Synopsis – Trial E02/04/SLIT1-M

Title of Trial
A randomised, double-blind, placebo-controlled trial assessing the efficacy of SLITone in house dust mite allergic patients.

Investigators
5 investigators participated from Spain. The coordinating investigator was: Dr. [redacted]

Trial Centres
5 trial centres participated (Spain). The coordinating investigator was located at [redacted] Spain.

Publications
None

Trial Period
First subject first visit – 22 June 2006
Last subject last visit – 26 December 2008

Objectives
Primary objective:
To evaluate the efficacy of specific immunotherapy with SLITone *Dermatophagoides* mix compared to placebo in subjects with house dust mite (HDM) allergic asthma, based on asthma medication[1] use during a period of 2 months with a high environmental exposure to mites (autumn 2008).

Secondary objectives:
To evaluate the efficacy of specific immunotherapy with SLITone *Dermatophagoides* mix (active) compared to placebo in subjects with HDM allergic asthma based on the following intermediate objectives:

- Differences in asthma medication[1] use between active and placebo groups during a period of 2 months in autumn 2007.
- Differences in asthma control medication[1] between active and placebo groups.
- Differences in frequency of asthma well-days between active and placebo groups.
- Differences in rhinoconjunctivitis symptoms and medication scores between active and placebo groups.
- Differences in asthma control between active and placebo groups.
- Differences in asthma related quality of life between active and placebo groups.
- Differences in subjective evaluation of the treatment and allergic symptoms between active and placebo groups.
- Differences in frequency of asthma exacerbations between active and placebo groups.
- Differences in peak expiratory flow (PEF) variability between active and placebo groups.
- Differences in specific IgE and IgX[3] serum levels between active and placebo groups.
- Differences in number of lost schooldays/workdays between active and placebo groups.[2]
- Differences in mite allergen exposure between active and placebo groups (Der p 1, Der f 1 and Der 2).

To evaluate the tolerability of SLITone *Dermatophagoides* mix compared to placebo in subjects with HDM allergic asthma based on the following objective:

- Adverse event (AE) recording.

[1]Definition of:

- *Asthma medication: Asthma rescue + control medication (=salbutamol, budesonide/formoterol, prednisone).*
- *Asthma control medication (= budesonide/formoterol).*

[2]Differences in number of lost school/work days are not analysed in this ICTR.
[3]IgX (added as objective in Amendment 2) is presented as IgE-blocking factor (1-IgX) in this ICTR.

Methodology
This trial was conducted as a multi-centre, randomised, double-blind, parallel-group, placebo-controlled phase III trial, assessing the efficacy of SLITone *Dermatophagoides* mix in adults (18-65 years).
HDM allergic asthmatics were randomised to receive either SLITone *Dermatophagoides* mix (active) or placebo treatment (1:1) for approximately 1 year. The trial duration was extended to 2 years (Amendment 1).
Subjects were kept in asthma control during the entire trial (2 years). Except for during 2 evaluation periods of 2

months in autumn 2007 and autumn 2008, subjects used the medications prescribed by their physician. During the 2 evaluation periods of 2 months in autumn 2007 and autumn 2008, subjects used provided and standardised rhinoconjunctivitis and asthma medications. The asthma medication use was to reflect the subject's asthma status. This was done by treatment with a low maintenance dose of control medication supplemented with rescue medication as needed.

Number of Subjects Planned and Analysed

The number of subjects planned and analysed were as follows:

Subjects planned to participate	120
Subjects enrolled	124
Subjects randomised 1:1 (active: placebo)	124
Subjects treated with SLITone *Dermatophagoides* mix	63
Subjects treated with placebo	61
Subjects completing the trial	75
Subjects withdrawn*	49
Full analysis set (FAS) analysed	124
Per protocol analysis set (PP) analysed	71

*: Reason for withdrawal: withdrawal of consent (7), lack of efficacy (1), lost to follow-up (6), pregnancy (5), adverse events (11) or other reasons (19).

Diagnosis and Main Inclusion Criteria

A clinical history of HDM allergic mild to moderate persistent asthma (with or without rhinoconjunctivitis) of at least 1 year. Positive skin prick test response to *Dermatophagoides* mix (wheal diameter ≥ 3 mm). Demonstrated positive specific IgE (≥ CAP class 2) against *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* within a year.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers

SLITone *Dermatophagoides* mix dose: 200 ST-U (200 µl) per monodose container.
SLITone *Dermatophagoides* mix batch no: A0263, EC-A230, EC-B039 and EC-B149.
Placebo dose: 200 µl per monodose container.
Placebo batch no: EC-A029, EC-A210 and EC-B148.
Mode of administration: The solution of one monodose container was emptied under the tongue and kept for 2-3 minutes prior to swallowing on a daily basis, preferably in the morning.

Treatment regimen

Treatment with the investigational medicinal product (IMP): 63 subjects received active treatment (SLITone *Dermatophagoides* mix) and 61 subjects received placebo.

Treatment with rhinoconjunctivitis and asthma medication: Subjects were kept in asthma control during the entire trial (2 years). Except for during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008, subjects used the medications prescribed by their physician. During 2 evaluation periods of 2 months in autumn 2007 and autumn 2008, subjects used provided and standardised rhinoconjunctivitis and asthma medications as follows:

Rhinoconjunctivtis medication during the 2 evaluation periods in autumn 2007 and autumn 2008

To standardise the medication used to relieve rhinoconjunctivitis symptoms, subjects were provided with the following free medications as needed:

- Desloratadine tablet (5 mg per tablet; anti-histamine; Aerus®)
- Budesonide nasal spray (64 µg per puff; inhaled corticosteroid)
- Prednisone tablet (5 mg per tablet; oral corticosteroid)

Subjects were instructed to use this medication instead of their usual medication during the 2 evaluation periods in autumn 2007 (between visit 7 and 9) and autumn 2008 (between visit 14 and 16), and to record the used medication and symptoms in the daily diary.

Asthma medication during the evaluation period in autumn 2007

Prior to the 2 months evaluation period in autumn 2007, the asthma control medication use was interrupted to obtain a medication-free period. Subjects were provided with the following free medications to standardise the treatment used to relieve asthma symptoms:

- Salbutamol inhaler (200 µg per puff; a short acting β_2-agonist; Ventilastin®).
- Budesonide/formoterol inhaler (80/4.5 µg per inhalation; a combination of inhaled corticosteroids and long acting β_2-agonist; Symbicort®).

- Prednisone tablet (5 mg per tablet; oral corticosteroid).

Subjects were instructed to use this medication instead of their usual medication during the evaluation period in autumn 2007 (between visit 7 and 9) as follows:
They were to use salbutamol inhaler as asthma rescue medication until they either:

- needed more than 4 inhalations of salbutamol per day for 2 consecutive days
- suffered from nocturnal asthma forcing them to wake up
- suffered from exercise-induced dyspnoea doing ordinary tasks

In these cases, subjects were to contact the investigator to determine the amount of budesonide/formoterol to use as daily asthma control medication. The budesonide/formoterol inhaler was thereafter to be used as rescue medication as needed instead of salbutamol. Prednisone could be used as a last option.

Asthma medication during the evaluation period in autumn 2008
At the 2 months evaluation period in autumn 2008 (visit 14 to 16), subjects were maintained at a low dose of budesonide/formoterol (daily asthma control medication) and they used the budesonide/formoterol inhaler as rescue medication as needed. Prednisone could be used as a last option.

Medication used to relieve asthma symptoms during the evaluation periods in autumn 2007 and autumn 2008 were recorded in the daily diary.

Duration of Treatment
Treatment duration was extended (Amendment 1) from 1 year to approximately 2 years.

Criteria for Evaluation – Efficacy

Primary efficacy endpoint:

- Average daily asthma medication score, during a 2 months evaluation period in autumn 2008.

Secondary efficacy endpoints:

1. Average daily asthma medication score, during a 2 months evaluation period in autumn 2007.
2. Asthma control medication, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008.
3. Average daily asthma symptom score, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008.
4. Frequency of asthma well-days, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008.
5. Average daily rhinoconjunctivitis medication score, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008.
6. Average daily rhinoconjunctivitis symptom score, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008.
7. Asthma control (ACQ), at the end of each of the 2 evaluation periods in autumn 2007 and autumn 2008.
8. Asthma quality of life (AQLQ), at the end of each of the 2 evaluation periods in autumn 2007 and autumn 2008.
9. Allergic symptoms (subjective evaluation using a visual analogue scale (VAS)), at the end of each of the 2 evaluation periods in autumn 2007 and autumn 2008.
10. Global Evaluation of efficacy by the subject and investigator, at the end of each of the 2 evaluation periods in autumn 2007 and autumn 2008.
11. Frequency of asthma exacerbations, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008, as well as in the second treatment period (visit 10 to 16).
12. PEF variability, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008.
13. % predicted forced expiratory volume in 1 second (FEV_1), at the end of each of the 2 evaluation periods in autumn 2007 and autumn 2008.
14. IgE and IgE-blocking factor levels, at end of the evaluation period in autumn 2008.
15. Average EQ-5D[3] index values, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008.
16. Average (modified) EQ-VAS[3] score, during 2 evaluation periods of 2 months in autumn 2007 and autumn 2008.

[3]*Pharmaco-economic questionnaires (descriptive: EQ-5D and VAS: EQ VAS) indicating the health state of the subject*

Criteria for Evaluation – Safety
AEs, vital signs, physical examinations and global evaluation of tolerability by subject and investigator.

Statistical Methods

The following analysis sets were used:

Full-analysis set (FAS): Comprises all randomised subjects following the Intent-To-Treat (ITT) ICH principle. The FAS is the primary analysis set.

Per-protocol set (PP): Comprises all subjects with no major protocol deviations and therefore comprises subjects who:

- Did not take prohibited medication to close to or during the 2 months evaluation period in autumn 2008 that could have influenced the primary efficacy endpoint.
- Had sufficient pre-treatment with SLITone *Dermatophagoides* mix prior to the start of the 2 months evaluations period in autumn 2008 defined as at least 1.5 year of pre-treatment.
- Had sufficient IMP compliance defined as an intake of IMP of at least 75% of the days.
- Had at least 50% daily diary registrations during the 2 months evaluation period in autumn 2008 (the number of diary records divided by the number of days between the first diary date and the last diary date was greater than 50%).
- Had a total number of daily diary records in the 2 months evaluation period in autumn 2008 of at least 30.
- Did not have any other significant protocol deviations influencing the primary endpoint.

Safety Analysis Set (SS): Comprises all randomised subjects.

ALK-Abelló A/S was responsible for carrying out the statistical analyses. All statistical tests were performed using a significance level of 5% and all tests and confidence intervals were 2-sided.

The primary endpoint was analysed using a linear mixed effect (LME) model with the average daily asthma medication score during the 2 months evaluation period in autumn 2008 as response variable, treatment as fixed effect and centre as a random effect. Different residual variances were specified for each treatment group. The primary hypotheses tested using the LME model was the null hypothesis of no difference between SLITone and placebo versus the alternative hypothesis of a difference. The difference in adjusted means between SLITone and placebo with coherent p-values and confidence intervals were reported. Other secondary efficacy endpoints with a continues response were also analysed using an LME model. Secondary efficacy endpoints with binary responses were analysed by means of a generalised linear mixed model (GLMM) and Fishers exact test. Analyses of secondary efficacy endpoints with an ordered categorical response were done using a proportional odds regression. Safety endpoints where primarily analysed using descriptive statistics.

With only one primary efficacy analysis no adjustments for multiplicity were needed. Secondary efficacy analyses are not regarded as confirmatory.

Demography and Trial Population Characteristics

No major differences were observed between the 2 treatment groups. More females than males (63% versus 37%) and a majority of non-smokers (63%) were included in the trial.

FAS	Placebo N = 61	Active N = 63	All N = 124
Gender (N)			
N	61	63	124
Female (%)	39 (64)	39 (62)	78 (63)
Male (%)	22 (36)	24 (38)	46 (37)
Age (Years)			
N	61	63	124
Mean (SD)	30 (9.0)	32 (8.0)	31 (8.6)
Median	30	32	31
Q25% - Q75%	23-34	26-38	25-36.5
Min - Max	18-57	18-48	18-57
Smoking habit (N)			
N	61	63	124
Smoker (%)	8 (13)	9 (14)	17 (14)
Non-smoker (%)	38 (62)	40 (63)	78 (63)
Previous smoker (%)	15 (25)	14 (22)	29 (23)
Years with HDM allergic asthma			
N	61	63	124
Mean (SD)	11.0 (7.6)	10.5 (8.7)	10.8 (8.1)
Median	10	8	9
Q25% - Q75%	5-16	4-15	4-16
Min – Max	1-30	1-36	1-36
Years with rhinitis and/or conjunctivitis			
N	57	57	114
Mean (SD)	12.3 (7.8)	10.4 (8.0)	11.3 (7.9)
Median	12	8	10
Q25% - Q75%	5 - 18	4-15	5-17
Min – Max	0-30	0-33	0-33

Allergy and Asthma Medical history	Placebo N = 61		Active N = 63		All N = 124	
	N	(%N)	N	(%N)	N	(%N)
HDM allergic asthma	61	(100)	63	(100)	124	(100)
Mild persistent	49	(80)	48	(76)	97	(78)
Moderate	12	(20)	15	(24)	27	(22)
Other asthma types	-	-	1	(2)	1	(<1)
Mild persistent	-	-	1	(2)	1	(<1)
Rhinitis and/or conjunctivitis	57	(93)	57	(90)	114	(92)
Mild	33	(54)	30	(48)	63	(51)
Moderate	25	(41)	29	(46)	54	(44)

N: Number of subjects; %: Percentage of subjects of the full analysis set (FAS) in the treatment group; SD: Standard deviation; Q25%: 25% quartile; Q75%: 75% quartile; Active: SLITone *Dermatophagoides* mix.

Efficacy Results
This trial did not meet its primary efficacy endpoint. No statistically significant difference was found between subjects treated with SLITone *Dermatophagoides* mix and subjects treated with placebo in the average daily asthma medication score in the 2 months evaluation period in autumn 2008.
A statistical significant difference was found between treatment groups, in favour of SLITone *Dermatophagoides* mix treatment, in the global evaluation of efficacy by investigator at the end of the evaluation period in autumn 2008.
The following secondary efficacy endpoints were also not found to be statistically significantly different between subjects treated with SLITone *Dermatophagoides* mix and subjects treated with placebo during/at the end of the evaluation periods in autumn 2007 and autumn 2008:

- Average daily asthma medication score (autumn 2007)
- Asthma control medication
- Average daily asthma symptom score
- Frequency of asthma well-days
- Average daily rhinoconjunctivitis medication score
- Average daily rhinoconjunctivitis symptom score
- Asthma control (ACQ)
- Asthma quality of life (AQLQ)
- Subjective evaluation of allergic symptoms (VAS)
- Global evaluation of efficacy by subjects
- Global evaluation by investigator (autumn 2007)
- Frequency of asthma exacerbation (during autumn 2007, autumn 2008, the second treatment period (visit 10 to 16) and the entire trial period (2 years))
- PEF variability
- % predicted FEV_1
- EQ-5D index
- EQ VAS score

No statistically significant difference was found between subjects treated with SLITone *Dermatophagoides* mix and subjects treated with placebo in the immunological response, as measured by specific IgE and IgE-blocking factor serum levels at the trial completion visit (visit 16; autumn 2008).

Safety Results

- Treatment with SLITone *Dermatophagoides* mix was well-tolerated in HDM allergic asthmatics.
- 220 AEs were reported by 88 subjects, equally distributed between treatment groups, and the majority was mild in severity.
- 22 AEs were judged to be IMP related, of which 21 were mild in severity and 1 moderate.
- The most frequently reported AEs were assessed as unlikely related to IMP.
- None of the AEs assessed as severe and/or serious were related to IMP.
- No systemic allergic reactions were reported.
- 11 subjects (6 in the placebo group and 5 in the active group) withdrew due to 13 AEs. 7 of these were IMP related AEs (mild in severity), equally distributed between treatment groups.
- The majority of subjects and the majority of investigators judged the IMP tolerability to be “very good”.
- No safety concerns were observed for vital signs or physical examinations.

Conclusions
This trial did not meet its primary endpoint (average daily asthma medication score, autumn 2008). The global evaluation of efficacy by the investigators at the end of the evaluation period in autumn 2008 was statistically significant, in favour of SLITone *Dermatophagoides* mix treatment.
It was not possible to show a consistent treatment effect of SLITone *Dermatophagoides* mix with this trial design and the number and characteristics of included subjects.
Treatment with SLITone *Dermatophagoides* mix was well-tolerated by HDM allergic asthmatics.

Date of the Report
Final: 5 February 2010

This trial was conducted in compliance with the principles of ICH *Good Clinical Practice*.