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