



Clinical trial results:

Efficacy and Safety of sublingual immunotherapy with Allergoid LAIS Birch tablets for patients with tree pollen-induced allergic rhinoconjunctivitis with or without mild controlled asthma

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-002596-18 |
| Trial protocol | IT |
| Global end of trial date | 30 June 2020 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 07 April 2023 |
| First version publication date | 21 April 2022 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set A correction is needed after data checking. |

Trial information

Trial identification

| | |
|-----------------------|------------------------|
| Sponsor protocol code | Lais-Birch-Alder-18-19 |
|-----------------------|------------------------|

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 | Allergy and Immunology Specialist - Scientific Direction & Clinical Trials, Scientific Direction & Clinical Trials LOFARMA S.p.A. 20143. Milano. Italy, +39 02581981, |
| Scientific contact | Allergy and Immunology Specialist - Scientific Direction & Clinical Trials , Scientific Direction & Clinical Trials LOFARMA S.p.A. 20143. Milano. Italy, +39 02581981, |

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 | 30 July 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the efficacy and safety of tablet-based SLIT with the allergoid LAIS Birch tablets compared to placebo in patients with tree pollen-induced allergic rhinoconjunctivitis with or without mild asthma.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles which have their origin in the Declaration of Helsinki,, protocol, Guideline for Good Clinical Practice (GCP) CPMP/ICH/135/95 as well as the requirements of national drug and data protection.

Investigators informed trial participants prior to their inclusion in the study about the nature of the trial, of its aims, of the methods and means to be used, and of the estimated duration of the study. All patients were informed of the possible risks linked with administration of the products and of the possible effects which to his/her knowledge might occur. Patients were allowed to ask question. Written informed consent forms were signed by patients prior to their enrolment in the clinical trial, name filled in and personally dated by the patient.

The Patient Information and the Informed Consent Form was previously approved by the local Ethics Committee. Two copies per patient were provided to the sites and both were signed by the Investigator and the patient. One copy of the written Patient Informed Consent Form and of Patient Information Form was handed out to the patient. One copy was kept with the Investigator.

All patients were informed that they had the right to withdraw from the study at any time without prejudicing future medical care.

Background therapy:

The assumption of Rescue Medications was expected as needed.

Escalation scheme for their intake is the following:

Step 1 Loratadine (oral) and/or Levocabastine (eyedrops) 1 x 10 mg 2 x 1 drop per eye

Step 2 Beclomethasone(nasal) 1 x 0,05 mg /side nose

Step 3 Prednisone (oral) 5 mg

The assumption of Rescue Medications was reported on the patient diary.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 November 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 6 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 116 |
| Worldwide total number of subjects | 116 |
| EEA total number of subjects | 116 |

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) | 109 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Territory: Italy

The total number of patients were recruited and screened for inclusion and exclusion criteria.

Pre-assignment

Screening details:

88 patients were randomized. 6 patients for both groups didn't complete the study: 1 protocol deviation, 4 adverse event non -fatal and 1 consent withdrawn by subject for verum group and 1 physician decision, 1 adverse event, non-fatal, 1 consent withdrawn by subject and 3 lost to follow-up for placebo . Finally 76 patients finished the study

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 116 |
| Number of subjects completed | 88 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 3 |
| Reason: Number of subjects | screening failure: 21 |
| Reason: Number of subjects | site suspended: 4 |

Period 1

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

Blinding implementation details:

Sealed envelopes have been provided to the investigators. The sealed envelopes have been returned to the sponsor at the end of the study. CRO and Sponsor were blinded at treatments as the Investigators. A copy of the list of randomization codes was kept at the CRO.

The sealed envelopes would be opened only in case of any patient-related event that requires unblinding even if knowledge of treatment may influence gement of this event.

The opened envelope should be signed and adated on the top.

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | LAIS® Birch/Alder |

Arm description:

Treatment group 1 (1,000 UA): Patients receiving sublingual immunotherapy with monomeric allergoids of tree pollen extract (one tablet of 1,000 UA once daily) pre-/co-seasonally and standard rescue therapy with antisympomatic medication during the tree pollen season.

| | |
|--|--------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LAIS® Birch/Alder sublingual tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Sublingual tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

Every patient received 1 tablet of IMP immediately after the randomization, waiting in the Center, for at least 60 minutes, in order to be assisted in case of some allergic drug reaction. The tablet was placed under the tongue and retained until its complete dissolution, i.e. 1 or 2 minutes before swallowing.

The patients were instructed to assume a tablet of treatment every day, without food, until the End of Study (Visit 5).

The assumption of the treatment was reported on a patient diary.

| | |
|---|-------------------|
| Arm title | Placebo |
| Arm description: | |
| Treatment group 2 (placebo): Patients receiving sublingual placebo preparation (one tablet once daily) pre-/co-seasonally and standard rescue therapy with anti-symptomatic medication during the tree pollen season. | |
| The study medication was provided in form of identical containers of the LAIS® Birch/Alder tablets. All containers or content were identical in shape, size, weight, color, taste, and smell to ensure blinding. | |
| 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:

Every patient received 1 tablet of Placebo immediately after the randomization, waiting in the Center, for at least 60 minutes, in order to be assisted in case of some allergic drug reaction. The tablet was placed under the tongue and retained until its complete dissolution, i.e. 1 or 2 minutes before swallowing.

The patients were instructed to assume a tablet of treatment every day, without food, until the End of Study (Visit 5).

The assumption of the treatment was reported on a patient diary.

| Number of subjects in period 1^[1] | LAIS® Birch/Alder | Placebo |
|---|-------------------|---------|
| Started | 42 | 46 |
| Completed | 36 | 40 |
| Not completed | 6 | 6 |
| Consent withdrawn by subject | 1 | 1 |
| Physician decision | - | 1 |
| Adverse event, non-fatal | 4 | 1 |
| Lost to follow-up | - | 3 |
| Protocol deviation | 1 | - |

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: Worldwide number enrolled correspond to screened subjects. In subjects in the baseline period are the assigned subjects.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Tree pollen |
|-----------------------|-------------|

Reporting group description: -

| Reporting group values | Tree pollen | Total | |
|------------------------|-------------|-------|--|
| Number of subjects | 88 | 88 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-75) | 88 | 88 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 47.9 | | |
| standard deviation | ± 12.2 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 57 | 57 | |
| Male | 31 | 31 | |

Subject analysis sets

| | |
|----------------------------|--------------|
| Subject analysis set title | Per-Protocol |
|----------------------------|--------------|

| | |
|---------------------------|--------------|
| 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 two successive missing single evaluations of the rhinoconjunctivitis total symptom score (RTSS) is acceptable; the total number of missing single evaluations of the RTSS must not exceed 25% over the entire course of the peak pollen period. The missing values are established by using the Last Value Option as described in the next section. An additional confirmatory analysis of the primary efficacy variable will be performed on this subgroup.

| | |
|----------------------------|-----|
| Subject analysis set title | FAS |
|----------------------------|-----|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The Full Analysis Set (FAS) incorporated all patients who received at least 1 dose of investigational treatment and filled -in diary data during the peak period.

| | |
|----------------------------|-----|
| Subject analysis set title | SES |
|----------------------------|-----|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The safety evaluation set (SES) comprised all randomized subjects having received at least 1 dose of the investigational product.

| Reporting group values | Per-Protocol | FAS | SES |
|------------------------|--------------|-----|-----|
| Number of subjects | 43 | 73 | 88 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-75) | 43 | 73 | 88 |

| | | | |
|--------------------|---|---|--------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | 47.9 |
| standard deviation | ± | ± | ± 12.2 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | | | 57 |
| Male | | | 31 |

End points

End points reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | LAIS® Birch/Alder |
|-----------------------|-------------------|

Reporting group description:

Treatment group 1 (1,000 UA): Patients receiving sublingual immunotherapy with monomeric allergoids of tree pollen extract (one tablet of 1,000 UA once daily) pre-/co-seasonally and standard rescue therapy with antisymptomatic medication during the tree pollen season.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Treatment group 2 (placebo): Patients receiving sublingual placebo preparation (one tablet once daily) pre-/co-seasonally and standard rescue therapy with anti-symptomatic medication during the tree pollen season.

The study medication was provided in form of identical containers of the LAIS® Birch/Alder tablets. All containers or content were identical in shape, size, weight, color, taste, and smell to ensure blinding.

| | |
|----------------------------|--------------|
| Subject analysis set title | Per-Protocol |
|----------------------------|--------------|

| | |
|---------------------------|--------------|
| 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 two successive missing single evaluations of the rhinoconjunctivitis total symptom score (RTSS) is acceptable; the total number of missing single evaluations of the RTSS must not exceed 25% over the entire course of the peak pollen period. The missing values are established by using the Last Value Option as described in the next section. An additional confirmatory analysis of the primary efficacy variable will be performed on this subgroup.

| | |
|----------------------------|-----|
| Subject analysis set title | FAS |
|----------------------------|-----|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The Full Analysis Set (FAS) incorporated all patients who received at least 1 dose of investigational treatment and filled -in diary data during the peak period.

| | |
|----------------------------|-----|
| Subject analysis set title | SES |
|----------------------------|-----|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The safety evaluation set (SES) comprised all randomized subjects having received at least 1 dose of the investigational product.

Primary: TCS 14D Efficacy

| | |
|-----------------|------------------|
| End point title | TCS 14D Efficacy |
|-----------------|------------------|

End point description:

Assessment of the efficacy of the sublingual immunotherapy with the allergoid LAIS® Birch tablets on a "Total Combined Score (TCS)" for the consecutive 14-days of maximum pollen load within the peak of the birch pollen season taking into account:

- a "Rhinoconjunctivitis Total Symptom Score (RTSS)", of the six rhinoconjunctivitis symptoms sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes (as sum of the symptoms daily evaluated by the patient, using a score from 0 to 3, divided by the number of symptoms (6):

- a "Total Rescue Medication Score (TRMS)", taking into account the use of oral antihistamines, Levocabastine eye drops and nasal corticosteroids, oral corticosteroids (according to the following point values for scoring use:

Step 1 Loratadine (oral, 1 x 10 mg) and/or Levocabastine (eyedrops, 2 x 1 drop per eye), score 1

Step 2 Beclomethasone (nasal, 1 x 0,05 mg /side nose), score 2

Step 3 Prednisone (oral, 5 mg), score 3.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

for the consecutive 14-days of maximum pollen load within the peak of the birch pollen season

| End point values | LAIS® Birch/Alder | Placebo | FAS | |
|---|---------------------------|---------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 36 | 40 | 73 | |
| Units: Score | | | | |
| arithmetic mean (confidence interval 95%) | 1.0579 (0.8447 to 1.2710) | 1.7240 (1.5574 to 1.8905) | -0.70 (-0.94 to -0.40) | |

Statistical analyses

| Statistical analysis title | TCS Difference (LAIS – Placebo) between means |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Values as determined by the patients in their diary are combined to a daily TCS by adding up RTSS and TRMS.

An analysis of variance for repeated measures. The multiple test procedure was applied based on the between-subject factor p-values obtained from this model. Treatment specific means were estimated from this model as least squares means. Statistical tests were set on two-side and at the 5% level of significance.

| | |
|---|-----------------------------|
| Comparison groups | LAIS® Birch/Alder v Placebo |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | ANOVA |

Notes:

[1] - Compared to placebo, the treatment group had lower symptom score RTSS (P=0.0150) and made less use of rescue medication (P<0.0001). TCS values were significantly lower in the treatment group compared to placebo (P<0.0001).

Primary: Subgroup TCS 14D

| | |
|-----------------|------------------|
| End point title | Subgroup TCS 14D |
|-----------------|------------------|

End point description:

In this study a subpopulation analysis on the primary endpoint was carried out by excluding from the overall patients those belonging to the Genoa hospital. The analyzes was motivated by virtue of the fact that Liguria, like Southern Italy and the islands macro area, never reached the peak pollen (from 15 to 22 maximum level reached for 7 consecutive days. The endpoints evaluated was the TCS.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

consecutive 14-days of maximum pollen load within the peak of the birch pollen season

| End point values | LAIS® Birch/Alder | Placebo | | |
|---|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 34 | | |
| Units: Score | | | | |
| arithmetic mean (confidence interval 95%) | 1.0180 (0.8015 to 1.2345) | 1.7375 (1.5621 to 1.8989) | | |

Statistical analyses

| Statistical analysis title | TCS 14D Difference (LAIS – Placebo) between means |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

In this study a subpopulation analysis on the primary endpoint was carried out by excluding from the overall patients those belonging to the Genoa hospital. The analyzes was motivated by virtue of the fact that Liguria, like Southern Italy and the islands macro area, never reached the peak pollen (from 15 to 22 maximum level reached for 7 consecutive days. The endpoints evaluated were the TCS, the RTSS and the TRMS.

| | |
|---|-----------------------------|
| Comparison groups | LAIS® Birch/Alder v Placebo |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [2] |
| Method | ANOVA |

Notes:

[2] - Compared to placebo, the treatment group had lower symptom score RTSS (P<0.0001) and made less use of rescue medication (P=0.0027). TCS values were significantly lower in the treatment group compared to placebo (P<0.0001)

Primary: TCS 30D Efficacy

| | |
|-----------------|------------------|
| End point title | TCS 30D Efficacy |
|-----------------|------------------|

End point description:

Total Combined Score (TCS) both at 30-day peak in birch pollen season The analysis on modified ITT (FAS) was based on all investigational centers.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30-day peak in birch pollen season.

| End point values | LAIS® Birch/Alder | Placebo | FAS | |
|---|---------------------------|---------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 36 | 40 | 76 | |
| Units: Score | | | | |
| arithmetic mean (confidence interval 95%) | 0.9109 (0.7430 to 1.0788) | 1.5121 (1.3629 to 1.6614) | -0.60 (-0.83 to -0.38) | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | TCS 30D compare between groups |
| Comparison groups | LAIS® Birch/Alder v Placebo |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | ANOVA |

Notes:

[3] - As to TCS for the birch pollen peak at 30 days, these values were significantly lower in the treatment group compared to placebo (difference in mean -0.60; L95%CI, U95%CI: -0.83 to -0.38. P<0.0001)

Secondary: TCS 60D efficacy

| | |
|-----------------|------------------|
| End point title | TCS 60D efficacy |
|-----------------|------------------|

End point description:

Total Combined Score (TCS) for the overall 60-day birch pollen season of (March to April). The analysis on ITT was based on all investigational centers.

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

End point timeframe:

overall 60-day birch pollen season (March to April)

| End point values | LAIS® Birch/Alder | Placebo | FAS | |
|---|---------------------------|---------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 36 | 40 | 76 | |
| Units: Score | | | | |
| arithmetic mean (confidence interval 95%) | 0.9486 (0.8803 to 1.0168) | 1.1936 (1.1373 to 1.2499) | -0.25 (-0.33 to -0.16) | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | TCS 60D compare between groups |
| Comparison groups | LAIS® Birch/Alder v Placebo |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | ANOVA |

Notes:

[4] - TCS values referring to the overall 60-day birch pollen season (March to April) were significantly lower in the treatment group compared to the placebo group (difference in mean -0.25; L95%CI, U95% CI: -0.33 to -0.16. P<0.0001)

Secondary: Well Days 60D

| | |
|-----------------|---------------|
| End point title | Well Days 60D |
|-----------------|---------------|

End point description:

The "well days", being defined as days of the entire tree pollen season with a maximum symptom score of 2 and no rescue medication use according to Dahl (2006) and Durham (2006). The number of "well days" will be compared between arms fitting a generalized linear model as defined by Nelder and

Wedderburn. To this aim, a Poisson distribution for the related variable will be assumed as well as the default natural logarithm link function. The two-sided 95% confidence interval will be calculated according the Poisson distribution assumed for the statistical test;

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 60 days of the entire birch pollen season | |

| End point values | LAIS® Birch/Alder | Placebo | | |
|---|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 40 | | |
| Units: Score | | | | |
| arithmetic mean (confidence interval 95%) | 39.0000 (37.0641 to 41.0370) | 34.4500 (32.6783 to 36.3178) | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | WII Days60D between group means |
| Comparison groups | LAIS® Birch/Alder v Placebo |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.0009 |
| Method | t-test, 2-sided |

Notes:

[5] - The "well days", being defined as "days of the entire birch pollen season with a maximum symptom score of 2 and no rescue medication", were significantly higher than the placebo.(difference in mean 4.55; L95%CI, U95%CI:; 2.52 to 6.58. P=0.0009).

Secondary: Global Evaluation

| | |
|-----------------|-------------------|
| End point title | Global Evaluation |
|-----------------|-------------------|

End point description:

A global evaluation carried out by the patient for the total tree pollen season

The following scale will be used:

0 = worsening

1 = no change

2 = slight to moderate improvement

3 = good to excellent improvement

the global evaluation was processed as described for the individual symptom scores.

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

End point timeframe:

total tree pollen season

| End point values | LAIS® Birch/Alder | Placebo | FAS | |
|---|---------------------------|---------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 29 | 35 | | |
| Units: Score | | | | |
| arithmetic mean (confidence interval 95%) | 2.7241 (2.4187 to 3.0296) | 2.6857 (2.4077 to 2.9638) | 0.04 (-0.37 to 0.45) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Global Evaluation Difference Between Group means |
| Comparison groups | LAIS® Birch/Alder v Placebo |
| Number of subjects included in analysis | 64 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.8531 |
| Method | t-test, 2-sided |

Notes:

[6] - The Treatment Satisfaction was significantly higher in the treatment group compared to placebo (difference in mean 0.04; L95%CI, U95%CI: -0.37 to 0.45. P=0.8531)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

To document the safety of the treatment by the physical examinations, the safety laboratory data and the description of the adverse events (frequency, intensity, severity and duration of adverse events) during the treatment with LAIS® Birch/Alder tablets

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Lais birch alder |
|-----------------------|------------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Lais birch alder | Placebo | |
|---|--|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 46 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | Additional description: symptoms of pulmonary embolism with severe intensity, no change of therapy has been done, patient was hospitalized, the event was resolved | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 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 | Lais birch alder | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 42 (50.00%) | 16 / 46 (34.78%) | |
| Vascular disorders | | | |
| Essential hypertension | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oedema mucosal | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 46 (4.35%) | |
| occurrences (all) | 1 | 2 | |
| Immune system disorders | | | |
| Oral allergy syndrome | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Throat irritation | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 46 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Rhinitis allergic | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cough | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 46 (2.17%) | |
| occurrences (all) | 2 | 1 | |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal discomfort | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 46 (2.17%) | |
| occurrences (all) | 1 | 2 | |
| Nasal inflammation | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 46 (4.35%) | |
| occurrences (all) | 0 | 2 | |
| Asthma | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 3 / 46 (6.52%) | |
| occurrences (all) | 0 | 4 | |
| nasal obstruction | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 3 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 4 | |
| Status asthmaticus | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |

| | | | |
|---|---------------------|---------------------|--|
| Myocarditis subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 0 / 46 (0.00%) 0 | |
| Nervous system disorders | | | |
| Somnolence subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 3 | 0 / 46 (0.00%) 0 | |
| Aphonia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 0 / 46 (0.00%) 0 | |
| Epilepsy subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 0 / 46 (0.00%) 0 | |
| Headache subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | 2 / 46 (4.35%) 2 | |
| Migraine with aura subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 0 / 46 (0.00%) 0 | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 2 | 0 / 46 (0.00%) 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 46 (2.17%) 1 | |
| Eye disorders | | | |
| Conjunctivitis allergic subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 46 (2.17%) 1 | |
| Eye pruritus subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 46 (2.17%) 1 | |
| Lacrimation increased subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 46 (2.17%) 1 | |
| Gastrointestinal disorders | | | |

| | | | |
|--|----------------|----------------|--|
| Abdominal mass | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 46 (4.35%) | |
| occurrences (all) | 0 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 46 (2.17%) | |
| occurrences (all) | 2 | 1 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 46 (2.17%) | |
| occurrences (all) | 1 | 1 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 46 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Rash erythematous | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rosacea | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 46 (4.35%) | |
| occurrences (all) | 1 | 2 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Rheumatic fever | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Gingival abscess | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 46 (2.17%) | |
| occurrences (all) | 1 | 1 | |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 46 (2.17%) | |
| occurrences (all) | 1 | 1 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 46 (2.17%) | |
| occurrences (all) | 4 | 1 | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral pharyngitis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 46 (2.17%) | |
| occurrences (all) | 1 | 1 | |
| Conjunctivitis | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 46 (4.35%) | |
| occurrences (all) | 0 | 3 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 46 (4.35%) | |
| occurrences (all) | 0 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 04 October 2018 | Version 2.00: Is based on Version 1.00 and was created as part of the response to the "Letter of Content-Related Deficiencies" by the AIFA (28 SEP 2018) |
| 15 March 2019 | Version 3.00: Changes due to recovery of the trial and its execution in the 2019/2020 pollinic season. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported