# Clinical trial results:
# A Dose Response Evaluation of SLIToneULTRA HDM Mix Immunotherapy

## Summary

| | |
|---|---|
| EudraCT number | 2012-002177-62 |
| Trial protocol | ES |
| Global end of trial date | 04 September 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 16 February 2016 |
| First version publication date | 26 July 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | SU-M-01 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | ALK-Abelló A/S |
| Sponsor organisation address | Bøge Allé 1, Hørsholm, Denmark, 2970 |
| Public contact | Global Clinical Development, ALK-Abelló A/S, +45 45747576, ClinicalTrials@alk.net |
| Scientific contact | Global Clinical Development, ALK-Abelló A/S, +45 45747576, ClinicalTrials@alk.net |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 25 August 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 September 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the dose-response relationship with regards to change in immunological parameters and safety for SLIToneULTRA house dust mite (HDM) mix in adult subjects with moderate to severe HDM allergic rhinitis.

Protection of trial subjects:

Safety surveillance, use of symptomatic medications allowed

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 November 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 91 |
| Country: Number of subjects enrolled | France: 128 |
| Worldwide total number of subjects | 219 |
| EEA total number of subjects | 219 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 218 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited in France and Spain

### Pre-assignment

Screening details:

The subjects eligible for the trial were adults with HDM allergic rhinitis. The clinical history was consistent with moderate to severe persistent HDM allergic rhinitis with or without asthma, with allergic rhinitis symptoms despite having received symptomatic treatment of at least one year prior to trial entry.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | 50 SRU |

Arm description:

No updosing
Maintenance: 50 SRU/day

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | SLIToneULTRA HDM mix |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for oral solution |
| Routes of administration | Sublingual use |

Dosage and administration details:

The solution was to be administered once daily. The solution was to be placed under the tongue (sublingual) and kept there for 2 minutes before swallowing. Eating and drinking was to be avoided for the next 5 minutes.

| | |
|---|---|
| **Arm title** | 150 SRU |

Arm description:

Updosing for 5 days: 50 SRU/day
Maintenance for the rest of the trial: 150 SRU/day

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | SLIToneULTRA HDM mix |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for oral solution |
| Routes of administration | Sublingual use |

Dosage and administration details:

The solution was to be administered once daily. The solution was to be placed under the tongue (sublingual) and kept there for 2 minutes before swallowing. Eating and drinking was to be avoided for the next 5 minutes.

| | |
|---|---|
| **Arm title** | 300 SRU |

Arm description:

Updosing: 50 SRU/day for 5 days, then 150 SRU/day for 5 days
Maintenance for the rest of the trial: 300 SRU/day

| | |
|---|---|
| Arm type | Active comparator |

| | |
|---|---|
| Investigational medicinal product name | SLIToneULTRA HDM mix |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for oral solution |
| Routes of administration | Sublingual use |

Dosage and administration details:

The solution was to be administered once daily. The solution was to be placed under the tongue (sublingual) and kept there for 2 minutes before swallowing. Eating and drinking was to be avoided for the next 5 minutes.

| **Number of subjects in period 1** | 50 SRU | 150 SRU | 300 SRU |
|---|---|---|---|
| Started | 73 | 73 | 73 |
| Completed | 67 | 65 | 64 |
| Not completed | 6 | 8 | 9 |
| Consent withdrawn by subject | 1 | - | - |
| Lost to follow-up | 3 | - | - |
| Adverse event, non-fatal | 2 | 3 | 5 |
| Pregnancy | - | 1 | - |
| Lost to follow-up | - | 2 | 2 |
| Other causes, not specified | - | 2 | - |
| Protocol deviation | - | - | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | 50 SRU |
| Reporting group description: | |
| No updosing<br>Maintenance: 50 SRU/day | |
| Reporting group title | 150 SRU |
| Reporting group description: | |
| Updosing for 5 days: 50 SRU/day<br>Maintenance for the rest of the trial: 150 SRU/day | |
| Reporting group title | 300 SRU |
| Reporting group description: | |
| Updosing: 50 SRU/day for 5 days, then 150 SRU/day for 5 days<br>Maintenance for the rest of the trial: 300 SRU/day | |

| Reporting group values | 50 SRU | 150 SRU | 300 SRU |
|---|---|---|---|
| Number of subjects | 73 | 73 | 73 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 73 | 73 | 72 |
| From 65-84 years | 0 | 0 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 32 | 32 | 32 |
| standard deviation | ± 10 | ± 9 | ± 10 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 41 | 39 | 38 |
| Male | 32 | 34 | 35 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 219 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |

| | | | |
|---|---|---|---|
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 218 | | |
| From 65-84 years | 1 | | |
| 85 years and over | 0 | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 118 | | |
| Male | 101 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | 50 SRU |
| Reporting group description: | |
| No updosing<br>Maintenance: 50 SRU/day | |
| Reporting group title | 150 SRU |
| Reporting group description: | |
| Updosing for 5 days: 50 SRU/day<br>Maintenance for the rest of the trial: 150 SRU/day | |
| Reporting group title | 300 SRU |
| Reporting group description: | |
| Updosing: 50 SRU/day for 5 days, then 150 SRU/day for 5 days<br>Maintenance for the rest of the trial: 300 SRU/day | |

### Primary: Change in IgE-blocking factor for Dermatophagoides pteronyssinus

| | |
|---|---|
| End point title | Change in IgE-blocking factor for Dermatophagoides pteronyssinus |
| End point description: | |
| Change in IgE-blocking factor for Dermatophagoides pteronyssinus from baseline to end-of-trial using Last Observation Carried Forward (LOCF) for missing data | |
| End point type | Primary |
| End point timeframe: | |
| Baseline to visit 4 (6 months) | |

| End point values | 50 SRU | 150 SRU | 300 SRU | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73[1] | 70[2] | 72[3] | |
| Units: kU/l | | | | |
| arithmetic mean (standard deviation) | 0.09 (± 0.15) | 0.14 (± 0.19) | 0.17 (± 0.17) | |

Notes:

[1] - All subjects with valid samples

[2] - All subjects with valid samples

[3] - All subjects with valid samples

### Statistical analyses

| Statistical analysis title | Primary analysis |
|---|---|

Statistical analysis description:

Changes in IgE-blocking factor were assessed using Analysis of Covariance (ANCOVA) including group as factor and baseline IgE-blocking testing the hypothesis of no difference between doses with respect to IgE-blocking factor

| | |
|---|---|
| Comparison groups | 50 SRU v 150 SRU v 300 SRU |

| | |
|---|---|
| Number of subjects included in analysis | 215 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.0152 [5] |
| Method | ANCOVA |

Notes:

[4] - Test for overall difference between groups

[5] - Significant overall difference between doses

| **Statistical analysis title** | Primary analysis |
|---|---|

Statistical analysis description:

Pairwise comparison of 50 SRU and 300 SRU

| | |
|---|---|
| Comparison groups | 50 SRU v 300 SRU |
| Number of subjects included in analysis | 145 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0075 [6] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.06999 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1211 |
| upper limit | -0.01886 |
| Variability estimate | Standard deviation |

Notes:

[6] - Significantly superior change in 300 SRU versus 50 SRU

| **Statistical analysis title** | Primary analysis |
|---|---|

Statistical analysis description:

Pairwise comparison of 150 SRU and 300 SRU

| | |
|---|---|
| Comparison groups | 300 SRU v 150 SRU |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0602 [7] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.04951 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1012 |
| upper limit | 0.0021 |
| Variability estimate | Standard deviation |

Notes:

[7] - Not statistically significantly difference between 300 SRU and 150 SRU

| **Statistical analysis title** | Primary analysis |
|---|---|

| Statistical analysis description: | |
|---|---|
| Pairwise comparison of 50 SRU and 150 SRU | |
| Comparison groups | 150 SRU v 50 SRU |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4342 [8] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.02048 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0702 |
| upper limit | 0.03105 |
| Variability estimate | Standard deviation |

Notes:

[8] - Not statistically significantly difference between 50 SRU and 150 SRU

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Approximately 6 months | |
| Adverse event reporting additional description: | |
| From the first trial related activity after the subject signed the informed consent and until the follow up telephone contact | |
| Assessment type | Non-systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

| Reporting groups | |
|---|---|
| Reporting group title | 50 SRU |
| Reporting group description: | |
| No updosing<br>Maintenance: 50 SRU/day | |
| Reporting group title | 150 SRU |
| Reporting group description: | |
| Updosing for 5 days: 50 SRU/day<br>Maintenance for the rest of the trial: 150 SRU/day | |
| Reporting group title | 300 SRU |
| Reporting group description: | |
| Updosing: 50 SRU/day for 5 days, then 150 SRU/day for 5 days<br>Maintenance for the rest of the trial: 300 SRU/day | |

| Serious adverse events | 50 SRU | 150 SRU | 300 SRU |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 1 / 73 (1.37%) | 0 / 73 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | 50 SRU | 150 SRU | 300 SRU |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 73 (49.32%) | 36 / 73 (49.32%) | 41 / 73 (56.16%) |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | 1 / 73 (1.37%) | 1 / 73 (1.37%) |
| occurrences (all) | 4 | 1 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 73 (2.74%) | 4 / 73 (5.48%) | 4 / 73 (5.48%) |
| occurrences (all) | 4 | 9 | 5 |
| Gastrointestinal disorders | | | |
| Oral pruritus | | | |
| subjects affected / exposed | 10 / 73 (13.70%) | 11 / 73 (15.07%) | 17 / 73 (23.29%) |
| occurrences (all) | 12 | 12 | 18 |
| Tongue pruritus | | | |
| subjects affected / exposed | 6 / 73 (8.22%) | 3 / 73 (4.11%) | 5 / 73 (6.85%) |
| occurrences (all) | 6 | 3 | 5 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | 7 / 73 (9.59%) | 5 / 73 (6.85%) |
| occurrences (all) | 4 | 9 | 5 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| NA |

Notes: