



# SQ HDM SLIT-tablet (ALK) in treatment of asthma – *Post hoc* results from a randomised trial

F. de Blay <sup>a,\*</sup>, P. Kuna <sup>b</sup>, L. Prieto <sup>c</sup>, T. Ginko <sup>d</sup>, D. Seitzberg <sup>e</sup>,  
B. Riis <sup>e</sup>, G.W. Canonica <sup>f</sup>

<sup>a</sup> Chest Disease Department, University Hospital of Strasbourg, Federation of Translational Medicine, EA 3072, 67091 Strasbourg University, France

<sup>b</sup> Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, ul. Kopcińskiego 22, 90-153 Łódź, Poland

<sup>c</sup> Departamento de Medicina, Universidad de Valencia, Av. Blasco Ibáñez, 15, 46101 Valencia, Spain

<sup>d</sup> Private Practice, Vorgebirgsstraße 43, 53119 Bonn, Germany

<sup>e</sup> Global Clinical Development, ALK, Bøge Allé 6-8, 2970 Hørsholm, Denmark

<sup>f</sup> Allergy & Respiratory Dis. Clinic, DIMI, University of Genova, IRCCS AOU San Martino, Largo R. Benzi 10, 16132 Genova, Italy

Received 12 February 2014; accepted 29 July 2014

Available online 7 August 2014

## KEYWORDS

House dust mite;  
Asthma;  
SLIT-tablet;  
ICS reduction;  
Asthma quality of life

## Summary

**Introduction:** In a double-blind, placebo-controlled trial (EudraCT identifier: 2006-001795-20), the standardised quality (SQ) house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet (ALK, Denmark) was investigated.

**Method:** The trial included 604 subjects,  $\geq 14$  years, with mild-moderate HDM allergic asthma. Subjects were randomised 1:1:1:1 to 1, 3 or 6 SQ-HDM or placebo once daily. The primary endpoint was reduction in inhaled corticosteroid (ICS) after one year. ICS reduction, asthma quality of life questionnaire (AQLQ) and asthma control questionnaire (ACQ) score was analysed *post hoc* in a subgroup with daily ICS use of 400–800  $\mu\text{g}$  and ACQ score of 1–1.5, corresponding to partly controlled asthma ( $N = 108$ ).

**Results:** The trial met its primary endpoint. In the subgroup, the difference between placebo and 6 SQ-HDM in change from baseline in daily ICS use was 327  $\mu\text{g}$  ( $p < 0.0001$ ), while it was 0.52 ( $p = 0.010$ ) for AQLQ. The treatment effect on ICS reduction and AQLQ was increased for the subgroup versus the residual population (ICS reduction:  $p < 0.001$ ); AQLQ:  $p = 0.044$ ).

\* Corresponding author. Chest Disease Department, University Hospital of Strasbourg, 1 Place de l'Hôpital, BP 426, 67091 Strasbourg Cedex, France. Tel.: +33 369550381; fax: +33 369551830.

E-mail address: [Frederic.DEBLAY@chru-strasbourg.fr](mailto:Frederic.DEBLAY@chru-strasbourg.fr) (F. de Blay).

**Conclusion:** In this subgroup, including only patients with partly controlled asthma, the benefit of 1 year of treatment with SQ HDM SLIT-tablet was significantly higher than for the less severe full population, both in terms of increased asthma control and improved quality of life.

© 2014 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

## Introduction

Allergic rhinitis and asthma are increasingly common diseases of the respiratory tract. They often co-exist, with symptoms of rhinitis found in 75–80% of patients with asthma [1]. Asthma and bronchial hyper responsiveness are more common and severe with perennial allergies (e.g. house dust mite (HDM) and cat dander allergy) compared to seasonal allergies [2,3].

Asthma is associated with substantial indirect costs that increase significantly as disease control decreases [4]. Although the costs of rhinitis and asthma are independently high, medical care costs are higher in those with asthma and rhinitis compared with those with asthma alone [5].

Allergy immunotherapy (AIT) addresses the underlying cause of allergy through immunomodulation, and thus treats both manifestations of respiratory allergic disease.

Subcutaneous immunotherapy (SCIT) has been shown to reduce the use of inhaled corticosteroid (ICS) in adults and children with house dust mite (HDM) related asthma [6,7]. Further, a trial with 3 years of standardized SCIT treatment, suggested a preventive effect on development of asthma in children with seasonal rhinitis [8–10]. Recently, evidence was published on reduction of seasonal asthma symptoms in grass pollen allergic children and adults by treatment with a standardised quality (SQ) grass tablet for sublingually administered AIT (SLIT) [11,12]. However, investigation of AIT in the treatment of asthma was not included in EMA guidelines until recently [13–15], and its benefits are being debated in global treatment guidelines [16].

A trial investigating the effect of SQ HDM SLIT-tablet in HDM respiratory allergic disease, based on reduction in daily use of ICS (standardised to budesonide), has been conducted [17]. The trial showed a statistically significant treatment effect on ICS use in favour of the highest dose group (6 SQ-HDM<sup>1</sup>) without affecting asthma control endpoints; implying a reduced ICS dose required to maintain asthma control. As a substantial number of asthma patients worldwide is suffering from severe asthma [18] and thus is being at higher risk of frequent exacerbations [19], the medical need for new treatments in asthma is more pertinent for the severe part of the trial population.

Therefore, the present *post hoc* subgroup analysis included subjects with a medium–high dose use of ICS

(>400 µg ICS per day) but still only partly controlled by the ICS and thus having a medical need for additional treatment.

## Methods

Full information about the trial is published elsewhere [17]. Briefly, the trial was a multi-national, multiple-dose, randomised, double-blind, parallel-group, placebo-controlled trial including 604 subjects (EudraCT identifier: 2006-001795-20). Written informed consent was obtained from all subjects (and parents/guardians for subjects below 18 years) before any trial related procedures, in accordance with the Declaration of Helsinki. Main inclusion criteria included: 14 years or above; a clinical history of HDM-related mild to moderate persistent asthma (defined as medication steps 2 and 3 in GINA 2002 [20]); daily use of ICS (corresponding to 100–800 µg budesonide/day) for control of asthma symptoms, a clinical history consistent with HDM-induced allergic rhinitis, and positive diagnostic tests (specific IgE and skin prick tests).

The investigational medicinal product (IMP) was a fast-dissolving oral lyophilisate for sublingual administration. The active ingredients were standardised extracts of *Dermatophagoides (D.) pteronyssinus* and *D. farinae* in a 1:1 ratio. Placebo was similar in appearance, smell and taste, but without active ingredients. Subjects were randomised (1:1:1:1) to double-blind, daily treatment with 1, 3 or 6 SQ-HDM SLIT-tablet (ALK, Denmark) or placebo for approximately 12 months.

The trial design is shown in Fig. 1. Prior to randomisation, ICS use was standardised to budesonide and tapered to the lowest possible ICS dose to maintain adequate asthma control as defined by an asthma control questionnaire (ACQ) score <1.5 [21,22]. The lowest ICS dose was found by reducing the subject's ICS dose in steps with intervals of 3–4 weeks until loss of control (as defined by an ACQ score of >1.5) was provoked. Hereafter, the ICS dose was increased to the previous step to regain control (ACQ score <1.5). The tapering was followed by an ICS stable period, regarded as a baseline period prior to randomisation. The primary endpoint was reduction in ICS use after one year of treatment, assessed by a new ICS tapering and ICS stable period.

The subgroup described here, includes the subset of the trial population with a medium–high dose use of ICS and partly controlled asthma. In practise, subjects in the subgroup were selected by ICS use of 400–800 µg/day and an ACQ score of 1–1.5 at randomisation. Within this range, asthma was neither considered well-controlled nor uncontrolled [22].

<sup>1</sup> The SQ HDM SLIT-tablet contains 2 drug substances: allergen extracts from the HDM species *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* that are standardised against an in-house reference based on biological activity.

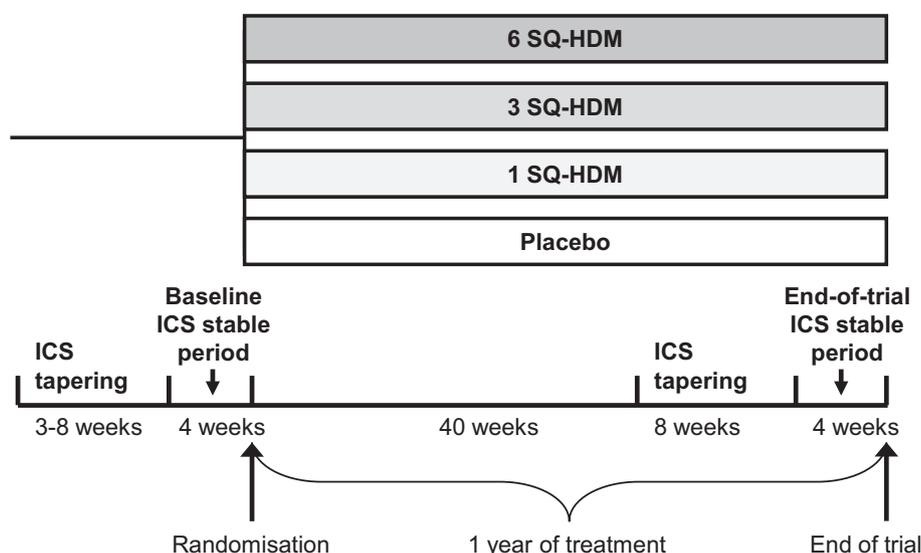


Figure 1 Overall trial design.

ICS reduction from baseline, asthma control by means of the ACQ questionnaire, and asthma quality of life by means of the asthma quality of life questionnaire with standardised activities (AQLQ(S) [23,24]) were investigated.

Adverse events (AEs) were reported in agreement with ICH guidelines (described in details elsewhere [17]). AEs occurring after first IMP intake and reported by subjects in the subgroup are included here.

## Statistics

For ICS reduction, treatment groups were compared with a linear mixed model using data from all 4 treatment groups. The model included treatment group and baseline ICS dose (recorded for the ICS stable periods) as fixed effects and trial site as a random effect. Two-sided 95% confidence intervals for the adjusted mean differences are presented as well as the corresponding *p*-values. The categorical variable of relative reduction in ICS use was summarised by frequency.

The ACQ includes 7 questions (5 symptoms, forced expiratory volume in the first second (FEV<sub>1</sub>) in % of predicted value, and short-acting bronchodilator use). Subjects were to recall how their asthma had been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale from 0 (no impairment) to 6 (maximum impairment). Clinic staff scored FEV<sub>1</sub>% predicted according to a specified 7-point scale. The questions were equally weighted and the ACQ score was the mean of the 7 questions and therefore between 0 and 6. The analysis of change from baseline for the average overall ACQ score (averaged over the ICS stable periods) was performed with a linear mixed model similarly to the ICS reduction analysis.

The AQLQ(S) comprises 32 questions in four domains (symptoms, activity limitation, emotional function and environmental stimuli), each scored on a 7-point scale from 1 (maximum impairment) to 7 (no impairment). When responding, subjects were to recall their experience during the last 2 weeks. Overall scores and domain scores were

calculated for each subject at baseline (end of baseline ICS stable period) and at the end-of-trial visit. The change from baseline to end-of-trial was calculated for each subject and analysed similarly to the ICS reduction with a linear mixed model including treatment group and baseline value as fixed effects and site as random effect.

The impact of belonging to the subgroup was analysed in a linear mixed model including site as random effect and treatment group, baseline value (ICS/AQLQ(S)), subgroup (Y/N) and interaction of subgroup with treatment (Y/N) as fixed effects.

The analyses of ICS reduction, ACQ, and AQLQ in the subgroup correspond to the pre-defined analyses for the full analysis set. The subgroup analyses are considered exploratory and no multiplicity control has been applied.

## Results

### Subgroup demographics

The subgroup included 108 subjects (18% of the full analysis set) equally distributed over the 4 treatment groups. 98

Table 1 Baseline ICS use, AQLQ(S) and ACQ score in subgroup versus full analysis set.

	Mean ICS use [µg]		Mean AQLQ(S) score		Mean ACQ score	
	Subgroup	FAS	Subgroup	FAS	Subgroup	FAS
Overall	615	449	5.61	5.97	1.18	0.80
Placebo	641	465	5.52	5.94	1.20	0.82
1SQ-HDM	636	438	5.75	6.08	1.21	0.80
3SQ-HDM	648	433	5.58	5.93	1.16	0.81
6SQ-HDM	541	462	5.62	5.92	1.15	0.77

ICS: inhaled corticosteroid (here: budesonide); AQLQ(S): (standardised version of) asthma quality of life questionnaire; ACQ: asthma control questionnaire; Subgroup: subjects with daily ICS use of 400–800 µg and ACQ score of 1–1.5 (*N* = 108); FAS: full analysis set (*N* = 604).

subjects (91%) completed the trial, while 10 subgroup subjects discontinued the trial prematurely due to withdrawal of consent ( $N = 1$ ), lost to follow up ( $N = 4$ ), non-compliance with protocol ( $N = 3$ ), or AEs ( $N = 2$ ; both from the 3 SQ-HDM group). Baseline demographics for the subgroup resembled the full analysis set, though the subgroup were slightly older (mean age 34.7 years versus 31.1 years) and had asthma and rhinitis for a correspondingly longer period of time.

The mean ICS use at randomisation for the subgroup was 615  $\mu\text{g}$ , compared with 449  $\mu\text{g}$  in the full analysis set (Table 1). The mean AQLQ(S) score was 5.61 in the subgroup versus 5.97 in the full analysis set and the mean ACQ score was 1.18 in the subgroup versus 0.80 in the full analysis set (Table 1).

## Efficacy

The trial met its primary endpoint, with a statistically significant difference in the ICS reduction between 6 SQ-HDM and placebo (81  $\mu\text{g}/\text{day}$ , [ $\text{CI}_{95\%}$ : 27–136  $\mu\text{g}/\text{day}$ ],  $p = 0.004$ ). In the subgroup, the difference in adjusted mean to placebo in the 6 SQ-HDM group during the end of trial ICS stable period was 327  $\mu\text{g}/\text{day}$ , [ $\text{CI}_{95\%}$ : 182–471  $\mu\text{g}/\text{day}$ ],  $p < 0.0001$  (see Fig. 2A). The ICS reduction in the 1 SQ-HDM and 3 SQ-HDM groups was less pronounced and not significantly different from placebo. The effect of the interaction of subgroup with treatment was statistically significant ( $p < 0.001$ ), implying that the treatment effect on ICS reduction was increased for the subgroup as compared to the residual group.

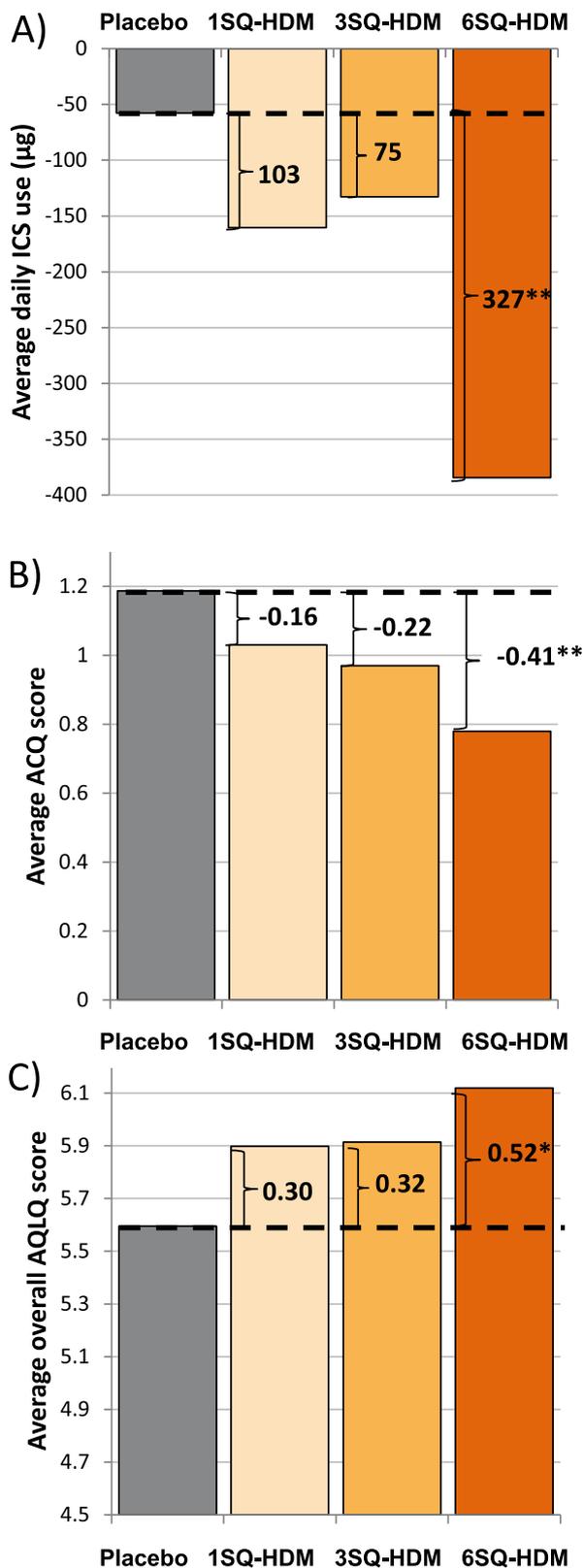
In the 6 SQ-HDM group, 17 subjects (59%) were able to reduce ICS use by 75%–100% without impairment in asthma control (Table 2), and 13 subjects (45%) withdrew ICS use completely. In the placebo group 1 subject (4%) was able to withdraw ICS. No subjects on 6 SQ-HDM increased their ICS use during the 1-year trial, while this was the case for 5 subjects (19%) in the placebo group (Table 2).

Lung function (in terms of mean  $\text{FEV}_1$ ) was around 85% of predicted value in all treatment groups at all visits during the trial (mean changes from randomisation were within  $\pm 4\%$  with no apparent pattern; data not shown).

The difference from baseline in overall ACQ score at the end of trial ICS stable period was statistically significantly lower in the 6 SQ-HDM group than in the placebo group (difference:  $-0.41$ ,  $p = 0.0002$ ; see Fig. 2B), implying better asthma control after treatment in the 6 SQ-HDM group. In the 1 SQ-HDM and 3 SQ-HDM groups, differences were not statistically significant.

There was also a statistically significant difference in asthma quality of life between placebo and 6 SQ-HDM in terms of a difference in overall AQLQ(S) scores of 0.52,  $p = 0.010$  (see Fig. 2C). The differences to placebo were lower in the 1 SQ-HDM and 3 SQ-HDM groups (0.30 and 0.32) and not statistically significant. The difference to placebo in the subgroup was significantly higher than for the rest of the population ( $p = 0.044$ ).

The increased AQLQ(S) score in the 6 SQ-HDM group was primarily related to the symptoms domain (difference to placebo 0.61,  $p = 0.006$ ) and to the activity limitation domain (difference to placebo 0.52,  $p = 0.011$ ).



**Figure 2** A) Change from baseline in adjusted mean daily ICS use ( $\mu\text{g}$ ); B) Average ACQ score; and C) Average overall AQLQ(S) score; all at end-of-trial with difference to placebo in numbers; \*:  $p < 0.05$ ; \*\*:  $p < 0.001$ .

**Table 2** Relative reduction in ICS use for the subgroup from randomisation to end of trial.

Reduction in ICS	Placebo (N = 27)		1 SQ-HDM (N = 25)		3 SQ-HDM (N = 27)		6 SQ-HDM (N = 29)	
	N	%	N	%	N	%	N	%
75%–100%	1	(4%)	6	(24%)	5	(19%)	17	(59%)
50%–<75%	4	(15%)	5	(20%)	5	(19%)	3	(10%)
25%–<50%	6	(22%)	4	(16%)	2	(7%)	2	(7%)
0%–<25%	11	(41%)	7	(28%)	9	(33%)	7	(24%)
<0%	5	(19%)	3	(12%)	6	(22%)	0	(0%)

ICS: inhaled corticosteroid (here: budesonide); Subgroup: subjects with daily ICS use of 400–800 µg and asthma control questionnaire score of 1–1.5 (N = 108).

## Safety and tolerability

Treatment was well-tolerated by all subjects in the subgroup. The numbers, causality and severity of reported AEs in the subgroup are in line with what was reported for the full analysis set [17]. There was a dose-dependent increase in IMP-related AEs (defined as possibly or probably related to the IMP), from 0.1 IMP-related AEs/subject in the placebo group to 1.1 IMP-related AEs/subject in the 6 SQ-HDM group (see Fig. 3), but the majority of AEs were mild or moderate in intensity and only 5 severe AEs (bacterial infection in the 1 SQ-HDM group, phlebitis, alopecia areata, nasopharyngitis and foot fracture in the 3 SQ-HDM group) were reported.

The most frequent AEs were oral pruritus, nasopharyngitis, asthma, and ear pruritus, with nasopharyngitis being reported with similar frequency in active and placebo groups while oral pruritus, asthma, and ear pruritus were more frequent in the active groups than in placebo. There was a higher incidence of reporting of asthma as an AE in the subgroup (11 subjects, 10%) as compared with the full analysis set (18 subjects, 3%).

No IMP-related serious (as per ICH E2A definitions [25]) AEs were reported.

## Discussion

This *post hoc* analysis on a subgroup from a phase II/III DBPC trial on SQ HDM SLIT-tablet [17] showed that subjects with a daily ICS use of 400–800 µg and partly controlled asthma (defined as ACQ score between 1 and 1.5) at randomisation had significantly higher treatment effect in terms of ICS reduction than the residual trial population with less severe asthma. Additionally, the 6 SQ-HDM group had significant improvements in asthma control and asthma-related quality of life at the end of trial (i.e. after one year of AIT treatment). The HDM-tablet was well-tolerated and effective in this subgroup, with a safety profile similar to the full analysis set. The trial provides proof of concept for SQ HDM SLIT-tablet in the treatment of asthma, and the subgroup analysis suggests that the most favourable benefit–risk profile may be expected in patients with partly controlled HDM allergic asthma despite medium–high dose use of ICS.

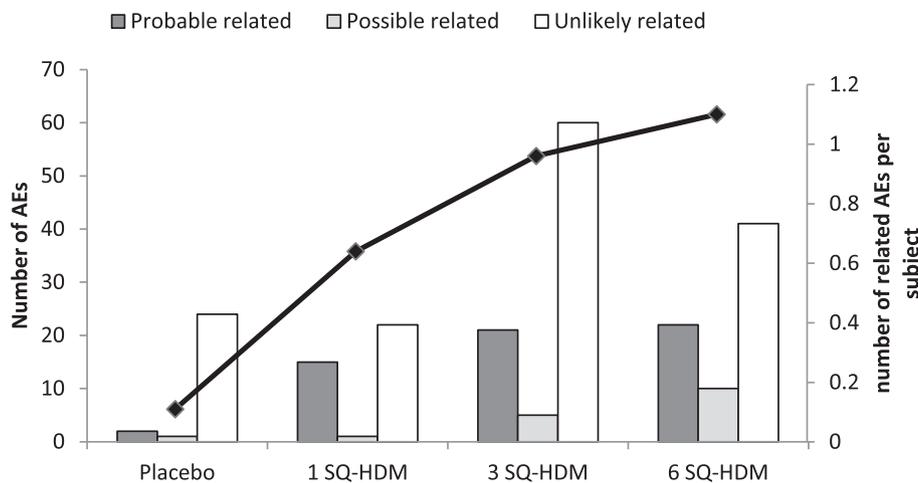
Per definition, results from *post hoc* analyses should be interpreted with caution, and the hypothesis created should be confirmed in new trials before firm conclusions can be drawn. The low *p*-value (<0.0001) for ICS reduction

in this subgroup, reduces the likelihood of the result being a type I error (a false positive). A phase III trial has recently been conducted, confirming the efficacy of HDM AIT-tablet in asthma in a population resembling this subgroup (manuscript in preparation). To fulfil regulatory requirements, the primary endpoint in this trial was modified to measure asthma control shown by risk reduction for asthma exacerbations during ICS reduction, rather than through maintained control during ICS reduction (EudraCT #2010-018621-19). This is in line with the GINA update from 2011, where focus is increasingly placed on asthma control [16].

Asthma control can both be defined in the short term by achieving good control of the current clinical manifestations of asthma, and in the long term by reducing risk to the patient (i.e. the risk of adverse outcomes such as exacerbations, poor control, accelerated decline in lung function, and side effects of treatment) [26]. Some of these risks may result from lack of control of the underlying disease process. AIT is the only treatment of respiratory allergy that treats the underlying cause of the disease and therefore has disease-modifying potential. This potential has been confirmed in trials with the corresponding grass SLIT-tablet [12,27]. As immunotherapy targets the immunological background in allergic asthma, it is expected to lead to long-term improvement of asthma [28], but this remains to be documented. The potential of the grass SLIT-tablet to prevent disease progression from allergic rhinitis to allergic asthma is currently being investigated in the Grazax Asthma Prevention (GAP) trial [29].

ICS treatment is the cornerstone of asthma therapy in both children and adults because it targets the airway inflammation. However, ICS treatment does not alter the disease progression, and some patients fail to achieve adequate control. In the described subgroup with partly controlled asthma, the addition of 6 SQ-HDM for one year not only increased asthma control significantly, but resulted in a significant reduction of ICS and a clinically relevant improvement in asthma-related quality of life. The design of the trial with ICS tapering periods is by nature an artificial set-up, yet in agreement with the GINA strategy for asthma management, stating the importance of establishing the lowest dose of treatment necessary to maintain control [16]. The level of reduction in ICS was comparable to that of montelukast [30] and theophylline [31].

A dilemma for use of AIT in the treatment of asthma is that patients with severe asthma are at increased risk in case of systemic adverse events as these may trigger severe



**Figure 3** The bars show numbers of AEs reported in the subgroup per treatment group and according to investigator assessed causality (left y-axis). The line shows numbers of related (probable or possible) AEs per subject (right y-axis).

asthma exacerbations. This is based primarily on experience from subcutaneous products and has led to some AIT products being contraindicated for patients with severe or uncontrolled asthma. Based on the GINA 2002 definitions of asthma severity [20], patients with FEV<sub>1</sub> below 70% of predicted value with appropriate medication were excluded from the present trial. In the subgroup, all subjects had FEV<sub>1</sub> around 85% of predicted value at randomisation, which is within limits of normal FEV<sub>1</sub>. With the updated GINA terminology [32], which puts focus on control rather than severity, a post hoc analysis of control status for the full trial population based on ACQ items was included in the primary publication of this trial [17]. The analysis showed that part of the population was in fact uncontrolled by means of frequent symptoms or nocturnal awakenings, and data confirmed that lung function in terms of FEV<sub>1</sub> contributed little to the asthma control classification.

Together with the benign safety profile shown for HDM SLIT-tablet in the subgroup and the significantly increased disease-specific quality of life in the 6 SQ-HDM group, our data suggest that in patients with partly or even uncontrolled asthma according to GINA definitions, whose lung function is not severely impaired, treatment with SQ HDM SLIT-tablet may be well tolerated and beneficial in terms of increased asthma control.

## Conclusion

In a subgroup with partly controlled HDM-related asthma despite medium–high daily dose of ICS, the benefit of treatment with SQ HDM SLIT-tablet for 1 year was significantly higher than for the entire trial population with less severe asthma. Despite statistically significantly lowered ICS dose in the 6 SQ-HDM group, the subjects reported improved asthma-related quality of life as well as asthma control. Treatment was well-tolerated in the subgroup population.

Thus, this post-hoc analysis suggest, that patients with HDM related asthma, who are not adequately controlled on medium–high daily doses of ICS, may benefit significantly

from SQ HDM SLIT-tablet treatment, both in terms of increased asthma control (as shown by reduced need for ICS and reduced ACQ score) and improved quality of life.

## Conflicts of interest

F. de Blay reports grants and personal fees from Stallergènes, ALK, Novartis, Mundipharma (outside the submitted work); P. Kuna reports other financial support from Allergopharma, Stallergènes, ALK, Hal, AstraZeneca, MSD, GSK, Adamed, Novartis (outside the submitted work); G.W. Canonica reports grants and personal fees from Stallergènes, ALK, Allergy Therapeutics, HAL, Lofarma (outside the submitted work); L. Prieto, and L. Ginko reports no relevant conflicts of interest to disclose; Mrs. Seitzberg and Mrs. Riis are employed by ALK.

## Acknowledgements

The authors present this publication on behalf of all the involved investigators. The trial was funded by ALK and in this context the authors would like to thank Britta Smedegaard Andersen, Charlotte Bjernved Nielsen, Janne Hartmann, Pernille Saxov, Berit Weber and Birgitte Båstrup for clinical project management and operational oversight on behalf of ALK. Peter Fejerskov, ALK, was the trial safety adviser; Dorthe Ebbesen, ALK, was responsible for data management; Christian Ljørring, ALK, was the trial statistician; Bente Riis, ALK, was responsible for medical writing, editorial, and journal submission assistance for this manuscript.

## References

- [1] Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S, Ryan D, Walker SM, Clark AT, Dixon TA, Jolles SR, Siddique N, Cullinan P, Howarth PH, Nasser SM. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 2008;38(1):19–42.

- [2] Marogna M, Massolo A, Berra D, Zanon P, Chiodini E, Canonica GW, Passalacqua G. The type of sensitizing allergen can affect the evolution of respiratory allergy. *Allergy* 2006; 61(10):1209–15.
- [3] Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van WC, Agache I, it-Khaled N, Bachert C, Blaiss MS, Bonini S, Boulet LP, Bousquet PJ, Camargos P, Carlsen KH, Chen Y, Custovic A, Dahl R, Demoly P, Douagui H, Durham SR, van Wijk RG, Kalayci O, Kaliner MA, Kim YY, Kowalski ML, Kuna P, Le LT, Lemiere C, Li J, Lockey RF, Mavale-Manuel S, Meltzer EO, Mohammad Y, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Ouedraogo S, Palkonen S, Papadopoulos N, Passalacqua G, Pawankar R, Popov TA, Rabe KF, Rosado-Pinto J, Scadding GK, Simons FE, Toskala E, Valovirta E, Van CP, Wang DY, Wickman M, Yawn BP, Yorgancioglu A, Yusuf OM, Zar H, nnesi-Maesano I, Bateman ED, Ben KA, Boakye DA, Bouchard J, Burney P, Busse WW, Chan-Young M, Chavannes NH, Chuchalin A, Dolen WK, Emuzyte R, Grouse L, Humbert M, Jackson C, Johnston SL, Keith PK, Kemp JP, Klossek JM, Larenas-Linnemann D, Lipworth B, Malo JL, Marshall GD, Naspitz C, Nekam K, Niggemann B, Nizankowska-Mogilnicka E, Okamoto Y, Orru MP, Potter P, Price D, Stoloff SW, Vandenplas O, Viegi G, Williams D. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(Suppl. 86):8–160.
- [4] Accordini S, Corsico AG, Braggion M, Gerbase MW, Gislason D, Gulsvik A, Heinrich J, Janson C, Jarvis D, Jogi R, Pin I, Schoefer Y, Bugiani M, Cazzoletti L, Cerveri I, Marcon A. de MR. The cost of persistent asthma in Europe: an international population-based study in adults. *Int Arch Allergy Immunol* 2013;160(1):93–101.
- [5] Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol* 1999;103(1 Pt 1):54–9.
- [6] 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(7):843–8.
- [7] Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2010; 126(5):942–9.
- [8] Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, Koivikko A, Norberg LA, Valovirta E, Wahn U, Moller C. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007;62(8):943–8.
- [9] Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, Urbanek R, Valovirta E, Wahn U. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;109(2):251–6.
- [10] Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A, Koivikko A, Koller DY, Norberg LA, Urbanek R, Valovirta E, Wahn U, Moller C. Five-year follow up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006;61:855–9.
- [11] Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, Knecht R, Stephan V, Tholstrup B, Weisshaar C, Kaiser F. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123(1):167–73.
- [12] Durham SR, Emminger W, Kapp A, De Monchy JG, Rak S, Scadding GK, Wurtzen PA, Andersen JS, Tholstrup B, Riis B, Dahl R. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012; 129(3):717–25.
- [13] EMA. DRAFT note for guidance on the clinical investigation of medicinal products in the treatment of asthma. CPMP/EWP/2922/01 Rev.1; 2013. London.
- [14] EMEA. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. CHMP/EWP/18504/2006[Final]; 2008.
- [15] EMEA. Note for guidance on the clinical investigation of medicinal products in the treatment of asthma. CPMP/EWP/2922/01. London: EMEA; 2002.
- [16] GINA Executive Committee. Global initiative for asthma; global strategy for asthma management and prevention. Bethesda, Maryland, USA.: National Heart, Lung and Blood Institute, National Institute of Health; 2011 [GINA Guidelines].
- [17] Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Prieto Andres L, Malcus I, Ljørring C, Canonica GW. SQ HDM SLIT-tablet (ALK) reduces ICS while keeping asthma control – a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014. <http://dx.doi.org/10.1016/j.jaci.2014.03.019>.
- [18] Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, Weiss ST. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114(1):40–7.
- [19] Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, Calhoun WJ, Castro M, Chung KF, Clark MP, Dweik RA, Fitzpatrick AM, Gaston B, Hew M, Hussain I, Jarjour NN, Israel E, Levy BD, Murphy JR, Peters SP, Teague WG, Meyers DA, Busse WW, Wenzel SE. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's severe asthma research program. *J Allergy Clin Immunol* 2007;119(2):405–13.
- [20] National Institutes of Health. WHO/GINA workshop report: global strategy for asthma management and prevention. NIH publication No 02-3659; 2002. p. 1–192.
- [21] Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14(4):902–7.
- [22] Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the asthma control questionnaire. *Respir Med* 2006;100(4): 616–21.
- [23] Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the asthma quality of life questionnaire. *Chest* 1999;115(5):1265–70.
- [24] 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(2):76–83.
- [25] ICH. ICH harmonised tripartite guideline topic E2A. Clinical safety data management: definitions and standards for expedited reporting; 1994.
- [26] Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, de Jongste JC, Kerstjens HA, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stoloff SW, Sullivan SD, Szefer SJ, Thomas MD, Wenzel SE. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180(1):59–99.
- [27] Durham SR, Emminger W, Kapp A, Colombo G, De Monchy JG, Rak S, Scadding GK, Andersen JS, Riis B, Dahl R. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis

- after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010;125(1):131–8.
- [28] Nagata M, Nakagome K. Allergen immunotherapy in asthma: current status and future perspectives. *Allergol Int* 2010; 59(1):15–9.
- [29] Valovirta E, Berstad AK, de BJ, Bufe A, Eng P, Halcken S, Ojeda P, Roberts G, Tommerup L, Varga EM, Winnergard I. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. *Clin Ther* 2011;33(10):1537–46.
- [30] Lofdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, Seidenberg BC, Capizzi T, Kundu S, Godard P. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *BMJ* 1999;319(7202):87–90.
- [31] Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997;337(20):1412–8.
- [32] GINA Executive Committee. Global initiative for asthma; global strategy for asthma management and prevention. Bethesda, Maryland, USA: National Heart, Lung and Blood Institute, National Institute of Health; 2009. p. 1–112 [GINA Guidelines].