose at randomization (Table 1).

The investigational SLIT product was well tolerated. The adverse event profile was consistent with that previously described for SLIT (5, 17), with mainly mild, local, transient adverse events; this profile may be due to SLIT's particular

mechanism of action (18, 19). Furthermore, the low number of asthma exacerbations (0.06 ± 0.38, standardized over a year) in the SLIT group did not differ significantly from that recorded in the placebo group and was similar to the lowest value reported in the GOAL study (0.05) (10). Likewise, the small and similar reductions in FEV_1% in the two groups indicate worsened respiratory function but no more so in the SLIT group than in the placebo group. However, these changes were observed in a context of ICS dose reductions. Very encouragingly, we did not observe any significant differences in the incidence of TEAEs in general and in the number of patients with asthma exacerbations requiring oral corticoids in particular when performing active *vs* placebo comparisons in patients with mild asthma (16% *vs* 12%, respectively) and those with moderate asthma (21% *vs* 29%, respectively). This encourages us to consider that although AIT will be avoided in patients with severe asthma, this therapy could safely benefit patients with moderate asthma (20). Further studies are required to establish whether HDM SLIT can maintain control in mild asthmatics after the withdrawal of controller therapies. The GINA 2012 update (7) does not comment in detail on the safety of AIT in asthma. However, given the good safety profile and clinical benefit seen here in moderate asthma, SLIT appeared to be clinically relevant.

Why, then, did this large, well-executed study with high levels of treatment compliance fail to meet the primary efficacy criterion in the overall population? The strong improvements in the ACQ and AQLQ scores in the active treatment and placebo groups during the baseline period (Table 1) suggest (i) a 'nursing effect' (due to regular medical monitoring) and (ii) improvement in symptoms due to initiation of ICS treatment in previously untreated patients. In view of the high WCA rate, the ACQ and AQLQ scores at randomization and the proportion of mild asthmatics (57%), the potential for clinically meaningful improvement with SLIT was low. Nevertheless, we consider that our choice of WCA as the primary efficacy criterion was justified and will remain so for future research, in view of the broad, rapid uptake of the GINA guidelines and the value of 'asthma control' as a tool for assessing drug efficacy (21). However, other study design parameters (e.g. the number of participants and the level of control at baseline) may have to be adjusted accordingly when WCA is used in trials.

Our results for moderate asthma confirmed literature reports whereby SLIT can have a significant steroid-sparing effect. In Blumberga et al.'s (22) DBPC RCT of HDM SCIT in 42 patients with moderate asthma, a post hoc analysis revealed a strong steroid-sparing effect after several years of SCIT with HDM extracts (with respective median reductions of 50% and 25% in the SCIT and placebo groups after 2 years and 90% and 42% after 3 years).

The reduction in wheal size and the increase in serum-specific IgG4 and IgE antibody levels during our study in the active treatment group (but not the placebo group) shows that the dose of allergen used here had an immunological effect [as reported in other studies (23)].

Our study had several limitations. Firstly, exposure to HDM allergens in each patient's home was not measured. However, chemical and physical methods aimed at reducing exposure to HDM may fail to improve asthma (24). A second potential limitation was the relatively short treatment duration of 12 months. In their longer-term studies, Pajno et al., Marcucci et al. and Tabar et al. (25–27) observed greater improvements in the second and/or third years (relative to the first years). In contrast, HDM SLIT tablets have demonstrated their efficacy in AR after 4 months of treatment, with the persistence of a therapeutic effect after 1 year of treatment (28). Similar results have been obtained in a recent study performed in an environmental exposure chamber (29), although the time–course of the response to HDM SLIT may be different in asthma and AR. Thirdly, *post hoc* procedures must always be applied and interpreted with caution. Nevertheless, our choice of large, well-balanced subgroups (GINA 2 *vs* GINA 3) was clinically relevant. The test can therefore be considered as a robust, a posteriori subgroup analysis and was confirmed by the sensitivity tests. Lastly, our findings in China may not necessarily be applicable to other ethnicities or to countries in which access to health resources differs.

In conclusion, our study of HDM SLIT in asthma featured a large sample size, a relevant primary efficacy criterion (WCA) and a well-defined ICS dose step-down phase. In a large subgroup of patients with moderate, persistent asthma, HDM SLIT was safe and appeared to be effective in achieving asthma control and steroid sparing.

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Author contributions

Jia Yin (principal investigator), Lianglu Wang, Philippe Devillier, Riad Fadel, Armelle Montagut and Olivier de Beaumont all made substantial contributions to conception and design of the study and acquisition, analysis and/or interpretation of data. They all contributed to drafting the article or revising it critically for important intellectual content and have given their final approval of the version submitted for consideration for publication.

Conflicts of interest

Philippe Devillier has received consulting fees, honoraria for lectures and/or research funding from Schering-Plough-MSD, Sanofi-Aventis, GlaxoSmithKline, Chiesi, AstraZeneca, ALK and Stallergenes. Riad Fadel, Armelle Montagut and Olivier de Beaumont are employees of Stallergenes. Other authors declare no conflicts of interest.

References

1. Platts-Mills TAE, Erwin EA, Heymann PW, Woodfolk JA. Pro: The evidence for a causal role of dust mites in asthma. *Am J Respir Crit Care Med* 2009;**180**:109–121.
2. Bousquet J, Lockey R, Malling HJ, eds. World Health Organization Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;**53** (Suppl. 44):1–42.
3. Calamita Z, Saconato H, Pelá AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006;**61**:1162–1172.
4. Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy* 2009;**64**:1570–1579.
5. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009;**64**(Suppl. 91):1–59.
6. Radulovic S, Wilson D, Calderón M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011;**66**:740–752.
7. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. December 2012 update of the NHLBI/WHO Workshop Report 1995. Available from: http://www.ginasthma.org/.
8. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;**31**:43–78.
9. Pedersen S. From asthma severity to control: a shift in clinical practice. *Prim Care Resp J* 2010;**19**:3–9.
10. Bateman E, Boushey HO, Bousquet J. Can guideline-defined asthma control be achieved? *Am J Resp Crit Care Med* 2004;**170**:836–844.
11. Masoli M, Fabian D, Holt SBeasley R for the Global Initiative for Asthma (GINA). The global burden of asthma: executive summary of the GINA Dissemination Committee Report. *Allergy* 2004;**59**:469–478.
12. Li J, Sun B, Huang Y, Lin X, Zhao D, Tan G et al. A multicentre study assessing the prevalence of sensitizations in patients with asthma and/or rhinitis in China. *Allergy* 2009;**64**:1083–1092.
13. Juniper EF, Bousquet J, Abetz L, Batman ED. Identifying "well-controlled" asthma using the asthma control questionnaire. *Respir Med* 2006;**100**:616–621.
14. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;**47**:76–83.
15. Wald A. Tests of statistical hypotheses concerning several parameters when the number of observations is large. *Trans Am Math Soc* 1943;**54**:426–482.
16. Casale TB, Canonica GW, Bousquet J, Cox L, Lockey R, Nelson HS et al. Recommendations for appropriate sublingual immunotherapy clinical trials. *J Allergy Clin Immunol* 2009;**124**:665–670.
17. Cox LS, Larenas-Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;**117**:1021–1035.
18. Calderón MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy* 2012;**67**:302–311.
19. Novak N, Bieber T, Allam JP. Immunological mechanisms of sublingual allergen-specific immunotherapy. *Allergy* 2011;**66**:733–739.
20. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy* 2008;**63**:S8–S160.
21. Concept paper on the need for revision of the CHMP note for guidance on the clinical development of medicinal products in the treatment of asthma. London, UK, Oct 2009 Draft CPMP/EWP/2922/01. Committee for Medicinal Products for Human Use at the European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500006234.pdf. Last accessed 5 March 2013.
22. Blumberga G, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. *Allergy* 2006;**61**:843–848.
23. Pham-Thi N, Scheinmann P, Fadel R, Combebias A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol* 2007;**18**:47–57.
24. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. *Allergy* 2008;**63**:646–659.
25. Pajno GB, Morabito L, Barberio G. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy* 2000;**55**:842–849.
26. Marcucci F, Sensi L, Di Cara G, Salvatori S, Bernini M, Pecora S et al. Three-year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing sub-lingual immunotherapy. *Pediatr Allergy Immunol* 2005;**16**:519–526.
27. Tabar AI, Arroabarren E, Echechipia S, Garcıa BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol* 2011;**127**:57–63.
28. Roux M, Yang WH, Viatte A, Cadic V, Abiteboul K, Zeldin et al. Efficacy of house dust mite sublingual immunotherapy in adults with allergic rhinitis: results of an environmental exposure chamber study. *J Allergy Clin Immunol* 2013;**131**:AB37
29. Demoly P, Bergmann KC, Melac M, Nguyen H, Frereux M, Zeldin RK. Onset of action of sublingual tablets of house dust mite allergen extracts in adults. *J Allergy Clin Immunol* 2013;**131**:AB37.