Integrated Clinical Trial Report

Trial Title

Multicentre, randomised, double-blind, placebo-controlled parallel group study to demonstrate the efficacy of a 12-month subcutaneous specific immunotherapy with *ALK-depot SQ Milbenmischung* in patients with atopic dermatitis and proven IgE-mediated sensitisation to house dust mites

Investigational Medicinal Product:	*ALK-depot SQ 510 Milbenmischung* (Alutard SQ® 510 mite mix)
Clinical Trial ID:	SHX0556
EudraCT No.:	2005-004675-37
Development Phase:	III
Indication:	IgE-mediated allergic sensitisation to house dust mites manifested as atopic dermatitis
First subject first visit:	04 April 2006
Last subject last visit:	28 May 2009
Investigator:	Signatory Investigator: Prof. Dr. med. [redacted]
Trial Centres:	14 centres in DE
Sponsor:	ALK-Abelló Arzneimittel GmbH Feldstraße 170, DE-22880 Wedel Phone: +49 4103 7017 0 Fax : +49 4103 7017 730
Project Manager	Dr. rer. nat. [redacted] ALK-Abelló Arzneimittel GmbH
Medical Writer:	Dr. rer. nat. [redacted]
Document Status:	Final
Date:	12 December 2011

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

Synopsis – Trial SHX0556

Title of Trial Multicentre, randomised, double-blind, placebo-controlled parallel group study to demonstrate the efficacy of a 12-month subcutaneous specific immunotherapy with *ALK-depot SQ Milbenmischung* in patients with atopic dermatitis and proven IgE-mediated sensitisation to house dust mites
Signatory Investigator Prof. Dr. med. [redacted]
Trial Centres 1. Prof. Dr. med. [redacted] 2. Prof. Dr. med. [redacted] 3. Prof. Dr. med. [redacted] 4. PD Dr. med. [redacted] 5. Prof. Dr. med. [redacted] 6. Prof. Dr. med. [redacted] 7. Dr. med. [redacted] 8. Prof. Dr. med. [redacted] 9. Prof. Dr. med. [redacted] 10. Prof. Dr. med. [redacted] 11. Prof. Dr. med. [redacted] 12. Prof. Dr. med. [redacted] 13. Prof. Dr. med. [redacted] 14. Prof. Dr. med. [redacted]
Publication None
Trial Period First subject first visit – 04 April 2006 Last subject last visit – 28 May 2009
Objectives To demonstrate the efficacy and safety of specific immunotherapy with *ALK-depot SQ Milbenmischung* as compared with placebo.
Methodology This was a multi-centre, randomised, double-blind, placebo-controlled, parallel-group trial to demonstrate the efficacy of a 12-month subcutaneous specific immunotherapy with *ALK-depot SQ 510 Milbenmischung* in subjects with atopic dermatitis sensitised to house dust mites.

Number of Subjects Planned and Analysed
140 subjects were planned for inclusion; 214 subjects were screened; 154 subjects were randomised and 152 subjects were treated (2 subjects discontinued before start of trial medication).

Population	ALK-depot SQ	Placebo	Overall
All-Subjects-Treated	**76 (100.0%)**	**76 (100.0%)**	**152 (100.0%)**
Early drop-outs*	**7 (9.2%)**	**6 (7.9%)**	**13 (8.6%)**
Reason for drop-out			
▪ Non-Compliance	4	6	10
▪ Withdrawal of consent	1	–	1
▪ Other reasons	2	–	2
Full Analysis Set	**69 (90.8%)**	**70 (92.1%)**	**139 (91.4%)**
Subject withdrawals	15 (19.7%)	12 (15.8%)	27 (17.8%)
Reason for withdrawal			
▪ Adverse events	–	1	1
▪ Adverse events + withdrawal of consent	–	1	1
▪ Adverse events + insufficient efficacy	1	2	3
▪ Withdrawal of consent	2	2	4
▪ Insufficient efficacy	1	2	3
▪ Insufficient efficacy + non-compliance	1	–	1
▪ Non-compliance	5	1	6
▪ Protocol violation	1	1	2
▪ Other reasons	4	2	6
Subjects completed	**54 (71.1%)**	**58 (76.3%)**	**112 (73.7%)**

*: no efficacy data upon therapy available

Main Selection Criteria
Subjects aged 18 to 55 years with atopic dermatitis (SCORAD ≥ 25 score points) and proven IgE-mediated sensitisation to house dust mites.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers
ALK-depot SQ 510 Milbenmischung (Alutard SQ 510 mites; *Dermatophagoides pteronyssinus / farinae*).
16 increasing doses up to the maintenance dose of 100.000 SQ-U.
Subcutaneous injections.

Batch numbers:

Vial	Batch number	Expiry date
1	0000091120 0000101698	15 Sep 2007 07 Nov 2008
2	0000091121 0000101699	15 Sep 2007 07 Nov 2008
3	0000091122 0000101700	15 Sep 2007 07 Nov 2008
4	0000091123 0000101701 0000102527	06 Jul 2008 10 Oct 2009 08 Nov 2009

Batch numbers used in the trial:
- 2451, expiry date: 06 Jul 2007
- 4087, expiry date: 07 Nov 2008.

Before expiry date of the second batch, the study medication was relabelled for prolongation of expiry until 08 Nov 2009.

Reference Therapy, Dose and Mode of Administration, Batch Numbers
Placebo.
Matching injection scheme. Subcutaneous injections.

Batch numbers:

Vial	Batch number	Expiry date
1	0000092220 0000104444	25 Oct 2007 27 Feb 2009
2	0000092222 0000104442	25 Oct 2007 27 Feb 2009
3	0000092224 0000104441	25 Oct 2007 27 Feb 2009
4	0000092226 0000104439	25 Oct 2007 27 Feb 2009

Batch numbers used in the trial:
- 2451, expiry date: 06 Jul 2007
- 4087, expiry date: 07 Nov 2008.

Before expiry date of the second batch, the study medication was relabelled for prolongation of expiry until 08 Nov 2009.

Duration of Treatment
12 months

Criteria for Evaluation – Efficacy
Primary endpoint: Standardised summary score of changes from baseline in SCORAD total score and Elidel / Dermatop consumption.
Secondary endpoint: Standardised summary score of changes from baseline in SCORAD intensity score and Elidel / Dermatop consumption; standardised summary score of changes from baseline in EASI score and Elidel / Dermatop consumption.
Exploratory efficacy criteria: Changes from baseline in SCORAD extent criterion, SCORAD index, SCORAD subjective symptoms, other organ manifestations, and IGA score; amount of oral rescue medication; exacerbations of atopic dermatitis; CGI Item 2 (improvement); quality of life DLQI; treatment expectation questionnaire FBD.

Criteria for Evaluation – Safety
Adverse events, serious adverse events, severe adverse events, adverse events at least possibly related to the trial medication (adverse drug reactions); local allergic reactions, systemic allergic reactions, and other adverse events; adverse drug reactions in the updosing and maintenance period; global assessment of tolerability.

Statistical Methods
Construction of primary and secondary endpoints as summary scores according to O'Brien; analysis of primary, secondary, and exploratory endpoints by means of t-test, ANCOVA, and U test; repeated measurement ANCOVA (mixed model); χ^2 test.

Demography of Trial Population

Parameter		ALK-depot SQ	Placebo	Overall
Number of subjects		76	76	152
Age [years]	min – max	18 – 54	18 – 49	18 – 54
	median	26.0	25.5	26.0
	mean (SD)	30.1 (9.8)	28.3 (8.8)	29.2 (9.4)
Gender	male	39 (51.3%)	39 (51.3%)	78 (51.3%)
	female	37 (48.7%)	37 (48.7%)	74 (48.7%)
Ethnic origin	Caucasian	75 (98.7%)	70 (92.1%)	145 (95.4%)
	other	1 (1.3%)	6 (7.9%)	7 (4.6%)
Number of major features of AD according to Hanifin and Rajka				
	3	19 (25.0%)	15 (19.7%)	34 (22.4%)
	4	57 (75.0%)	61 (80.3%)	118 (77.6%)
Age at first occurrence of AD [years]	min – max	0 – 44	0 – 39	0 – 44
	median	2.0	0.0	1.0
	mean (SD)	6.5 (10.9)	4.4 (8.4)	5.5 (9.8)
History of mites allergy	no	–	–	–
	yes	76 (100.0%)	76 (100.0%)	152 (100.0%)
History of rhinoconjunctivitis	no	15 (19.7%)	12 (15.8%)	27 (17.8%)
	yes	61 (80.3%)	64 (84.2%)	125 (82.2%)
History of bronchial asthma	no	48 (63.2%)	37 (48.7%)	85 (55.9%)
	yes	28 (36.8%)	39 (51.3%)	67 (44.1%)

N (%) = number of subjects (percent of subjects)

Efficacy Results

The atopic dermatitis improved in both treatment groups as was demonstrated by clinically relevant and statistically significant decreases of SCORAD (mean ± SD; ALK-depot SQ: –14.31 ± 15.51, p<0.0001; placebo: –17.20 ± 15.21, p<0.0001), EASI (ALK-depot SQ: –5.56 ± 6.90, p<0.0001; placebo: –5.86 ± 6.80, p<0.0001), and IGA (ALK-depot SQ: –0.75 ± 0.86, p<0.0001; placebo: –0.84 ± 0.89, p<0.0001).

No advantages in favour of ALK-depot SQ were detected. No significant differences concerning quality of life and treatment expectation were observed, either.

Regarding other organ manifestations, the following changes from baseline were observed in the Full Analysis Set (mean ± SD):

- eye symptoms
  - ALK-depot SQ: –1.13 ± 2.58 (p=0.0003)
  - Placebo : –1.14 ± 2.97 (p=0.0035)
- nose symptoms
  - ALK-depot SQ: –1.69 ± 2.98 (p<0.0001)
  - Placebo : –1.36 ± 2.97 (p=0.0007)
- bronchial symptoms
  - ALK-depot SQ: –0.63 ± 2.50 (p=0.0476)
  - Placebo : –0.64 ± 1.78 (p=0.0006).

Efficacy Results *[cont.]*
The treatment differences with respect to other organ manifestations were also insignificant. The mean changes from baseline corresponded to improvement rates of

- eye symptoms
  - ALK-depot SQ: 41/60 (68.3%)
  - Placebo : 40/65 (61.5%)
- nose symptoms
  - ALK-depot SQ: 45/64 (70.3%)
  - Placebo : 39/65 (60.0%)
- bronchial symptoms
  - ALK-depot SQ: 23/41 (56.1%)
  - Placebo : 30/46 (65.2%).

Like for the skin symptoms, improvements at an expected level were observed for other organ manifestations under ALK-depot SQ. The lack of discrimination between the trial medications is due to high placebo effects in this trial.

Safety Results
No marked differences between *ALK-depot SQ 510 Milbenmischung* and placebo were observed with respect to the profile of adverse events, however, higher incidences of injection site reactions were determined for ALK-depot SQ.
'Atopic dermatitis' was documented as adverse event in 16 subjects (21.1%) treated with ALK-depot SQ and 14 subjects (18.4%) treated with placebo. A higher proportion of subjects suspected a relationship of the AD aggravation to the trial medication in the ALK-depot SQ group (n=13, 17.1%) as compared with the placebo group (n=8, 10.5%). Therefore, the safety results were consistent with the indifferent efficacy results.

The overall assessment of tolerability by the investigator showed a tendency in favour of placebo with respect to very good judgements:
- ALK-depot SQ: 31.1%
- Placebo : 44.6%.

However, a very good or good judgement was obtained in well comparable frequencies:
- ALK-depot SQ: 87.8%
- Placebo : 83.8%.

In all, the safety results showed an expected advantage for placebo with respect to injection site reactions but comparable good to very good overall assessments of tolerability.

Conclusions
In this trial high placebo effects were observed with regard to skin, eye, nose, and bronchial symptoms. Therefore, the trial did not meet the goal of demonstrating superiority of *ALK-depot SQ 510 Milbenmischung* (Alutard SQ® 510 mite mix) in the treatment of AD in subjects sensitised to house dust mites as compared to placebo.
As expected, higher incidences of injection site reactions were observed upon ALK-depot SQ. With respect to other adverse events no significant treatment differences were observed. However, a slightly higher incidence of deteriorated AD findings were seen in actively treated subjects.

Date of the Report
12 December 2011

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