



## Clinical trial results:

**A prospective, multicenter, double-blind, placebo-controlled randomized study to assess efficacy and safety of LAIS® Grass pollen tablets in patients with seasonal grass pollen-induced allergic rhinoconjunctivitis**  
**Summary**

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2019-001532-65    |
| Trial protocol           | IT                |
| Global end of trial date | 24 September 2020 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 22 April 2022 |
| First version publication date | 22 April 2022 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | LGT03-19 |
|-----------------------|----------|

#### 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               | CRO, CD PHARMA GROUP SRL, +39 02581981, |
| Scientific contact           | CRO, CD PHARMA GROUP SRL, +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                       | 15 December 2021  |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 24 September 2020 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy and safety of tablet-based sublingual immunotherapy (SLIT) with the monomeric allergoid LAIS® Grass tablets compared to placebo in patients with grass pollen-induced allergic rhinoconjunctivitis with or without controlled asthma.

Protection of trial subjects:

The study was conducted in accordance with the protocol, under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP).

With the exception of those drugs listed among non-permitted medications participants were allowed to use any concomitant medication (necessary for the treatment of preexisting concomitant pathologies or for intercurrent diseases), that did not interfere with the study evaluation parameters.

Decongestants (oral, nasal spray, drops) were allowed for symptom relief for short term needs (i.e. to provide relief after the TNPT, in occurrence of a cold or flu).

Asthma medications not influencing the study outcomes (i.e. inhaled corticosteroids, short-acting and long acting beta-2-agonists) were admitted to maintain asthma control along the whole trial duration.

Background therapy:

Standard rescue therapy with anti-symptomatic medication during the grass pollen season: Desloratadine (oral), Levocabastine (eyedrops), Mometasone furoate (nasal) 50 mcg, Prednisone (oral) 5 mg.

The score was assigned as follows:

Score = 1: use of oral/ocular antihistamines;

Score = 2: use of nasal corticosteroids;

Score = 3: use of oral corticosteroids.

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

For adolescents included in the trial, parents were responsible for the management of rescue medications and careful clinical diary completion

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 18 November 2019 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 9 Months         |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 98 |
| Worldwide total number of subjects   | 98        |
| EEA total number of subjects         | 98        |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                 | 17 |
| Adults (18-64 years)                      | 81 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Territory: Italy

The total number of participants in each treatment group was recruited and screened for inclusion and exclusion criteria. Recruitment was greatly slower than planned. Limitation of a reduced sample size was due to the premature termination of the study enrolment.

### Pre-assignment

Screening details:

Patients with a confirmed diagnosis of moderate to severe ARC based on medical history underwent a skin prick test and nasal allergen provocation challenge with Grass pollen extract and serum specific IgE (>0.7 kU/l) for Phl p1-5.

### Period 1

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

Blinding implementation details:

The randomization was implemented in eCRF according to an algorithm generated and validated by CINECA. A paper copy of the complete randomization list was placed in a sealed envelope and retained in a secure, fire-proof room with restricted-access at the CRO. The MED.ID was then printed on the label of the medication prescribed by the randomization list. Breaking of this code was only valid under certain circumstances

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | Placebo - Group 1 |

Arm description:

Sublingual placebo preparation (one tablet once daily) for about 7-9 months pre-/coseasonally (from at least 16 weeks before the expected start of the pollen season to 30 June 2020) and standard rescue therapy with anti-symptomatic medication during the grass pollen season. Placebo and verum preparation were identical except of the active ingredient

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

Dosage and administration details:

Independent of the assigned treatment group, the patients ingested one sublingual tablet per day. The first dose had to be self-administered at the randomization visit (V1) at study site and patient was monitored for at least 30 minutes after tablet intake.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Lais Grass - Group 2 |
|------------------|----------------------|

Arm description:

Sublingual immunotherapy with grass pollen extract (one tablet of 1,000 UA once daily) for about 7-9 months pre-/co-seasonally (from at least 16 weeks before the expected start of the pollen season to 30 June 2020) and standard rescue therapy with anti-symptomatic medication during the grass pollen season.

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

|  |                               |
|--|-------------------------------|
| Investigational medicinal product name | Lais Grass sublingual tablets |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Sublingual tablet             |
| Routes of administration               | Sublingual use                |

Dosage and administration details:

Independent of the assigned treatment group, the patients ingested one sublingual tablet per day. The first dose had to be self-administered at the randomization visit (V1) at study site and patient was monitored for at least 30 minutes after tablet intake.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Placebo - Group 1 | Lais Grass - Group 2 |
|---|-------------------|----------------------|
| Started   | 47                | 47                   |
| Completed   | 38                | 37                   |
| Not completed                                       | 9                 | 10                   |
| No evaluable post-randomization data                | 9                 | 10                   |

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: Overall, 98 patients were randomised to receive the assigned treatment: 49 patients were randomised to receive LAIS grass and 49 patients were randomised to receive placebo. Two randomised patients in each treatment group did not receive at least one dose of the study medication and were therefore excluded. The study comprised 94 patients overall (95.9% of randomized), 47 (95.9%) in each treatment group.

## Baseline characteristics

### Reporting groups

|   |              |
|---|--------------|
| Reporting group title   | Grass pollen |
| Reporting group description:  |              |
| Female or male patients aged 12–64 years with a history of at least 2 years of grass pollen induced allergic rhinoconjunctivitis (ARC) with or without seasonal controlled allergic asthma; moderate/severe (interfering with usual daily activities or sleep) ARC defined according to ARIA guidelines; positive clinical history of grass pollen allergy; compliance and ability of the patient to complete a patient's diary for self-evaluation of the symptoms and antisymptomatic medication and treatment compliance; signed and dated patient's informed consent. |              |

| Reporting group values   | Grass pollen | Total |  |
|--|--------------|-------|--|
| Number of subjects   | 94           | 94    |  |
| Age categorical  |              |       |  |
| Female or male patients aged 12–64 years   |              |       |  |
| Units: Subjects  |              |       |  |
| 12-64 years  | 94           | 94    |  |
| Age continuous   |              |       |  |
| Units: years   |              |       |  |
| median   | 28           |       |  |
| full range (min-max)   | 12 to 54     | -     |  |
| Gender categorical   |              |       |  |
| The demographic characteristics were similar in the two groups, except for a slightly higher proportion of males in the LAIS group than in the placebo group |              |       |  |
| Units: Subjects  |              |       |  |
| Female   | 45           | 45    |  |
| Male   | 49           | 49    |  |

### Subject analysis sets

|  |                            |
|--|----------------------------|
| Subject analysis set title   | ITT population             |
| Subject analysis set type  | Intention-to-treat         |
| Subject analysis set description:  |                            |
| Randomized patients who met key eligibility and evaluability criteria. This dataset was defined by the availability of evaluable post-randomization data for at least one of the primary efficacy variables (dSS and dMS during the 14-days of highest pollen load)<br>The analysis of ITT population was based on 37 subjects in the treatment group and 38 in the control group from all investigational centers. All p-values reported refer to the analysis of variance.   |                            |
| Subject analysis set title   | Per-Protocol-Set (PP-set)  |
| Subject analysis set type  | Per protocol               |
| Subject analysis set description:  |                            |
| All patients in the FAS with no major protocol deviations, which would impact the primary efficacy (defined as 'critical'), and delivering a sufficient data set of measurements and evaluations of the primary efficacy variables: a maximum of two subsequent missing single evaluations of the rhinoconjunctivitis symptom score (dSS) was acceptable. The total number of missing single evaluations of the dSS had not to exceed 25 % over the entire course of the 14-days of highest pollen load within the peaks of the grass pollen season.<br>The analysis was based on 31 subjects in the treatment group and 32 in the control group from all investigational centers. |                            |
| Subject analysis set title   | Safety evaluation set- SES |
| Subject analysis set type  | Safety analysis            |

Subject analysis set description:

The safety evaluation set (SES), which included all randomized patients who received at least one dose of the study medication. This population was used for all safety analyses.

The analysis was based on 47 subjects in the treatment group and 47 in the control group from all investigational centers.

| Reporting group values   | ITT population | Per-Protocol-Set (PP-set) | Safety evaluation set- SES |
|--|----------------|---------------------------|----------------------------|
| Number of subjects   | 75             | 63                        | 94                         |
| Age categorical  |                |                           |                            |
| Female or male patients aged 12–64 years   |                |                           |                            |
| Units: Subjects  |                |                           |                            |
| 12-64 years  | 75             | 63                        | 94                         |
| Age continuous   |                |                           |                            |
| Units: years   |                |                           |                            |
| median   |                |                           |                            |
| full range (min-max)   | 12 to 54       | 12 to 54                  | 12 to 54                   |
| Gender categorical   |                |                           |                            |
| The demographic characteristics were similar in the two groups, except for a slightly higher proportion of males in the LAIS group than in the placebo group |                |                           |                            |
| Units: Subjects  |                |                           |                            |
| Female   | 34             | 31                        | 45                         |
| Male   | 41             | 32                        | 49                         |

## End points

### End points reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Placebo - Group 1 |
|-----------------------|-------------------|

Reporting group description:

Sublingual placebo preparation (one tablet once daily) for about 7-9 months pre-/coseasonally (from at least 16 weeks before the expected start of the pollen season to 30 June 2020) and standard rescue therapy with anti-symptomatic medication during the grass pollen season. Placebo and verum preparation were identical except of the active ingredient

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Lais Grass - Group 2 |
|-----------------------|----------------------|

Reporting group description:

Sublingual immunotherapy with grass pollen extract (one tablet of 1,000 UA once daily) for about 7-9 months pre-/co-seasonally (from at least 16 weeks before the expected start of the pollen season to 30 June 2020) and standard rescue therapy with anti-symptomatic medication during the grass pollen season.

|                            |                |
|----------------------------|----------------|
| Subject analysis set title | ITT population |
|----------------------------|----------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Randomized patients who met key eligibility and evaluability criteria. This dataset was defined by the availability of evaluable post-randomization data for at least one of the primary efficacy variables (dSS and dMS during the 14-days of highest pollen load)

The analysis of ITT population was based on 37 subjects in the treatment group and 38 in the control group from all investigational centers. All p-values reported refer to the analysis of variance.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Per-Protocol-Set (PP-set) |
|----------------------------|---------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

All patients in the FAS with no major protocol deviations, which would impact the primary efficacy (defined as 'critical'), and delivering a sufficient data set of measurements and evaluations of the primary efficacy variables: a maximum of two subsequent missing single evaluations of the rhinoconjunctivitis symptom score (dSS) was acceptable. The total number of missing single evaluations of the dSS had not to exceed 25 % over the entire course of the 14-days of highest pollen load within the peaks of the grass pollen season.

The analysis was based on 31 subjects in the treatment group and 32 in the control group from all investigational centers.

|                            |                            |
|----------------------------|----------------------------|
| Subject analysis set title | Safety evaluation set- SES |
|----------------------------|----------------------------|

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

Subject analysis set description:

The safety evaluation set (SES), which included all randomized patients who received at least one dose of the study medication. This population was used for all safety analyses.

The analysis was based on 47 subjects in the treatment group and 47 in the control group from all investigational centers.

### Primary: CSMS - 14D - Efficacy

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

End point description:

Assessment of the efficacy on the average daily total Combined Symptom-Medication score (CSMS) based on an equal weight of the dSS and dMS (maximum score 3 + 3 = 6) for the 14 days of highest pollen load within the peaks of the grass pollen season taking into account:

- Daily rhinoconjunctivitis total Symptom Score (dSS) of the six rhinoconjunctivitis symptoms over the previous 24 hours, which included itching, sneezing, rhinorrhea, obstruction, ocular itching/grittiness/redness and ocular tearing with scale from 0-3 per symptom (maximum score 18 points / divided by 6 symptoms = 3 points)

- Daily Medication Score (dMS) over the previous 24 hours:

0 = no rescue medication taken

1 = use of antihistamines (oral, ophthalmic, or both);

2 = use of nasal corticosteroids;

3 = use of oral corticosteroids

If more than 1 class of rescue medication was used on a particular day, the highest score was to be

retained for the dMS of that day (maximum score = 3).

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:   |         |
| 14-days of highest pollen load within the peaks of the grass pollen season |         |

| End point values                     | Placebo - Group 1  | Lais Grass - Group 2 |  |  |
|--------------------------------------|--------------------|----------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed          | 38                 | 37                   |  |  |
| Units: score                         |                    |                      |  |  |
| arithmetic mean (standard deviation) | 1.04 ( $\pm$ 1.25) | 0.84 ( $\pm$ 1.10)   |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | LMSs difference (Lais-Placebo)           |
| Statistical analysis description:   |  |
| A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework |  |
| Comparison groups   | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis   | 75                                       |
| Analysis specification  | Pre-specified                            |
| Analysis type   | superiority                              |
| P-value   | = 0.0002 <sup>[1]</sup>                  |
| Method  | Mixed models analysis                    |
| Parameter estimate  | LS Mean Difference                       |
| Confidence interval   |  |
| level   | 95 %                                     |
| sides   | 2-sided                                  |
| lower limit   | -0.44                                    |
| upper limit   | -0.16                                    |

Notes:

[1] - The difference in LMSs was -0.30 (95% CI, -0.44 to -0.16) that corresponds to a difference of -28% relative to placebo, and was statistically significant.

## Secondary: Average CSMS during the peak

|  |                              |
|--|------------------------------|
| End point title                                      | Average CSMS during the peak |
| End point description:                               |                              |
| Average CSMS   |                              |
| End point type                                       | Secondary                    |
| End point timeframe:                                 |                              |
| During the days with $\geq$ 50 pollen/m <sup>3</sup> |                              |

| End point values                     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed          | 38                | 37                   |  |  |
| Units: score                         |                   |                      |  |  |
| arithmetic mean (standard deviation) | 1.02 (± 1.29)     | 0.55 (± 0.96)        |  |  |

## Statistical analyses

| Statistical analysis title   | LMSs difference (Lais-Placebo)           |
|--|--|
| Statistical analysis description:<br>A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework |  |
| Comparison groups  | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis  | 75                                       |
| Analysis specification   | Pre-specified                            |
| Analysis type  | superiority                              |
| P-value  | < 0.0001 [2]                             |
| Method   | Mixed models analysis                    |
| Parameter estimate   | LS Mean Difference                       |
| Confidence interval  |  |
| level  | 95 %                                     |
| sides  | 2-sided                                  |
| lower limit  | -0.58                                    |
| upper limit  | -0.41                                    |

Notes:

[2] - The difference in LMSs was -0.49 (95% CI, -0.58 to -0.41) and was statistically significant (p<0.0001 between groups)

## Secondary: Average CSMS during the entire grass pollen season

| End point title                                    | Average CSMS during the entire grass pollen season |
|--|--|
| End point description:                             |  |
| End point type                                     | Secondary  |
| End point timeframe:<br>entire grass pollen season |  |

| End point values                     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed          | 38                | 37                   |  |  |
| Units: score                         |                   |                      |  |  |
| arithmetic mean (standard deviation) | 0.96 (± 1.25)     | 0.75 (± 1.04)        |  |  |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | LMSs difference (Lais-Placebo)           |
| Statistical analysis description:<br>A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework |  |
| Comparison groups  | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis  | 75                                       |
| Analysis specification   | Pre-specified                            |
| Analysis type  | superiority                              |
| P-value  | < 0.0001 <sup>[3]</sup>                  |
| Method   | Mixed models analysis                    |
| Parameter estimate   | LS Mean Difference                       |
| Confidence interval  |  |
| level  | 95 %                                     |
| sides  | 2-sided                                  |
| lower limit  | -0.33                                    |
| upper limit  | -0.22                                    |

Notes:

[3] - The difference in LMSs was -0.28 (95% CI, -0.33 to -0.22) and was statistically significant (p<0.0001 between groups)

## Secondary: Average dSS -14D

|  |                  |
|--|------------------|
| End point title  | Average dSS -14D |
| End point description:   |                  |
| End point type   | Secondary        |
| End point timeframe:   |                  |
| 14-days of highest pollen load within the peaks of the grass pollen season |                  |

| End point values                     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed          | 38                | 37                   |  |  |
| Units: score                         |                   |                      |  |  |
| arithmetic mean (standard deviation) | 0.47 (± 0.62)     | 0.44 (± 0.61)        |  |  |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | LMSs difference (Lais-Placebo)           |
| Statistical analysis description:<br>A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework |  |
| Comparison groups  | Placebo - Group 1 v Lais Grass - Group 2 |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 75                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.0058 <sup>[4]</sup> |
| Method                                  | Mixed models analysis   |
| Parameter estimate                      | LS Mean Difference      |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -0.16                   |
| upper limit                             | -0.01                   |

Notes:

[4] - The difference in LMSs was -0.08 (95% CI, -0.16 to -0.01) and was statistically significant (p=0.0058 between groups)

## Secondary: Average dSS during the peak

|                 |                             |
|-----------------|-----------------------------|
| End point title | Average dSS during the peak |
|-----------------|-----------------------------|

End point description:

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

End point timeframe:

During the days with  $\geq 50$  pollen/m<sup>3</sup>

| End point values                     | Placebo - Group 1  | Lais Grass - Group 2 |  |  |
|--------------------------------------|--------------------|----------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed          | 38                 | 37                   |  |  |
| Units: score                         |                    |                      |  |  |
| arithmetic mean (standard deviation) | 0.49 ( $\pm$ 0.67) | 0.30 ( $\pm$ 0.52)   |  |  |

## Statistical analyses

|                            |                                |
|----------------------------|--------------------------------|
| Statistical analysis title | LMSs difference (Lais-Placebo) |
|----------------------------|--------------------------------|

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

|   |  |
|---|--|
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.0001 <sup>[5]</sup>                  |
| Method                                  | Mixed models analysis                    |
| Parameter estimate                      | LS Mean Difference                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.26   |
| upper limit         | -0.17   |

Notes:

[5] - The difference in LMSs was -0.21 (95% CI, -0.26 to -0.17) and was statistically significant ( $p < 0.0001$  between groups)

### Secondary: Average dSS during the entire grass pollen season

|                            |   |
|----------------------------|---|
| End point title            | Average dSS during the entire grass pollen season |
| End point description:     |   |
| End point type             | Secondary   |
| End point timeframe:       |   |
| entire grass pollen season |   |

| End point values                     | Placebo - Group 1  | Lais Grass - Group 2 |  |  |
|--------------------------------------|--------------------|----------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed          | 38                 | 37                   |  |  |
| Units: score                         |                    |                      |  |  |
| arithmetic mean (standard deviation) | 0.48 ( $\pm$ 0.62) | 0.41 ( $\pm$ 0.59)   |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | LMSs difference (Lais-Placebo)           |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | $< 0.0001$ [6]                           |
| Method                                  | Mixed models analysis                    |
| Parameter estimate                      | LS Mean Difference                       |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.13                                    |
| upper limit                             | -0.08                                    |

Notes:

[6] - The difference in LMSs was -0.11 (95% CI, -0.13 to -0.08) and was statistically significant ( $p < 0.0001$  between groups)

### Secondary: Average dMS - 14D

|                        |                   |
|------------------------|-------------------|
| End point title        | Average dMS - 14D |
| End point description: |                   |

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| 14-days of highest pollen load within the peaks of the grass pollen season |           |

| End point values                     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed          | 38                | 37                   |  |  |
| Units: score                         |                   |                      |  |  |
| arithmetic mean (standard deviation) | 0.57 (± 0.83)     | 0.40 (± 0.63)        |  |  |

## Statistical analyses

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | LMSs difference (Lais-Placebo) |
|-----------------------------------|--------------------------------|

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

|   |  |
|---|--|
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.0004 <sup>[7]</sup>                  |
| Method                                  | Mixed models analysis                    |
| Parameter estimate                      | LS Mean Difference                       |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.3                                     |
| upper limit                             | -0.12                                    |

Notes:

[7] - The difference in LMSs was -0.21 (95% CI, -0.30 to -0.12) and was statistically significant (p=0.0004 between groups)

## Secondary: Average dMS during the peak

|                 |                             |
|-----------------|-----------------------------|
| End point title | Average dMS during the peak |
|-----------------|-----------------------------|

End point description:

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

End point timeframe:

during the days with ≥ 50 pollen/m<sup>3</sup>

| End point values                     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed          | 38                | 37                   |  |  |
| Units: score                         |                   |                      |  |  |
| arithmetic mean (standard deviation) | 0.52 (± 0.82)     | 0.25 (± 0.65)        |  |  |

## Statistical analyses

| Statistical analysis title | LMSs difference (Lais-Placebo) |
|----------------------------|--------------------------------|
|----------------------------|--------------------------------|

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

|   |  |
|---|--|
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.0001 <sup>[8]</sup>                  |
| Method                                  | Mixed models analysis                    |
| Parameter estimate                      | LS Mean Difference                       |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.34                                    |
| upper limit                             | -0.23                                    |

Notes:

[8] - The difference in LMSs was -0.28 (95% CI, -0.34 to -0.23) and was statistically significant (p<0.0001 between groups)

## Secondary: Average dMS during the entire grass pollen season

|                 |   |
|-----------------|---|
| End point title | Average dMS during the entire grass pollen season |
|-----------------|---|

End point description:

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

End point timeframe:

entire grass pollen season

| End point values                     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed          | 38                | 37                   |  |  |
| Units: score                         |                   |                      |  |  |
| arithmetic mean (standard deviation) | 0.48 (± 0.80)     | 0.34 (± 0.65)        |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | LMSs difference (Lais-Placebo)           |
| Statistical analysis description:   |  |
| A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework |  |
| Comparison groups   | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis   | 75                                       |
| Analysis specification  | Pre-specified                            |
| Analysis type   | superiority                              |
| P-value   | < 0.0001 <sup>[9]</sup>                  |
| Method  | Mixed models analysis                    |
| Parameter estimate  | LS Mean Difference                       |
| Confidence interval   |  |
| level   | 95 %                                     |

Notes:

[9] - The difference in LMSs was -0.17 (95% CI, -0.21 to -0.13) and was statistically significant (p<0.0001 between groups)

## Secondary: Average 6 individual symptom scores of dSS - 14D

|   |  |
|---|--|
| <b>End point title</b>  | Average 6 individual symptom scores of dSS - 14D |
| End point description:  |  |
| Each six individual symptom score of dSS were analyzed using a general linear mixed model having the same independent variable side structure as described for CSMS to reach the primary objective (treatment group as fixed effect, pollen region as random effect). |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| 14-days of highest pollen load within the peaks of the grass pollen season  |  |

| <b>End point values</b>                    | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--|-------------------|----------------------|--|--|
| Subject group type                         | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed                | 38                | 37                   |  |  |
| Units: score                               |                   |                      |  |  |
| arithmetic mean (standard deviation)       |                   |                      |  |  |
| Nasal itching mean 14D                     | 0.54 (± 0.87)     | 0.43 (± 0.70)        |  |  |
| Rhinorrhoea mean 14D                       | 0.49 (± 0.79)     | 0.47 (± 0.80)        |  |  |
| Nasal obstruction 14D                      | 0.56 (± 0.83)     | 0.50 (± 0.78)        |  |  |
| Sneezing mean 14D                          | 0.62 (± 0.80)     | 0.59 (± 0.79)        |  |  |
| Ocular itching/grittiness/redness mean 14D | 0.39 (± 0.73)     | 0.42 (± 0.73)        |  |  |
| Ocular tearing                             | 0.23 (± 0.60)     | 0.23 (± 0.64)        |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Nasal itching mean 14D                   |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.6145 <sup>[10]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[10] - The difference between groups was not statistically significant

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rhinorrhoea mean 14D                     |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.5905 <sup>[11]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[11] - The difference between groups was not statistically significant.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Nasal obstruction mean 14D               |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.7007 <sup>[12]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[12] - The difference between groups was not statistically significant.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Sneezing mean 14D                        |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.829 <sup>[13]</sup>                  |
| Method                                  | Mixed models analysis                    |

Notes:

[13] - The difference between groups was not statistically significant.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Ocular itching/grittiness/redness mean 14D |
|-----------------------------------|--|

|   |  |
|---|--|
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.5564 <sup>[14]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[14] - The difference between groups was not statistically significant.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Ocular tearing mean 14D                  |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.4247 <sup>[15]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[15] - The difference between groups was not statistically significant.

### Secondary: Average 6 individual symptom scores of dSS - during the peak

|                 |  |
|-----------------|--|
| End point title | Average 6 individual symptom scores of dSS - during the peak |
|-----------------|--|

End point description:

Average six individual symptom scores of the dSS: during the days with  $\geq 50$  pollen/m<sup>3</sup>

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

End point timeframe:

during the days with  $\geq 50$  pollen/m<sup>3</sup>

| End point values                            | Placebo - Group 1  | Lais Grass - Group 2 |  |  |
|---|--------------------|----------------------|--|--|
| Subject group type                          | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed                 | 38                 | 37                   |  |  |
| Units: score                                |                    |                      |  |  |
| arithmetic mean (standard deviation)        |                    |                      |  |  |
| Nasal itching mean peak                     | 0.59 ( $\pm$ 0.88) | 0.32 ( $\pm$ 0.62)   |  |  |
| Rhinorrhoea mean peak                       | 0.53 ( $\pm$ 0.84) | 0.30 ( $\pm$ 0.65)   |  |  |
| Nasal obstruction mean peak                 | 0.57 ( $\pm$ 0.90) | 0.35 ( $\pm$ 0.66)   |  |  |
| Sneezing mean peak                          | 0.60 ( $\pm$ 0.78) | 0.41 ( $\pm$ 0.69)   |  |  |
| Ocular itching/grittiness/redness mean peak | 0.42 ( $\pm$ 0.76) | 0.29 ( $\pm$ 0.60)   |  |  |
| Ocular tearing mean peak                    | 0.25 ( $\pm$ 0.62) | 0.15 ( $\pm$ 0.49)   |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Nasal itching mean peak                  |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.5722 <sup>[16]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[16] - The difference between groups was not statistically significant.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rhinorrhoea mean peak                    |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.6146 <sup>[17]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[17] - The difference between groups was not statistically significant.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Nasal obstruction mean peak              |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.6852 <sup>[18]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[18] - The difference between groups was not statistically significant.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Sneezing mean peak                       |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.7894 <sup>[19]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[19] - The difference between groups was not statistically significant.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ocular itching/grittiness/redness mean peak |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2    |
| Number of subjects included in analysis | 75  |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | superiority                                 |
| P-value                                 | = 0.7014 <sup>[20]</sup>                    |
| Method                                  | Mixed models analysis                       |

Notes:

[20] - The difference between groups was not statistically significant.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Ocular tearing mean peak                 |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.3058 <sup>[21]</sup>                 |
| Method                                  | Mixed models analysis                    |

Notes:

[21] - The difference between groups was not statistically significant.

### **Secondary: Average 6 individual symptom scores of dSS - during entire grass pollen season**

|   |  |
|---|--|
| End point title   | Average 6 individual symptom scores of dSS - during entire grass pollen season |
| End point description:<br>Average six individual symptom scores of the dSS: over the entire grass pollen season until the study end |  |
| End point type  | Secondary  |
| End point timeframe:<br>entire grass pollen season  |  |

| <b>End point values</b>                         | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|---|-------------------|----------------------|--|--|
| Subject group type                              | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed                     | 38                | 37                   |  |  |
| Units: score                                    |                   |                      |  |  |
| arithmetic mean (standard deviation)            |                   |                      |  |  |
| Nasal itching mean entire grass season          | 0.51 (± 0.79)     | 0.43 (± 0.71)        |  |  |
| Rhinorrhoea mean entire grass season            | 0.51 (± 0.79)     | 0.46 (± 0.78)        |  |  |
| Nasal obstruction mean entire grass season      | 0.54 (± 0.85)     | 0.47 (± 0.75)        |  |  |
| Sneezing mean entire grass season               | 0.62 (± 0.83)     | 0.57 (± 0.80)        |  |  |
| Ocular itching/grittiness/redness mean - season | 0.44 (± 0.79)     | 0.35 (± 0.67)        |  |  |
| Ocular tearing mean entire grass season         | 0.24 (± 0.58)     | 0.19 (± 0.52)        |  |  |

### **Statistical analyses**

No statistical analyses for this end point

### **Secondary: well days**

|   |           |
|---|-----------|
| End point title   | well days |
| End point description:<br>The "well days", being defined as days of the entire grass pollen season with a maximum ARC |           |

symptom score of 2 and no rescue medication use according to Dahl (Dahl et al., 2006) and Durham (Durham et al., 2006) (verum vs. placebo)

|                            |           |
|----------------------------|-----------|
| End point type             | Secondary |
| End point timeframe:       |           |
| entire grass pollen season |           |

| End point values                     | Placebo - Group 1    | Lais Grass - Group 2 |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 38                   | 37                   |  |  |
| Units: score                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 67.33 ( $\pm$ 21.68) | 69.56 ( $\pm$ 22.89) |  |  |

## Statistical analyses

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | LMSs difference (Lais-Placebo) |
|-----------------------------------|--------------------------------|

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

|   |  |
|---|--|
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.1702 <sup>[22]</sup>                 |
| Method                                  | Mixed models analysis                    |
| Parameter estimate                      | LS Mean Difference                       |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.02                                    |
| upper limit                             | 0.11                                     |

Notes:

[22] - The difference in LMSs was 0.04 (95% CI, -0.02 to 0.11) and was not statistically significant (p = 0.1702 between groups)

## Secondary: VAS score

|                 |           |
|-----------------|-----------|
| End point title | VAS score |
|-----------------|-----------|

End point description:

The VAS on 'nasal symptoms' was included as a simple, reliable, and fully validated subjective psychometric response scale in adults for symptoms in many indication areas to evaluate disease severity including AR and was, therefore, recommended by the EAACI. In this study, VAS was determined during the control visits to show differences between the treatment groups. the VAS score was analysed as described for the primary endpoints (i.e. applying the hierarchical testing procedure in case of statistically significant result for CSMS). The VAS score was the distance (in millimetres) from the left end of the line to the point where the patient's mark crossed the line

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

End point timeframe:  
entire grass season

| End point values                     | Placebo -<br>Group 1 | Lais Grass -<br>Group 2 |  |  |
|--------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed          | 38                   | 37                      |  |  |
| Units: millimetre(s)                 |                      |                         |  |  |
| arithmetic mean (standard deviation) | 19.50 (±<br>21.40)   | 22.14 (±<br>23.96)      |  |  |

### Statistical analyses

| Statistical analysis title              | Vas score                                |
|---|--|
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.5331 <sup>[23]</sup>                 |
| Method                                  | Mixed models analysis                    |
| Parameter estimate                      | LS Mean Difference                       |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -4.01                                    |
| upper limit                             | 7.69                                     |

Notes:

[23] - The difference between the groups was 1.84 mm (95% CI, -4.01 to 7.69 mm) and was not statistically significant (p = 0.5331)

### Secondary: Global evaluation for the entire grass pollen season

|  |  |
|--|--|
| End point title  | Global evaluation for the entire grass pollen season |
| End point description:   |  |
| A global evaluation was carried out by the patient for the entire grass pollen season, to evaluate the Treatment Satisfaction (verum vs placebo) with the scale: 0 = unsatisfied, 1 = little satisfied, 2 = satisfied, 3 = very satisfied. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| entire grass pollen season   |  |

| End point values                     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed          | 38                | 37                   |  |  |
| Units: score                         |                   |                      |  |  |
| arithmetic mean (standard deviation) | 3.13 (± 0.58)     | 2.95 (± 0.66)        |  |  |

## Statistical analyses

| Statistical analysis title              | Global evaluation                        |
|---|--|
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2 |
| Number of subjects included in analysis | 75                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.2186 <sup>[24]</sup>                 |
| Method                                  | Mixed models analysis                    |
| Parameter estimate                      | LS Mean Difference                       |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.47                                    |
| upper limit                             | 0.1                                      |

Notes:

[24] - The difference between the groups was - 0.19 (95% CI, -0.47 to 0.10) and was not statistically significant (p= 0.2186)

## Secondary: Global evaluation comparison of the current season versus the previous year

|                 |   |
|-----------------|---|
| End point title | Global evaluation comparison of the current season versus the previous year |
|-----------------|---|

End point description:

A global evaluation carried out by the patient in the overall comparison of the current grass pollen season versus the previous season (previous year); in order to permit a computation of a responder analysis, this aspect was investigated at the end of the treatment period, by asking subjects the following question "Compared to your symptoms in previous grass seasons, how have you felt overall in this grass pollen season?" with possible response categories: 0 = worsening; 1 = no change; 2 = slight to moderate improvement; 3 = good to excellent improvement

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

End point timeframe:

entire grass pollen season

| End point values                     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
|--------------------------------------|-------------------|----------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed          | 38                | 37                   |  |  |
| Units: score                         |                   |                      |  |  |
| arithmetic mean (standard deviation) | 3.03 (± 0.69)     | 2.95 (± 0.87)        |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Global evaluation comparison between seasons |
| Comparison groups                       | Placebo - Group 1 v Lais Grass - Group 2     |
| Number of subjects included in analysis | 75   |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.7184 <sup>[25]</sup>                     |
| Method                                  | Mixed models analysis                        |
| Parameter estimate                      | LS Mean Difference                           |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | -0.28  |
| upper limit                             | 0.44   |

Notes:

[25] - The difference between the groups was 0.08 (95% CI - 0.28 to 0.44) and was not statistically significant.

## Secondary: Excellence of rhinoconjunctivitis control during entire grass pollen season

|   |   |
|---|---|
| End point title   | Excellence of rhinoconjunctivitis control during entire grass pollen season |
| End point description:  |   |
| Excellence of rhinoconjunctivitis control during the entire grass pollen season = more than 50% well days in the grass pollen season; |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Entire grass pollen season  |   |

|                             |                   |                      |  |  |
|-----------------------------|-------------------|----------------------|--|--|
| <b>End point values</b>     | Placebo - Group 1 | Lais Grass - Group 2 |  |  |
| Subject group type          | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed | 38                | 37                   |  |  |
| Units: %                    |                   |                      |  |  |
| number (not applicable)     | 78.9              | 78.4                 |  |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Excellence of rhinoconjunctivitis control |
| Comparison groups                 | Lais Grass - Group 2 v Placebo - Group 1  |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 75                       |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.9688 <sup>[26]</sup> |
| Method                                  | Mixed models analysis    |
| Parameter estimate                      | LS Mean Difference       |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -1.31                    |
| upper limit                             | 1.26                     |

Notes:

[26] - The difference between groups was -0.02% (95% CI, -1.31 to 1.26%) and was not statistically significant (p= 0.9688 between groups).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 1 to end of follow up (observation period between V1 and V5)

Adverse event reporting additional description:

The patient diary for the recording of the Adverse Events was dispensed to patients. All treatment emergent adverse events (TEAEs) were assigned to a Preferred Term (PT) and classified by primary System Organ Class (SOC) according to the MedDRA.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 22     |

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Placebo - Group 1 |
|-----------------------|-------------------|

Reporting group description:

groups of subjects to whom placebo was administered

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Lais Grass - Group 2 |
|-----------------------|----------------------|

Reporting group description:

groups of subjects to whom Lais sublingual tablets (verum) was administered

| Serious adverse events                            | Placebo - Group 1  | Lais Grass - Group 2 |  |
|---|--|----------------------|--|
| Total subjects affected by serious adverse events |  |                      |  |
| subjects affected / exposed                       | 0 / 47 (0.00%)   | 1 / 47 (2.13%)       |  |
| number of deaths (all causes)                     | 0  | 0                    |  |
| number of deaths resulting from adverse events    | 0  | 0                    |  |
| Respiratory, thoracic and mediastinal disorders   |  |                      |  |
| Pneumothorax spontaneous                          | Additional description: Patient was a male subject aged 17 years . On 02 Mar 2000, the patient had pneumothorax spontaneous, which was of moderate intensity and required hospitalization. Treatment with IMP was discontinued and the event resolved on 15 Mar 2000 |                      |  |
| subjects affected / exposed                       | 0 / 47 (0.00%)   | 1 / 47 (2.13%)       |  |
| occurrences causally related to treatment / all   | 0 / 0  | 0 / 1                |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0                |  |

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

| Non-serious adverse events                            | Placebo - Group 1 | Lais Grass - Group 2 |  |
|---|-------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                   |                      |  |
| subjects affected / exposed                           | 27 / 47 (57.45%)  | 29 / 47 (61.70%)     |  |
| Vascular disorders                                    |                   |                      |  |

|  |   |  |  |
|--|---|--|--|
| Hypotension<br>subjects affected / exposed<br>occurrences (all)  | 0 / 47 (0.00%)<br>0   | 1 / 47 (2.13%)<br>1  |  |
| General disorders and administration site conditions<br>Application site pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 0 / 47 (0.00%)<br>0<br><br>0 / 47 (0.00%)<br>0  | 1 / 47 (2.13%)<br>1<br><br>1 / 47 (2.13%)<br>1   |  |
| Immune system disorders<br>Allergy to arthropod sting<br>subjects affected / exposed<br>occurrences (all)<br><br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 1 / 47 (2.13%)<br>1<br><br>1 / 47 (2.13%)<br>1  | 0 / 47 (0.00%)<br>0<br><br>1 / 47 (2.13%)<br>1   |  |
| Reproductive system and breast disorders<br>Premenstrual pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 47 (0.00%)<br>0   | 1 / 47 (2.13%)<br>1  |  |
| Respiratory, thoracic and mediastinal disorders<br>Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)<br><br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Sneezing<br>subjects affected / exposed<br>occurrences (all)<br><br>Throat irritation<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain | 9 / 47 (19.15%)<br>9<br><br>3 / 47 (6.38%)<br>3<br><br>1 / 47 (2.13%)<br>1<br><br>2 / 47 (4.26%)<br>2 | 8 / 47 (17.02%)<br>8<br><br>5 / 47 (10.64%)<br>5<br><br>4 / 47 (8.51%)<br>4<br><br>0 / 47 (0.00%)<br>0 |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                    | 1 / 47 (2.13%) | 2 / 47 (4.26%) |  |
| occurrences (all)                              | 1              | 2              |  |
| Epistaxis                                      |                |                |  |
| subjects affected / exposed                    | 0 / 47 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Nasal inflammation                             |                |                |  |
| subjects affected / exposed                    | 2 / 47 (4.26%) | 0 / 47 (0.00%) |  |
| occurrences (all)                              | 2              | 0              |  |
| Nasal discomfort                               |                |                |  |
| subjects affected / exposed                    | 0 / 47 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Nasal obstruction                              |                |                |  |
| subjects affected / exposed                    | 0 / 47 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Asthma   |                |                |  |
| subjects affected / exposed                    | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Apnoea   |                |                |  |
| subjects affected / exposed                    | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Dysphonia                                      |                |                |  |
| subjects affected / exposed                    | 3 / 47 (6.38%) | 0 / 47 (0.00%) |  |
| occurrences (all)                              | 3              | 0              |  |
| Rhinorrhoea                                    |                |                |  |
| subjects affected / exposed                    | 1 / 47 (2.13%) | 1 / 47 (2.13%) |  |
| occurrences (all)                              | 1              | 1              |  |
| Investigations                                 |                |                |  |
| Body temperature increased                     |                |                |  |
| subjects affected / exposed                    | 0 / 47 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Influenza virus test negative                  |                |                |  |
| subjects affected / exposed                    | 0 / 47 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Injury, poisoning and procedural complications |                |                |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 47 (0.00%)<br>0  | 1 / 47 (2.13%)<br>1  |  |
| Arthropod sting<br>subjects affected / exposed<br>occurrences (all)   | 1 / 47 (2.13%)<br>1  | 0 / 47 (0.00%)<br>0  |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 47 (2.13%)<br>1  | 0 / 47 (0.00%)<br>0  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 47 (8.51%)<br>4  | 8 / 47 (17.02%)<br>8 |  |
| Migraine without aura<br>subjects affected / exposed<br>occurrences (all)                                   | 4 / 47 (8.51%)<br>4  | 3 / 47 (6.38%)<br>3  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 47 (0.00%)<br>0  | 1 / 47 (2.13%)<br>1  |  |
| Neurological symptom<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 47 (0.00%)<br>0  | 1 / 47 (2.13%)<br>1  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 47 (0.00%)<br>0  | 1 / 47 (2.13%)<br>1  |  |
| Blood and lymphatic system disorders<br>Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all) | 1 / 47 (2.13%)<br>1  | 0 / 47 (0.00%)<br>0  |  |
| Eye disorders<br>Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all)                | 5 / 47 (10.64%)<br>5 | 3 / 47 (6.38%)<br>3  |  |
| Eyelid irritation<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 47 (2.13%)<br>1  | 0 / 47 (0.00%)<br>0  |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Eye pruritus<br>subjects affected / exposed<br>occurrences (all)         | 1 / 47 (2.13%)<br>1 | 0 / 47 (0.00%)<br>0 |  |
| Gastrointestinal disorders   |                     |                     |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 3 / 47 (6.38%)<br>3 | 0 / 47 (0.00%)<br>0 |  |
| Oral pruritus<br>subjects affected / exposed<br>occurrences (all)        | 2 / 47 (4.26%)<br>2 | 1 / 47 (2.13%)<br>1 |  |
| Anal fissure<br>subjects affected / exposed<br>occurrences (all)         | 1 / 47 (2.13%)<br>1 | 0 / 47 (0.00%)<br>0 |  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)            | 1 / 47 (2.13%)<br>1 | 0 / 47 (0.00%)<br>0 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 1 / 47 (2.13%)<br>1 | 1 / 47 (2.13%)<br>1 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 2 / 47 (4.26%)<br>2 | 0 / 47 (0.00%)<br>0 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 47 (2.13%)<br>1 | 0 / 47 (0.00%)<br>0 |  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 1 / 47 (2.13%)<br>1 | 0 / 47 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders                                   |                     |                     |  |
| Rash erythematous<br>subjects affected / exposed<br>occurrences (all)    | 2 / 47 (4.26%)<br>2 | 0 / 47 (0.00%)<br>0 |  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)               | 0 / 47 (0.00%)<br>0 | 1 / 47 (2.13%)<br>1 |  |
| Urticaria  |                     |                     |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Pruritus  |                |                |  |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 1 / 47 (2.13%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Dermatitis contact                              |                |                |  |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Renal and urinary disorders                     |                |                |  |
| Nephrolithiasis                                 |                |                |  |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Back pain                                       |                |                |  |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 3 / 47 (6.38%) |  |
| occurrences (all)                               | 1              | 3              |  |
| Neck pain                                       |                |                |  |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Musculoskeletal pain                            |                |                |  |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 1 / 47 (2.13%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Musculoskeletal stiffness                       |                |                |  |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Infections and infestations                     |                |                |  |
| Influenza                                       |                |                |  |
| subjects affected / exposed                     | 4 / 47 (8.51%) | 4 / 47 (8.51%) |  |
| occurrences (all)                               | 4              | 4              |  |
| Conjunctivitis                                  |                |                |  |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 1 / 47 (2.13%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Pharyngitis                                     |                |                |  |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 1 / 47 (2.13%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Cystitis  |                |                |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Bacterial rhinitis          |                |                |  |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Bronchitis                  |                |                |  |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Acute sinusitis             |                |                |  |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment   |
|--------------|---|
| 12 July 2019 | <p>The protocol initially submitted to the Italian Health Authority ('Agenzia Italiana del Farmaco', AIFA) was that named Version 1.3 of 23 April 2019. Then the IEC of the coordinating centre evaluated the study before AIFA and required changes and integrations that led to Protocol Version 1.4 of 12 July 2019, which was re-submitted to AIFA.</p> <p>Changes from Protocol Version 1.3 of 23 April 2019 to Version 1.4 of 12 July 2019</p> <ul style="list-style-type: none"><li>- Addition of information on the stepwise management of rescue medication;</li><li>- Change of time of waiting for the next incremental dosage in case of a negative TNPT result;</li><li>- Addition of specifications on the management of asthma exacerbations and on the management of treatments for asthma.</li></ul> |
| 23 July 2019 | <p>AIFA examined Protocol Version 1.4 of 12 July 2019 and required further changes and integrations that led to Protocol Version 1.5 of 23 July 2019</p> <p>Changes from Protocol Version 1.4 to Version 1.5</p> <ul style="list-style-type: none"><li>- Addition and specification of the secondary objective of the study;</li><li>- Addition of phone contact control visits;</li><li>- Addition of further specifications on the stepwise management of rescue medication;</li><li>- Addition of a clarification on highly effective method of contraception as inclusion criterion;</li><li>- Change from urine to serum pregnancy test at inclusion in the study;</li><li>- Minor formal changes</li></ul>  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported