# Clinical trial results:
# A Dose Finding Study of the Efficacy of LAIS® Mites Sublingual tablets in patients suffering from house dust mite-induced allergic rhinoconjunctivitis
# A prospective, double-blind, placebo-controlled randomized multi-centre trial.

## Summary

| | |
|---|---|
| EudraCT number | 2013-000617-20 |
| Trial protocol | DE |
| Global end of trial date | 13 May 2014 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 27 October 2021 |
| First version publication date | 27 October 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | SMART_2 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Lofarma Spa |
| Sponsor organisation address | Viale Cassala, 40, Milan, Italy, 20143 |
| Public contact | Scientific Director Lofarma SPA, Institut für Med. Statistik, Informatik u. Epidemiologie, +39 0258198287, |
| Scientific contact | Scientific Director Lofarma SPA, Institut für Med. Statistik, Informatik u. Epidemiologie, +39 0258198287, |

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 | 13 May 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 13 May 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The efficacy of sublingual immunotherapy with the allergoid LAIS® Mites Sublingual tablets will be assessed by the mean improvement in the allergic severity S between baseline and visit V4, comparing the five treatment groups.
Allergic severity S is rated by means of the severity stage integer values $0 \leq ci \leq 4$. Here i is a number of an attempt (titration stage), made to reach a positive allergic reaction within the Conjunctival Provocation Test (CPT). CPT is considered positive if the response is stage 2 or higher.
The maximum number of attempts (N) is restricted with the titration solutions available. If the severity stage is reached to be ci= 2, the CPT is considered as positive, the test is stopped for the current visit and N is the number of steps to reach a positive result (1, 2, 3).
The titrated conjunctival allergen challenge will be conducted with solutions containing 100, 1,000 and 10,000 SQ-E/ml mite allergens.

Protection of trial subjects:

Before including a patient, the investigator informed the patient in his own words of the nature of the trial, of its aims, of the methods and means to be used, and of the estimated duration of the study. He/she had also informed the patient of the possible risks linked with administration of the products and of the possible effects which to his/her knowledge might occur.
Moreover, the main procedures used to guarantee the subjects' anonymity especially during the analysis of their personal data were profoundly explained.
The patient was allowed to ask questions and had to be satisfied with all the investigator´s answers.
Before asking the patient to sign the consent form, the investigator ascertained that the patient entirely understood and agreed to all information provided.
The subject was free to withdraw from the study at any time without prejudicing future medical care and giving a reason.
If any new information became available that might have influenced the subject's decision to stay in the trial, it was transmitted without delay to the subject.

Background therapy:

All patients were supplied with a blister of an oral antihistamine (10 mg Loratadine) to be taken on demand as rescue medication for potentially appearing local side effects like oral pruritus and edema of mouth, tongue or lips.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 August 2013 |
| 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 | Germany: 165 |
| Worldwide total number of subjects | 165 |
| EEA total number of subjects | 165 |

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) | 165 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

It was planned to recruit 150 patients in total, with 30 participants in each treatment group. However, a total number of 165 patients were screened, 131 patients were randomized, with 127 being valid for the ITT analysis subset.

### Pre-assignment

Screening details:

Female or male patients aged 18–75 years with a history of at least two years of house dust mites (HDM) induced allergic rhinitis and/or allergic rhinoconjunctivitis with or without controlled asthma upon exposure to house dust mites [From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012]

### Period 1

| | |
|---|---|
| Period 1 title | Lais Mites (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description: -

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Sublingual tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

Placebo and verum preparations were identical except of the active substances. i.e. carbamylated, monomeric allergoids of mite.

| | |
|---|---|
| **Arm title** | LAIS® Mites 300 UA/Day |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LAIS® Mites 300 Ua/Day |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Sublingual tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

The treatment was randomly allocated to a subject. Each subjects treatment was scheduled for 12 weeks (84±7 days) and each subject ingested one sublingual tablet per day independent of the assigned group. The participants were instructed to place the tablet under the tongue and dissolved for two minutes before swallowing. The first application (day 0) was performed under supervision and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and administered by him- / herself.

| | |
|---|---|
| **Arm title** | Lais Mites 1,000 UA/day |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | LAIS® Mites 1,000 UA/day |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Sublingual tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

The treatment was randomly allocated to a subject. Each subjects treatment was scheduled for 12 weeks (84±7 days) and each subject ingested one sublingual tablet per day independent of the assigned group. The participants were instructed to place the tablet under the tongue and dissolved for two minutes before swallowing. The first application (day 0) was performed under supervision and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and administered by him- / herself.

| **Arm title** | LAIS® Mites 2,000 UA/Day |
|---|---|

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LAIS® Mites 2,000 UA/Day |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Sublingual tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

The treatment was randomly allocated to a subject. Each subjects treatment was scheduled for 12 weeks (84±7 days) and each subject ingested one sublingual tablet per day independent of the assigned group. The participants were instructed to place the tablet under the tongue and dissolved for two minutes before swallowing. The first application (day 0) was performed under supervision and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and administered by him- / herself.

| **Arm title** | LAIS® Mites 3,000 UA/Day |
|---|---|

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LAIS® Mites Sublingual 3,000 UA |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Sublingual tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

The treatment was randomly allocated to a subject. Each subjects treatment was scheduled for 12 weeks (84±7 days) and each subject ingested one sublingual tablet per day independent of the assigned group. The participants were instructed to place the tablet under the tongue and dissolved for two minutes before swallowing. The first application (day 0) was performed under supervision and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and administered by him- / herself.

| **Number of subjects in period 1[1]** | Placebo | LAIS® Mites 300 UA/Day | Lais Mites 1,000 UA/day |
|---|---|---|---|
| Started | 29 | 23 | 27 |
| Completed | 28 | 23 | 26 |
| Not completed | 1 | 0 | 1 |
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | 1 | - | - |

| **Number of subjects in period 1[1]** | LAIS® Mites 2,000 UA/Day | LAIS® Mites 3,000 UA/Day |
|---|---|---|
| Started | 26 | 26 |
| Completed | 26 | 25 |
| Not completed | 0 | 1 |
| Consent withdrawn by subject | - | 1 |
| Adverse event, non-fatal | - | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Since 34 patients resulted as screening failures, 131 patients were randomized into this study.

## Baseline characteristics

### Reporting groups

| Reporting group title | Lais Mites |
|---|---|

Reporting group description: -

| Reporting group values | Lais Mites | Total | |
|---|---|---|---|
| Number of subjects | 131 | 131 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18–75 years) | 131 | 131 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 37.48 | | |
| full range (min-max) | 18 to 70 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 64 | 64 | |
| Male | 67 | 67 | |

### Subject analysis sets

| Subject analysis set title | Safety set (S-set)/ Exposed Subjects |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

randomized subjects who have been exposed to the study medication at least once. Only safety analyses will be performed in this group.

| Subject analysis set title | Intention-To-Treat-set (ITT-set) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Randomized subjects who meet key eligibility and evaluability criteria. This dataset is defined by the existence of evaluable CPT data at baseline and V3 or later.

| Subject analysis set title | Per-Protocol-set (PP-set) |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

evaluable subjects who comply with the protocol in all points, delivering a complete data set of measurements and evaluations of the primary efficacy variable. A maximum of 25 % deviation from the planned intake of study medication was accepted as per protocol drug intake

| Subject analysis set title | Randomized |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

all subjects randomized into the study.

| Reporting group values | Safety set (S-set)/ Exposed Subjects | Intention-To-Treat-set (ITT-set) | Per-Protocol-set (PP-set) |
|---|---|---|---|
| Number of subjects | 131 | 127 | 119 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18–75 years) | 131 | 127 | 119 |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 37.48 | 37.48 | 37.44 |
| full range (min-max) | 18 to 70 | 18 to 70 | 18 to 70 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 64 | 63 | 59 |
| Male | 67 | 64 | 60 |

| **Reporting group values** | Randomized | | |
|---|---|---|---|
| Number of subjects | 131 | | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18–75 years) | 131 | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 37.48 | | |
| full range (min-max) | 18 to 70 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 64 | | |
| Male | 67 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | LAIS® Mites 300 UA/Day |
| Reporting group description: - | |
| Reporting group title | Lais Mites 1,000 UA/day |
| Reporting group description: - | |
| Reporting group title | LAIS® Mites 2,000 UA/Day |
| Reporting group description: - | |
| Reporting group title | LAIS® Mites 3,000 UA/Day |
| Reporting group description: - | |
| Subject analysis set title | Safety set (S-set)/ Exposed Subjects |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| randomized subjects who have been exposed to the study medication at least once. Only safety analyses will be performed in this group. | |
| Subject analysis set title | Intention-To-Treat-set (ITT-set) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Randomized subjects who meet key eligibility and evaluability criteria. This dataset is defined by the existence of evaluable CPT data at baseline and V3 or later. | |
| Subject analysis set title | Per-Protocol-set (PP-set) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| evaluable subjects who comply with the protocol in all points, delivering a complete data set of measurements and evaluations of the primary efficacy variable. A maximum of 25 % deviation from the planned intake of study medication was accepted as per protocol drug intake | |
| Subject analysis set title | Randomized |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| all subjects randomized into the study. | |

### Primary: Efficacy (allergic severity score S)

| | |
|---|---|
| End point title | Efficacy (allergic severity score S) |
| End point description: | |
| The primary outcome parameter of the study was the improvement of the allergic severity S between baseline and V4 (day 84 ± 7).<br>There was a distinct improvement of the allergic severity S between baseline and V3 and a more pronounced improvement between baseline and V4 in each study arm | |
| End point type | Primary |
| End point timeframe: | |
| between baseline and visit V4. | |

| End point values | Placebo | LAIS® Mites 300 UA/Day | Lais Mites 1,000 UA/day | LAIS® Mites 2,000 UA/Day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28 | 23 | 25 | 26 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| D Baseline - V4 | 0.30 (± 0.501) | 0.21 (± 0.373) | 0.37 (± 0.735) | 0.33 (± 0.462) |
| Mean Severity at V4 | 0.29 (± 0.50) | 0.14 (± 0.17) | 0.15 (± 0.13) | 0.10 (± 0.10) |

| End point values | LAIS® Mites 3,000 UA/Day | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| D Baseline - V4 | 0.27 (± 0.475) | | | |
| Mean Severity at V4 | 0.15 (± 0.09) | | | |

**Statistical analyses**

| Statistical analysis title | Placebo vs. 300 UA |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 300 UA/Day |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.251 |
| Method | t-test, 2-sided |

| Statistical analysis title | Placebo vs. 1,000 UA |
|---|---|
| Comparison groups | Placebo v Lais Mites 1,000 UA/day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.706 |
| Method | t-test, 2-sided |

| Statistical analysis title | Placebo vs. 2,000 UA |
|---|---|

Statistical analysis description:

In summary, the mean relative improvement of the allergic severity S was highest in the 2,000 UA/d-group (66,8%) with $p<0.1$ compared to the placebo group. Additionally, the percentage of patients with improved allergic severity between baseline and V4 was the highest in the treatment group with a daily dose of 2,000 UA. Therefore, the results of this clinical trial clearly demonstrated a general efficacy of the treatment with LAIS® mites tablets of 2,000 UA.

| | |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 2,000 UA/Day |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.093 |
| Method | t-test, 2-sided |

Notes:

[1] - The largest amount of patients having improved in the allergic severity S were in the group having received 2,000 UA/d (88,5%) (Table 14.1.5.1.2.2, Figure 11.3). However, comparing the proportion of patients with improvement of the allergic severity S of the placebo group and the actively treated groups statistical significance was not observed.

| **Statistical analysis title** | Placebo vs. 3,000 UA |
|---|---|
| Comparison groups | LAIS® Mites 3,000 UA/Day v Placebo |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.878 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | Mean Severity at V4 2000 UA |
|---|---|

Statistical analysis description:

The primary efficacy outcome parameter was the change in the allergic severity between baseline and the final visit V4, calculated from the reaction to the CPT

| | |
|---|---|
| Comparison groups | LAIS® Mites 2,000 UA/Day v Placebo v LAIS® Mites 300 UA/Day v Lais Mites 1,000 UA/day v LAIS® Mites 3,000 UA/Day |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | < 0.1 [3] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[2] - In the present study, the analysis of the CPT results by means of S (13) favours the active treatment dose of 2000 UA/day when compared to placebo. Likewise, the percentage of patients having an improved CPT threshold at the final visit is significantly higher in the group treated with 2000 UA/day than in the placebo group.

[3] - the mean S in the four active treatment groups was only one-third to one-half of the mean S in the placebo, favouring the treatment group 2000 UA/day, although not significant (P < 0.1)

## Secondary: CPT Result Score

| End point title | CPT Result Score |
|---|---|

End point description:

As a secondary objective, the changes of the threshold allergen concentration for a positive CPT between baseline and V3 as well as between baseline and V4 were analyzed by means of a CPT result score

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline - v3
Baseline - v4

| End point values | Placebo | LAIS® Mites 300 UA/Day | Lais Mites 1,000 UA/day | LAIS® Mites 2,000 UA/Day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28 | 23 | 25 | 26 |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| D Baseline - V3 | 0.54 (± 0.744) | 0.43 (± 0.728) | 0.64 (± 0.810) | 0.65 (± 0.846) |
| D Baseline - V4 | 0.86 (± 0.932) | 0.78 (± 0.671) | 0.88 (± 0.927) | 1.15 (± 0.675) |

| End point values | LAIS® Mites 3,000 UA/Day | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| D Baseline - V3 | 0.28 (± 0.678) | | | |
| D Baseline - V4 | 0.96 (± 0.735) | | | |

**Statistical analyses**

| Statistical analysis title | CPT baseline - V3 Placebo VS 300UA |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 300 UA/Day |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.908 |
| Method | t-test, 2-sided |

| Statistical analysis title | CPT baseline - V3 Placebo VS 1,000UA |
|---|---|
| Comparison groups | Placebo v Lais Mites 1,000 UA/day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.476 |
| Method | t-test, 2-sided |

| Statistical analysis title | CPT baseline - V3 Placebo VS 2,000UA |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 2,000 UA/Day |

| | |
|---|---|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.496 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | CPT baseline - V3 Placebo VS 3,000UA |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 3,000 UA/Day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.38 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | CPT baseline - V4 Placebo VS 300UA |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 300 UA/Day |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.958 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | CPT baseline - V4 Placebo VS 1,000UA |
|---|---|
| Comparison groups | Placebo v Lais Mites 1,000 UA/day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.76 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | CPT baseline - V4 Placebo VS 3,000UA |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 3,000 UA/Day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.544 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | n° Pt improved CPT Placebo Vs 300UA baseline - V3 |
|---|---|
| Statistical analysis description:<br>number of patients with improved CPT response threshold between actively treated and placebo group | |
| Comparison groups | Placebo v LAIS® Mites 300 UA/Day |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.725 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | n° Pt improved CPT Placebo Vs 1,000UA baseline-V3 |
|---|---|
| Statistical analysis description:<br>number of patients with improved CPT response threshold between actively treated and placebo group | |
| Comparison groups | Placebo v Lais Mites 1,000 UA/day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.344 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | n° Pt improved CPT Placebo Vs 2,000UA baseline-V3 |
|---|---|
| Statistical analysis description:<br>number of patients with improved CPT response threshold between actively treated and placebo group | |
| Comparison groups | Placebo v LAIS® Mites 2,000 UA/Day |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.424 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | n° Pt improved CPT Placebo Vs 3,000UA baseline-V3 |
|---|---|
| Statistical analysis description:<br>number of patients with improved CPT response threshold between actively treated and placebo group | |
| Comparison groups | Placebo v LAIS® Mites 3,000 UA/Day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.835 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | n° Pt improved CPT Placebo Vs 300UA baseline - V4 |
|---|---|

| | |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 300 UA/Day |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.465 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | n° Pt improved CPT Placebo Vs 1,000UA baseline-V4 |
|---|---|
| Comparison groups | Placebo v Lais Mites 1,000 UA/day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.358 |
| Method | t-test, 2-sided |

| **Statistical analysis title** | n° Pt improved CPT Placebo Vs 2,000UA baseline-V4 |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 2,000 UA/Day |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.04 [5] |
| Method | t-test, 2-sided |

Notes:

[4] - The rate of patients who had a worse or unchanged CPT response threshold between baseline and V4 was the lowest (11.5%) in the 2,000 UA/d-group.
[5] - Also, the maximum effect was achieved with a daily dose of 2,000 UA, while higher or lower doses showed less efficacy.

| **Statistical analysis title** | n° Pt improved CPT Placebo Vs 3,000UA baseline-V4 |
|---|---|
| Comparison groups | Placebo v LAIS® Mites 3,000 UA/Day |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.358 [6] |
| Method | t-test, 2-sided |

Notes:

[6] - Also, the maximum effect was achieved with a daily dose of 2,000 UA, while higher or lower doses showed less efficacy.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The treatment lasted from the 3rd quarter 2013 to the 2nd quarter 2014.
The study protocol defined a treatment duration of 84 ± 7 days. Finally, the minimum of treatment duration (V1-V4) was 56 days and the the maximum duration was 105 days.

Adverse event reporting additional description:

Of 131 patients in the safety analysis set, 37 patients (28%) reported a total number of 50 treatment emerged adverse events (AEs), of which one was a serious adverse event (SAE). The SAE was recorded as a mamma carcinoma in one patient of the placebo group. These numbers are identical for both ITT and safety analysis sets.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | nk |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | LAIS® Mites 300 UA/Day |
| Reporting group description: - | |
| Reporting group title | Lais Mites 1,000 UA/day |
| Reporting group description: - | |
| Reporting group title | LAIS® Mites 2,000 UA/Day |
| Reporting group description: - | |
| Reporting group title | LAIS® Mites 3,000 UA/Day |
| Reporting group description: - | |

| Serious adverse events | Placebo | LAIS® Mites 300 UA/Day | Lais Mites 1,000 UA/day |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 23 (0.00%) | 0 / 27 (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) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 23 (0.00%) | 0 / 27 (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 |

| Serious adverse events | LAIS® Mites 2,000 UA/Day | LAIS® Mites 3,000 UA/Day | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Placebo | LAIS® Mites 300 UA/Day | Lais Mites 1,000 UA/day |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 9 / 23 (39.13%) | 6 / 27 (22.22%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer female | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 23 (4.35%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 23 (4.35%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sensation of pressure | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Malaise | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 23 (4.35%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Ear pruritus | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 3 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 23 (4.35%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 23 (4.35%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral discomfort | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 2 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral pruritus | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Swollen tongue | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 23 (4.35%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 23 (4.35%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal swelling | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal blistering | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 4 |
| Sneezing | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Increased upper airway secretion | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 23 (4.35%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 23 (8.70%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 23 (8.70%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 23 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | LAIS® Mites 2,000 UA/Day | LAIS® Mites 3,000 UA/Day | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 26 (26.92%) | 9 / 26 (34.62%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer female | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| General disorders and administration site conditions | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |
| Sensation of pressure | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ear and labyrinth disorders | | | |
| Ear pruritus | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oral discomfort | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |
| Oral pruritus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 26 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Swollen tongue | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oropharyngeal swelling | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 2 / 26 (7.69%) | |
| occurrences (all) | 2 | 4 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |
| Oropharyngeal blistering | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Wheezing | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sneezing | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 26 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Increased upper airway secretion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 26 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Throat irritation | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 26 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 2 / 26 (7.69%) | |
| occurrences (all) | 0 | 2 | |
| Acute sinusitis | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | 3 / 26 (11.54%) | |
| occurrences (all) | 3 | 3 | |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences (all) | 0 | 1 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 January 2014 | In the initial version of the study protocol (version 2.0), it was specified that the specific CAP-RAST results to co-allergens had to be less than the CAP-RAST result to mite allergens (the difference had to be ≥ 1) and the results of the skin prick test against co-allergens had to be less than the result of the skin prick test against mite allergens. Allergy against mugwort, alternaria and ambrosia were regarded as exclusion criteria.<br>The final study protocol version 4.1 provided that patients with co-sensitizations to aero-allergens like grass or rye, could be included into the trial irrespective of the skin prick test results. Patients with co-sensitizations against perennial allergens like cat or dog dander could also be included irrespective of the skin prick test results, as long as they were not regularly exposed to these allergens and therefore show no symptoms.<br>Allergy against mugwort, ambrosia and alternaria did not represent an exclusion criterion according to this new version of the study protocol. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/27068870