Integrated Clinical Trial Report

Tolerability of allergen vaccines quantified in mass units and administered by sublingual route. A randomised, double-blind placebo-controlled trial in subjects with allergic respiratory disease

Investigational Medicinal Products:

SLITone® 6-grass secale
SLITone® *Dermatophagoides* mix
SLITone® *Dermatophagoides pteronyssinus*

Clinical trial ID:	E01/04/SLIT1-M
EudraCT no.	2004-001316-31
Indication:	Grass pollen or house dust mite induced rhinoconjunctivitis with/without asthma symptoms
Development phase:	IV
First subject first visit:	29 September 2004
Last subject last visit:	24 May 2005
Investigators:	5 investigators in Spain: Dr. [redacted], Dr. M[a] [redacted] Dr. [redacted] Dr. [redacted] Dr. [redacted]
Trial centres:	5 trial centres in Spain: [redacted]
Sponsor:	ALK-Abelló, S.A C/ Miguel Fleta, 19 28037 Madrid
Clinical trial manager:	Dr. [redacted] ALK-Abelló, S.A
Report no. and date:	Final version, 1 May 2006

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

Synopsis – Trial E01/04/SLIT1-M

Title of Trial

Tolerability of allergen vaccines quantified in mass units and administered by sublingual route. A randomised, double-blind placebo-controlled trial in subjects with allergic respiratory disease

Investigators

5 investigators in Spain: Dr. [redacted] Dr. M[a] [redacted] Dr. [redacted] Dr. [redacted] Dr. [redacted]

Trial Centres

5 trial centres in Spain: [redacted]

Publications

- Abstract accepted for AAAAI 2006: M Boquete, F Rodriguez, AI Tabar, MD Ibáñez, A Nieto, F Torre-Martínez: Assessment of a New Treatment Schedule in Sublingual Immunotherapy. A Randomised Double-Blind Placebo-Controlled Multicentre Study.
- Manuscript accepted for publication February 2006 in International Archives of Allergy and Immunology: F Rodriguez, M Boquete, MD Ibáñez-Sandín, A Nieto, F de la Torre-Martínez, AI Tabar: Once daily sublingual immunotherapy (SLIT) without updosing - a new treatment schedule

Trial Period

First subject first visit – 29 September 2004

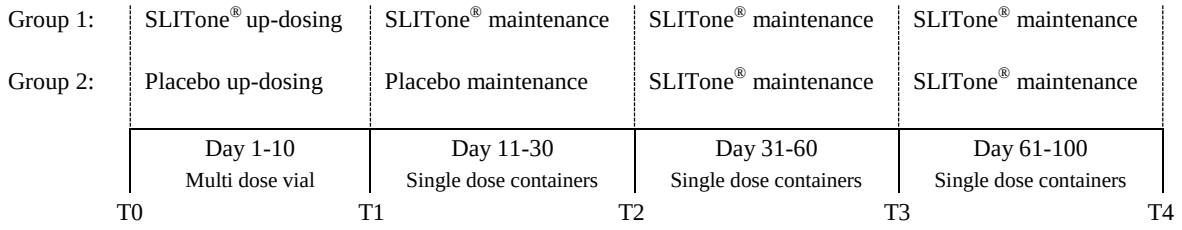
Last subject last visit – 24 May 2005

Objectives

- To evaluate the tolerability of SLITone®
- To evaluate the possibility of modifying the current treatment schedule by initiating treatment with SLITone® without an up-dosing phase

Methodology

Randomised, double-blind, placebo-controlled trial. Subjects were randomised into two groups. Group 1 received active SLITone® treatment throughout the trial. This included 10 days up-dosing (T0-T1), 20 days maintenance treatment (T1-T2), and two consecutive periods (T2-T3 and T3-T4) on maintenance treatment. Group 2 received placebo up-dosing during T0-T1, placebo maintenance during T1-T2, and initiated active SLITone® treatment (at maintenance dose) at T2 and continued active treatment until the end of the trial (T2-T3 and T3-T4).



Number of Subjects Planned and Analysed

A total of 135 subjects were randomised; of these 69 subjects were allocated to receive active SLITone® treatment throughout the trial (Group 1) and 66 subjects were allocated to receive placebo for the first 30 days of the trial (i.e. 10 days placebo up-dosing with multi dose vial and 20 days placebo maintenance treatment with single dose containers) and active SLITone® treatment for the rest of the trial (Group 2).

The subject disposition is shown below:

Treatment group	Group 1 N	%	Group 2 N	%	Overall N	%
Full Analysis Set ¤	69	(100%)	66	(100%)	135	(100%)
Grass mix treatment	33	(48%)	33	(50%)	66	(49%)
HDM treatment	36	(52%)	33	(50%)	69	(51%)
Withdrawn from trial	6	(9%)	6	(9%)	12	(9%)
Grass mix treatment	3	(4%)	2	(3%)	5	(4%)
HDM treatment	3	(4%)	4	(6%)	7	(5%)
Reasons for withdrawal						
Adverse event	3	(4%)	2	(3%)	5	(4%)
Change of residence	1	(1%)	1	(2%)	2	(1%)
Concomitant disease	1	(1%)			1	(<1%)
Patient decision	1	(1%)	1	(2%)	2	(1%)
Unknown			2	(3%)	2	(1%)

¤ Full Analysis Set includes all subjects randomised
N = Number of subjects
% = Percent of subjects of Full Analysis Set (all randomised subjects)
Group 1 = Treatment regimen with active up-dosing
Group 2 = Treatment regimen with placebo up-dosing
Cross-reference: Table 1.1

Diagnosis and Main Inclusion Criteria

Male and female subjects, age between 7 and 55 years, with a clinical history of moderate/severe rhinitis and/or rhinoconjunctivitis with or without asthmatic symptoms due to sensitisation to only one of the following allergens or groups of allergens: a) grasses (*Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis* and *Secale cereale*) or b) mites (*Dermatophagoides pteronyssinus* or *Dermatophagoides pteronyssinus* + *Dermatophagoides farinae*). Positive skin prick test to one of the allergens or groups of allergens mentioned above (prick test ALK-Abelló, S.A. 100 BU/ml > 3 mm Ø) and/or positive IgE (Pharmacia CAP class ≥ 2) to either *Dermatophagoides pteronyssinus* (in case of allergy to house dust mites) or *Lolium* or *Phleum* (in case of allergy to grasses).

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

The active treatment consisted of either SLITone® 6-grass secale, SLITone® *Dermatophagoides* mix or SLITone® *Dermatophagoides pteronyssinus*.

The treatment consisted of a multi dose vial with a volume of 5 ml (up-dosing phase) and single dose containers, each with a volume of 0.2 ml (extractable volume). Treatment was administered sublingually.

Batch numbers:

SLITone® 6-grass secale: EC-U152 (multi dose vial), EC-U140 (single dose containers)

SLITone® *Dermatophagoides* mix: EC-U145 (multi dose vial), EC-U155 (single dose containers)

SLITone® *Dermatophagoides pteronyssinus*: EC-U0208 (multi dose vial), EC-U154 (single dose containers)

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Placebo treatment contained the same excipients as the investigational medicinal products, but without the active ingredients. The treatment consisted of a multi dose vial with a volume of 5 ml (up-dosing phase) and single dose containers, each with a volume of 0.2 ml (extractable volume). Treatment was administered sublingually.

Batch numbers: EC-U141 (multi dose vial), EC-U142 (single dose containers)

Duration of Treatment

Approximately 100 days

Criteria for Evaluation – Safety

Adverse events (AEs)

Statistical Methods

All randomised subjects were included in the analyses (Full Analysis Set (FAS))

No efficacy measurements and analyses were performed.

Treatment emergent adverse events, i.e. events with onset after first dose, are presented by treatment group, system organ class and preferred term displaying number of subjects in each treatment group, number and frequency of subjects having the event as well as the number of events.

The following events are presented likewise:

- Common treatment emergent adverse events (events reported by > 5% of subjects)
- Related treatment emergent adverse events
- Treatment emergent adverse events occurring the first 30 days of active treatment (corresponding to adverse events from T0 to T2 for Group 1 and from T2 to T3 for Group 2)
- Treatment emergent adverse events for children (< 18 years) and adults, respectively
- Treatment emergent adverse events for subjects allergic to grass and mites, respectively
- Treatment emergent adverse events classified as local and systemic events, respectively
- Serious adverse events
- Adverse events leading to withdrawal

Furthermore, adverse events are summarised by treatment phase, relation to trial medication, treatment, age and treatment, classification (grade 1-4), seriousness, onset, action taken and outcome.

Demography of Trial Population

Demography of the trial population is summarised below:

Treatment group	Group 1 N (N=69)	%	Group 2 N (N=66)	%	Overall N (N=135)	%
Sex						
N	69		66		135	
Female	31	(45%)	35	(53%)	66	(49%)
Male	38	(55%)	31	(47%)	69	(51%)
Age class						
N	69		66		135	
< 18 years (children)	26	(38%)	22	(33%)	48	(36%)
>= 18 years (adults)	43	(62%)	44	(67%)	87	(64%)
Mean (SD)	22.6	(11.2)	22.0	(9.7)	22.3	(10.4)
Median	24.0		22.5		23.0	
Q25% - Q75%	12.0 - 29.0		12.0 - 28.0		12.0 - 29.0	
Min - Max	7 - 48		7 - 48		7 - 48	
Allergen treatment						
N	69		66		135	
Grass mix	33	(48%)	33	(50%)	66	(49%)
HDM	36	(52%)	33	(50%)	69	(51%)
HDM, mix	3	(4%)	2	(3%)	5	(4%)
HDM, Der p	33	(48%)	31	(47%)	64	(47%)
Children, Allergen treatment ¤						
N	26		22		48	
Grass mix	13	(50%)	14	(64%)	27	(56%)
HDM	13	(50%)	8	(36%)	21	(44%)
HDM, mix	3	(12%)	2	(9%)	5	(10%)
HDM, Der p	10	(38%)	6	(27%)	16	(33%)
Adults, Allergen treatment ¤						
N	43		44		87	
Grass mix	20	(47%)	19	(43%)	39	(45%)
HDM	23	(53%)	25	(57%)	48	(55%)
HDM, Der p	23	(53%)	25	(57%)	48	(55%)
Family history of atopy						
N	69		66		135	
Yes	31	(45%)	35	(53%)	66	(49%)
No	35	(51%)	30	(45%)	65	(48%)
Missing	3	(4%)	1	(2%)	4	(3%)
Personal history of atopy						
N	69		66		135	
Yes	15	(22%)	15	(23%)	30	(22%)
No	38	(55%)	33	(50%)	71	(53%)
Missing	16	(23%)	18	(27%)	34	(25%)
Concomitant disease						
N	69		66		135	
Yes	5	(7%)	5	(8%)	10	(7%)
No	60	(87%)	58	(88%)	118	(87%)
Missing	4	(6%)	3	(5%)	7	(5%)

¤ Subjects less than 18 years of age are regarded children. Adults are subjects of 18 years and above
N = Number of subjects
% = Percent of subjects
SD = Standard Deviation
Q25% - Q75% = Lower and upper quartiles
HDM = House Dust Mite
Der p = Dermatophagoides pteronyssinus
Group 1 = Treatment regimen with active up-dosing
Group 2 = Treatment regimen with placebo up-dosing
Cross-reference: Table 2.1 and 2.2

Safety Results

- Treatment with SLITone® was generally well tolerated and SLITone® can be initiated without up-dosing
- The most frequently reported adverse events were related to local reactions in and around the mouth
- One serious adverse event occurred during the trial (asthma attack in Group 1)
- Five subjects withdrew due to adverse events (three subjects from Group 1 and two from Group 2). Two subjects withdrew due to mouth oedema, one due to cough and dyspnoea, one due to dizziness and headache and one due to generalised pruritus and rhinitis. All of the events leading to withdrawal were considered related to treatment, except one with a missing relationship (cough).
- More children than adults reported adverse events during the trial
- The majority of adverse events during the trial were reported by subjects treated with SLITone® 6-grass secale

Conclusions

- Treatment with SLITone® is generally well tolerated
- Treatment with SLITone® can be initiated without up-dosing

Date of the Report

1 May 2006

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