# CLINICAL STUDY REPORT (Version No. 1)

## A randomised, parallel-group, double-blind, placebo-controlled, multicentre Phase III trial assessing the pharmacodynamic efficacy and safety of an intraseasonal short-time updosing schedule for Alutard SQ

**Study Number: SHX0562**

**CONFIDENTIAL**

## 1. TITLE PAGE

| | |
|---|---|
| *Study title* | A randomised, parallel-group, double-blind, placebo-controlled, multicentre Phase III trial assessing the pharmacodynamic efficacy and safety of an intraseasonal short-time updosing schedule for Alutard SQ |
| *Name of test drug / investigational product* | Alutard SQ 6 grass mix + rye (secale)<br>*ALK-depot SQ Gräsermischung und Roggen* |
| *Indication studied* | Grass pollen induced allergic rhinoconjunctivitis requiring treatment during the grass pollen season |
| *Study design* | A randomised, parallel group, double-blind, placebo-controlled, multicentre Phase III trial |
| *Sponsor* | ALK-Abelló Arzneimittel GmbH<br>Feldstraße 170, 22880 Wedel, Germany |
| *Study number* | SHX0562 |
| *Development phase of study* | Phase III |
| *Study initiation date* | Date of first patient enrolled : 14 April 2008 |
| *Study completion date* | Date of last patient completed : 31 October 2008 |
| *Principal investigator (Leiter der klinischen Prüfung according to German Drug Law)* | Prof. Dr. med. [redacted] |
| *Project manager* | Dr. rer. nat. [redacted]<br>ALK-Abelló Arzneimittel GmbH<br>Feldstraße 170, 22880 Wedel, Germany |
| *GCP* | This study was performed in compliance with ICH Good Clinical Practice (CPMP/ICH/135/95). |
| *Date of the report* | 26 January 2009 |

## 2. SYNOPSIS

| | |
|---|---|
| Name of sponsor | ALK-Abelló Arzneimittel GmbH<br>Feldstraße 170, 22880 Wedel, Germany |
| Name of finished product | ALK-depot SQ Gräsermischung und Roggen |
| Name of active ingredient | Equal parts of active allergen extracts:<br>• *Dactylis glomerata*<br>• *Lolium perenne*<br>• *Avena elatior*<br>• *Phleum pratense*<br>• *Poa pratensis*<br>• *Festuca pratensis*<br>• *Secale cereale*. |
| Study title | A randomised, parallel-group, double-blind, placebo-controlled, multicentre Phase III trial assessing the pharmacodynamic efficacy and safety of an intraseasonal short-time updosing schedule for Alutard SQ |
| Investigators | • Centre 1 : Prof. Dr. med. [redacted] *(Coordinating Investigator)*<br>• Centre 2 : Dr. med. [redacted]<br>• Centre 3 : Dr. med. [redacted]<br>• Centre 4 : Dr. med. [redacted]<br>• Centre 5 : PD Dr. med. [redacted]<br>• Centre 6 : Dr. med. [redacted]<br>• Centre 7 : Dr. med. [redacted]<br>• Centre 8 : Dr. med. [redacted]<br>• Centre 9 : PD Dr. med. [redacted]<br>• Centre 11 : Dr. med. [redacted]<br>• Centre 12 : Dr. med. [redacted]<br>• Centre 13 : [redacted]<br>• Centre 14 : Dr. med. [redacted]<br>• Centre 15 : Dr. med. [redacted]<br>• Centre 16 : Dr. med. [redacted] |
| Study centres | 15 centres in Germany |
| Publication (reference) | – |
| Study period | Date of first patient enrolled : 14 April 2008<br>Date of last patient completed : 31 October 2008 |
| Phase of development | III |
| Objectives | It is the objective of this study to test the pharmacodynamic efficacy and tolerability of a short-time intraseasonal updosing with the aim to induce changes of the immunosystem several months earlier compared to a delayed extraseasonal beginning of the therapy. |
| Methodology | Randomised, parallel-group, double-blind, placebo-controlled, multicentre Phase III trial |
| Number of patients | • Planned : N=144<br>• Screened : N=158<br>• Randomised : N=149<br>• Treated : N=148 (ALK-depot SQ: 112, placebo: 36)<br>• Full Analysis Set : N=144 (ALK-depot SQ: 109, placebo: 35)<br>• Per Protocol Set : N=114 (ALK-depot SQ: 87, placebo: 27). |

| | |
|---|---|
| Diagnosis and main criteria for inclusion | Grass pollen induced allergic rhinoconjunctivitis requiring treatment during the grass pollen season. |
| Test product | ALK-depot SQ Gräsermischung und Roggen |
| Dose | Updosing was performed in daily intervals starting with two injections of 0.1 mL and 0.3 mL of Vial No. I (1000 SQ-U/mL) and followed by 4 injections of 0.1, 0.3, 0.6, and 1 mL of Vial No. II (10000 SQ-U/mL). These injections were administered on 6 weekdays of the first 8 study days (e.g. days 1, 2, 3, 4, 5, and 8) and followed by two injections of 1 mL of Vial No. II after a two- and then a four-week interval. |
| Mode of administration | Subcutaneous injections |
| Batch no. | • Trial batch no. : 4103<br>• Manufacturer's batch no. Vial I : 0000100306<br>• Manufacturer's batch no. Vial II : 0000100305. |
| Duration of treatment | Approximately 50 days with a total of 8 injections, followed by two extraseasonal study termination days approximately 2 weeks after the 8$^{th}$ injection (= week 9). |
| Reference product | Placebo |
| Dose | According to test product |
| Mode of administration | Subcutaneous injections |
| Batch no. | • Trial batch no. : 4103<br>• Manufacturer's batch no. Vial I : 0000104559<br>• Manufacturer's batch no. Vial II : 0000104558. |
| Criteria for evaluation | |
| Efficacy | **Primary endpoint**<br>• To demonstrate a lower level of IgX at Visit 9 compared to placebo.<br><br>**Secondary endpoints**<br>• To demonstrate a lower level of IgX at Visits 6 and 7 compared to placebo.<br>• To demonstrate a higher level of $IgG_4$ at Visits 6, 7, and 9 compared to placebo.<br>• To demonstrate a lower nasal reactivity against challenge with *Phleum pratense* measured at study end with the titrated Nasal Provocation Test as compared to placebo.<br>• To demonstrate a lower skin reactivity against challenge with *Phleum pratense* measured at study end with the titrated Skin Prick Test as compared to placebo.<br><br>**Explorative endpoints**<br>• To evaluate the pharmacodynamic efficacy of specific immunotherapy with intra-seasonal updosing compared to placebo with respect to IgE measured at Visits 6, 7, and 9. |
| Safety | • Local reactions (per patient and injection<br>• Systemic reactions (per patient and injection<br>• Adverse events classified according to MedDRA 11.0<br>• Serious and other significant adverse events. |

| | |
|---|---|
| Statistical methods | • t-test<br>• Mann-Whitney-Wilcoxon U test<br>• Analysis of covariance for the repeated measurement design<br>• $\chi^2$ test<br>• 95% confidence intervals<br>• Significance level of $\alpha$=0.05 two-tailed. |

**Efficacy results**

➢ IgX at Visit 9 [FAS]

A significantly lower level of IgX at Visit 9 was seen upon ALK-depot SQ (0.90 ± 0.28) in comparison to placebo (1.08 ± 0.26; U test: p<0.0001).

➢ Further analyses of IgX

The result was confirmed in the PP Set, in the analysis of observed cases, and in the analysis of covariance for repeated measures using the baseline of IgX as covariate. Significant differences were detected after 3 weeks already.

➢ $IgG_4$ at Visit 9 [FAS]

A significantly higher level of $IgG_4$ at Visit 9 was seen upon ALK-depot SQ (median 62.23 AU/L) in comparison to placebo (36.38 AU/L; U test: p=0.0286).

➢ Further analyses of $IgG_4$

The result was confirmed in the PP Set, in the analysis of observed cases, and in the analysis of covariance for repeated measures using the baseline of $IgG_4$ as covariate. Based on the ANCOVA, significant differences were detected after 3 weeks already.

➢ IgE at Visit 9

An only slightly higher level of IgE was determined at Visit 9 upon ALK-depot SQ compared to placebo (PP; U test: p=0.0114). The analysis of observed cases and the ANCOVA showed significant treatment differences in the FAS after 3 weeks already.

➢ The NPT at Visit 9 remained indifferent.

➢ The SPT at Visit 9 remained indifferent.

➢ Patient's assessment of efficacy yielded no statistically significant differences between both trial groups. However, a remarkable difference was observed with respect to 'much better' condition in 2008 compared to 2006 and 2007. In the FAS, the incidences were

- ALK-depot SQ : N=13 (12.0%)
- placebo : N= 1 ( 3.0%).

**Safety results**

➢ No serious adverse events related to ALK-depot SQ were observed.

➢ The incidence of local reactions was markedly increased with ALK-depot SQ as compared to placebo (46.4% vs. 8.3% for patients and 23.3% vs. 1.8% for injections).

➢ A pre-medication was used for only 8.7% of the ALK-depot SQ injections. The risk of local reactions was not reduced by prophylactic measures, but this result might be biased because pre-medication was probably administered especially in high risk patients.

➢ Only small incidences of systemic reactions were observed (ALK-depot SQ vs. placebo: 7.1% vs. 5.6% for patients and 1.1% vs. 0.7% for injections). In patients who received pre-medication no systemic reactions were observed. Slightly higher incidences were seen if all events (including those not allocated to injections) were analysed: 10.7%:8.3% for patients and 2.5%:1.4% for injections. Except for 4 injections with 'early, mild systemic reactions', delayed reactions were seen.

➢ In total patient's and investigator's assessment of tolerability showed significant advantages of placebo. As was shown by the MedDRA classification of adverse events, this was caused solely by injection site reactions.

**Conclusion**

The pharmacodynamic targets could be verified as planned, but NPT and SPT as further secondary endpoints remained statistically indifferent.

The incidence of local reactions increased compared to placebo and usual application schedules – as expected. The rate of systemic reactions was not relevantly increased and comparatively low compared to other studies. Therefore, the intraseasonal updosing schedule for ALK-depot SQ can be regarded as safe and efficacious.