1.

Clinical Study Report

RANDOMIZED, OPEN, PARALLEL GROUP, PHASE IIIB STUDY ON THE EVALUATION OF EFFICACY OF SPECIFIC SUBLINGUAL IMMUNOTHERAPY IN PAEDIATRIC PATIENTS WITH ATOPIC DERMATITIS, WITH OR WITHOUT ASSOCIATED ALLERGIC RESPIRATORY DISEASES

PROTOCOL CODE: SLO-AD-1 Italy

EUDRACT Number: 2008-000196-23

Name of test product:	SLITone® (specific sublingual immunotherapy, containing the allergen extract *Dermatophagoides pteronyssinus* and *farinae*)
Pharmaceutical Form:	Glycerol solution for sublingual administration
Indication:	Mild to moderate atopic dermatitis, with or without associated allergic respiratory diseases
Study Design:	Multicentre, randomized, double blind, placebo controlled, parallel-group, dose finding, clinical study
Phase of development:	IIIb
Sponsor:	ALK-Abello Italy, Via Ramazzotti 12, Lainate (Milan), Italy
Co-ordinating Investigator and Centre:	Dr. [redacted] Italy
Sponsor's Medical expert and contact for any question:	Dr. [redacted] Italy; Phone number: [redacted] Fax number: [redacted]
Study Initiation Date (First Patient First Visit):	10 Apr 2009
Study Completion Date (Last Patient Last Visit):	17 Nov 2011
Report Date:	Final version, 09 December 2013

"This study was conducted in compliance with the Good Clinical Research Practices including the archiving of essential documents"

2. SYNOPSIS

Name of Company: ALK-Abello Italy	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: SLITone®		
Name of Active Ingredient: Specific sublingual immunotherapy, containing the allergen extract *Dermatophagoides pteronyssinus* and *farinae*	**Volume:** **Page:**	

Title of Study: Randomized, open, parallel group, phase IIIb study on the evaluation of efficacy of specific sublingual immunotherapy in paediatric patients with atopic dermatitis, with or without associated allergic respiratory diseases

Investigators: Six Principal Investigators in Italy

Study Centre(s): The study was conducted in 6 investigational study sites in Italy

Publication (reference): None

Studied Period: First patient enrolled: 10 Apr 2009; Last patient completed: 17 Nov 2011

Phase of development: IIIb

Objectives:

Primary:

The primary objective of the study was to assess the efficacy of sublingual immunotherapy (SLIT) performed with SLITone® containing *Dermatophagoides* extracts in paediatric patients with AD with or without associated allergic respiratory diseases. In particular, the SCORAD (Scoring Atopic Dermatitis) was the primary efficacy endpoint.

Secondary: The secondary objectives of the study were to assess:

- The changes of subjective perception of cutaneous symptoms (VAS, 0-10 scale) from baseline to any post-baseline time point.
- The difference between the values of SCORAD (baseline versus end of study) of a target lesion identified and documented through digital photography;
- The effects of treatment on the progress of rhinitis and/or asthma;
- The symptomatic drug usage, including topical drugs (steroids) and systemic drugs (oral antihistamines);
- The tolerability and safety of sublingual treatment;
- The compliance to treatment.

Methodology (Study Design):

This was an open-label, randomized, controlled, phase IIIb, parallel-group study. One group was treated with SLIT (SLITone®) and standard treatment, and the Control group was treated with the standard treatment alone. Only the use of topical products (moisturizers) was allowed as standard treatment.

The study duration was 72 weeks. Visits at the investigational study sites were performed at screening (Visit 1, week -4), at baseline/start of treatment (Visit 2, week 0), and after 4, 24, 48 and 72 weeks of treatment (Visits 3, 4, 5 and 6, respectively).

Number of patients (planned and analyzed):

	SLITone® group	Control group	Total
Planned evaluable patients	35	35	70
Randomised population	30	27	57
Safety population	30	27	57
ITT population	29	22	51
PP population	23	14	37

Diagnosis and main criteria for inclusion:

- Males and females aged > 5 years and <18 years;
- Subjects with a clinical history of chronic mild to moderate AD with no evidence of spontaneous remission at the age of 5 years, with or without intermittent moderate-severe or persistent mild-moderate rhinoconjunctivitis (in agreement with ARIA criteria) or asthma not requiring regular use of inhaled corticosteroids;
- Sensitization to *Dermatophagoides pteronyssinus* and *farinae* diagnosed by prick test (wheal diameter > 3 mm), by specific serum IgE (Class III or higher (ImmunoCAP RAST) and by positive Atopy Patch Test. A concomitant sensitization to pollen allergens was acceptable, provided that there were no exacerbations of AD during pollination;
- In the case of a positive history of allergy to foods in previous years with positive skin test results, these same foods had to be fully tolerated at enrolment, as confirmed by double-blind provocation, or had to be totally excluded from the diet;
- SCORAD > 8 and ≤ 40;
- Forced expiratory volume in one second (FEV_1) greater than 80% of the predicted normal value;
- Parents' or guardians' written informed consent.

Test product, dose and mode of administration, batch number:

The treated group (Group A) received SLIT with HDM extracts (SLITone®), standard treatment and pharmacological topical and/or systemic treatment on an as needed basis. The IMP product was an extract of *Dermatophagoides farinae* (50%) and *Dermatophagoides pteronyssinus* (50%) allergens in glycerol solution for sublingual administration (SLITone®). The preparation in single-dose vials was taken once per day (one single dose vial per day)

Batch numbers: EC-E2 12 (expiry 31/07/12), EC-E0 06 (expiry 31/08/11), EC-D1 04 (expiry 31/08/11) and C1796 (expiry 04/11/09)

Duration of treatment: 72 consecutive weeks

Reference therapy, dose and mode of administration, batch number:

The Control group (Group B) received standard treatment and pharmacological topical and/or systemic treatment, on an as needed basis. Standard treatment was defined as the exclusive use of topical products whose activity was limited to hydration.

Criteria for evaluation:

Efficacy:

Primary variables

The primary efficacy variable of the study was the change of the total SCORAD from the screening visit (Visit 1) to the visit at end of treatment (week 72). The measurement of the SCORAD took place in accordance with the Guidelines European Task Force on Atopic Dermatitis and was based on the evaluation of objective (extent and intensity of the lesions) and subjective (itching and loss of sleep) parameters.

Secondary variables

The secondary efficacy variables of the study were:

- Change of the total SCORAD from the screening visit (Visit 1) to any other post-baseline time point;
- Changes of subjective perception of cutaneous symptoms (VAS, 0-10 scale) from baseline (Visit 2) to any post-baseline time point;
- Changes of Nasal/Ocular symptoms (Total score) from baseline (Visit 2) to any post-baseline time point. The Nasal/Ocular symptoms (Stuffy nose, Runny nose, Sneezing, Itchy ears, Itchy nose, Itching eyes, Lacrimation, Sore eyes) were evaluated by means of a 0-4 rating score;
- Changes of Bronchial symptoms (Total score) from baseline (Visit 2) to any post-baseline time point. The Bronchial symptoms (Cough, Dyspnoea after physical exertion, Sensation of chest tightness, Sensation of air hunger, Nocturnal awakenings for dyspnoea) were evaluated by means of a 0-4 rating score;

- Investigator's Judgment on the effect of the application of treatment, by means of a 1-4 rating score;
- Change of the SCORAD value from baseline to the end of treatment (week 72) in a target lesion identified and documented through digital photography performed before randomization (Visit 2) and at end of trial (Visit 6). The target lesions was assessed in blind in a centralized manner by a specialist doctor who was not aware either of the sequence (before/after) or of the treatment group;
- Use of cortisone-like drugs or Calcineurin inhibitors;
- Compliance to treatment with SLITone®.

Safety:

The assessment of safety was based on the reporting of general adverse events (AEs) and of local (at the oral level) adverse reactions to SLITone®.

Statistical methods

The following populations were considered for data analysis: safety population, defined as all randomized patients who received at least one dose of the IMP; Intention-to-treat (ITT) population), defined as all randomized patients who received at least one dose of the IMP, had baseline evaluation and at least one post-baseline efficacy measurement; Per-protocol (PP) population, defined as all patients who completed the study without any major protocol violation assessed before locking the database, and had valid SCORAD values at baseline and at the end of treatment.

All data collected at baseline and during the study were described by means of summary descriptive statistics, with number of observations, mean, standard deviation (SD), standard error (SE), median and min-max for continuous variables, and absolute and relative frequency for categorical variables.

A Wilcoxon Ranks Sum test (Wilcoxon-Mann-Whitney test) was applied on SCORAD and VAS changes in both the ITT and the PP population. The Last Observation Carried Forward (LOCF) was used to deal with missing data of prematurely withdrawing patients.

As regards the secondary efficacy endpoints, a Wilcoxon Ranks Sum test (Wilcoxon-Mann-Whitney test) was applied on changes from baseline to any post-baseline time point.

The difference in physician's judgment on efficacy on treatment response after immunotherapeutic treatment versus standard treatment was analyzed by means of Chi-square test. Chi-square test was also used to compare the use of Cortisone-like drugs in the two treatment groups.

All adverse events were tabulated by treatment group. Severity and relationship to study drug were presented per each event.

Summary – Conclusions:

Efficacy Results

Primary variable (SCORAD)

In the ITT population, the mean SCORAD total score markedly decreased from baseline to any post-baseline time point in the SLITone® group, compared to small decreases from baseline to week 4, 24 and 72, and no substantial changes at week 48, in the control group.

The mean (± SD) change from baseline to the final visit (week 72) was -11.9 ± 22.38 in the SLITone® group and -2.78 ± 15.44 in the Control group. The comparison between groups of changes from baseline showed statistically significant differences, in favour of the SLITone® group, at week 48 ($p = 0.021$) and at week 72 ($p = 0.016$), whereas the difference between groups at week 4 and at week 24 was not statistically significant. The results in the PP population were consistent with those observed in the ITT population.

Secondary variables

Subjective perception of cutaneous symptoms (VAS)

The mean VAS score of subjective symptoms decreased from baseline to any post-baseline time point in both groups. The extent of the decrease was more marked in the Control group than in the SLITone® group at week 4 and week 24, whereas was more marked SLITone® group than in the Control group at week 48 and week 72.

The mean (± SD) change from baseline to the final visit (week 72) was -2.48 ± 3.481 in the SLITone® group and -1.77 ± 3.054 in the Control group. The comparison between groups of changes from baseline did not show statistically significant differences at any post-baseline time point. The results in the PP population were consistent with those observed in the ITT population.

Nasal and ocular symptoms

The mean score of nasal and ocular symptoms decreased from baseline to any post-baseline time point in both groups. The mean (± SD) change from baseline to the final visit (week 72) was -2.72 ± 4.765 in the SLITone® group and -4.05 ± 6.849 in the Control group. The comparison between groups of changes from baseline did not show statistically significant differences at any post-baseline time point.

The results in the PP population were consistent with those observed in the ITT population.

Bronchial symptoms

The mean score of bronchial symptoms decreased from baseline to any post-baseline time point in both groups, except for a small increase in the Control group at week 4. The mean (± SD) change from baseline to the final visit (week 72) was -0.72 ± 2.698 in the SLITone® group and -0.91 ± 2.776 in the Control group. The comparison between groups of changes from baseline did not show statistically significant differences at any post-baseline time point.

The results in the PP population were consistent with those observed in the ITT population.

Use of Cortisone-like drugs or Calcineurin inhibitors

Only few patients in both groups used Cortisone-like drugs or Calcineurin inhibitors at any visit during the study. The comparison between groups did not show statistically significant differences at any post-baseline time point.

Investigator's Judgment on Efficacy

The results of Investigator's judgment of efficacy showed a more favourable Investigator's judgment for SLITone® than for standard therapy.

In the SLITone® group, 9 patients (39.13%) were considered as much improved, 11 (47.83%) as improved and 3 (13.04%) as unchanged. In the Control group, 1 patient (6.67%) was considered as much improved, 8 (53.33%) as improved, 2 (13.33%) as unchanged and 4 (26.67%) as worsened. The comparison between groups showed a statistically significant difference (p = 0.02), in favour of the SLITone® group.

Safety Results:

Adverse events:

Eight adverse events (AEs) were reported in 5 patients (16.67%) in the SLITone® group and 2 AEs were reported in 2 patients (7.41%) in the Control group. The AEs in the SLITone® group consisted of immediate and transient local reactions (4 cases of burning at the mouth, 3 cases of itching at the mouth and 1 case of heartburn) and none of patients reported late reactions (after 6 hours) to treatment at any visit. The AEs in the Control group consisted of consent withdrawn in both cases. Following the end of the study, 4 serious adverse events (SAEs) occurred in one patient in the control group (3 episodes of Staphylococcical infection and 1 episode of asthma) were notified.

None of the AEs in the SLITone® group was serious, and all AEs were of mild severity, had intermittent frequency, did not require a specific treatment and were resolved at follow-up. Furthermore, All the AEs were tolerated and none of patients in the SLITone® group discontinued the study due to AEs.

Conclusions:

- Treatment with SLITone® for 72 weeks in paediatric patients with AD was associated with statistically significant improvements in the primary variable SCORAD total score compared to standard treatment.
- The results of the subjective perception of cutaneous symptoms, of nasal and ocular symptoms, and of bronchial symptoms, showed improvements from baseline to end of treatment in both groups, without statistically significant differences between groups.
- A significantly better Investigator's judgment of efficacy was reported for SLITone® compared to standard therapy.
- An excellent level of compliance in the SLITone® group was observed at any time point.
- Treatment with SLITone® was well tolerated. Few patients reported immediate and transient local reactions.

Date of the report: 09 December 2013