Clinical trial results:
A double-blind, placebo-controlled dose-escalation study of carbamylated monomeric tree pollen drops in patients with a history of allergic rhinoconjunctivitis.

Summary

EudraCT number	2017-003063-34
Trial protocol	DE
Global end of trial date	06 November 2018

Results information

Result version number	v1 (current)
This version publication date	04 August 2021
First version publication date	04 August 2021

Trial information

Trial identification

Sponsor protocol code	GSDL_DE_17

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	Coordinating Investigator, CRI - Clinical Research International Ltd. , 0049 1722056230, management@cri-ltd.de
Scientific contact	Coordinating Investigator, CRI - Clinical Research International Ltd. , 0049 1722056230, management@cri-ltd.de

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	06 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2018
Global end of trial reached?	Yes
Global end of trial date	06 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to assess the safety and clinical tolerability of Lais® Frühblüher sublingual drops in patients with birch pollen-induced allergic rhinoconjunctivitis.

Protection of trial subjects:

To guarantee the patients' safety during the treatment with Lais® Frühblüher, a Data Safety Monitoring Board (DSMB) was established, consisting of two independent experienced physicians in the field of allergy and one statistician. The DSMB was also supported by the Medical Monitor of the trial. The chairman of the DSMB checked the eCRF for information regarding treatment and (serious) AE reports, findings were discussed during weekly telephone conferences (during treatment phase), respectively.

Background therapy:

The following rescue medication was provided; its use was restricted to the relief of local reactions induced by the investigational product and/or to relieve rhinoconjunctivitis symptoms:
Fexofenadine tablets 120 mg

Evidence for comparator:

placebo comparation

Actual start date of recruitment	18 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	37
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 5 German sites (6 sites planned but 5 initiated). Forty-eight patients were planned. Thirty-seven patients were screened. Of those, 21 were randomized. Two patients dropped-out (Physician Decision and Consent Withdrawal) First enrolment on January 18th, 2018. Last completed on June 21st, 2018.

Pre-assignment

Screening details:

Female or male patients aged 18 - 64 years. Having the diagnosis of allergy based on the following criteria: medical history of moderate to severe allergic rhinoconjunctivitis for birch pollen for at least 2 years, a positive skin prick test, specific IgE against birch pollen and positive response to conjunctival provocation test.

Period 1

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

Blinding implementation details:

During the dose escalation phase the investigational product doses were increased incrementally to reach the patient's individual maximum tolerable dosage. The maintenance dose of 50,000 UA daily was self-administered by the patient from day 9 up to day 71.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo solution was supplied in vials containing 9.0 mL of aqueous solutions containing sodium chloride, sodium hydrogen bicarbonate, glycerol and purified water having the same concentration as in the investigational product vial.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Sublingual use

Dosage and administration details:

Same amounts of drops and same administration schedule of the IMP has been followed in order to maintain blinding condition.

Arm title	LAIS® Frühblüher sublingual drops

Arm description:

LAIS® Frühblüher: At day 1: ultra-rush schedule of three doses to reach 17,000UA. From Day 2 to day 3: single dose of 10,000UA. At day 4: two doses to reach 40,000UA. From day 5 to Day 7: single dose of 25,00UA. Dose of 50,000 UA was self-administered daily by the patient from day 9 up to day 71.

Arm type	Experimental
Investigational medicinal product name	LAIS® Frühblüher sublingual drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Sublingual use

Dosage and administration details:

At day 1: ultra-rush schedule of three doses to reach 17,000UA. From Day 2 to day 3: single dose of 10,000UA. At day 4: two doses to reach 40,000UA. From day 5 to Day 7: single dose of 25,00UA. Dose of 50,000 UA was self-administered daily by the patient from day 9 up to day 71. A dose adjustment of the investigational product was foreseen for safety reasons under particular conditions and following specific rules.

Number of subjects in period 1[1]	Placebo	LAIS® Frühblüher sublingual drops
Started	6	15
Completed	6	13
Not completed	0	2
Consent withdrawn by subject	-	1
Physician decision	-	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: Altogether, 37 patients were screened during the study. 15 patients did not meet the inclusion/non-inclusion criteria and one patient withdrew consent after the screening visit. Therefore, 21 patients were randomised and received study medication. 6 patients were treated with placebo and 15 patients with
Lais® Frühblüher.

Baseline characteristics

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo solution was supplied in vials containing 9.0 mL of aqueous solutions containing sodium chloride, sodium hydrogen bicarbonate, glycerol and purified water having the same concentration as in the investigational product vial.

Reporting group title	LAIS® Frühblüher sublingual drops

Reporting group description:

LAIS® Frühblüher: At day 1: ultra-rush schedule of three doses to reach 17,000UA. From Day 2 to day 3: single dose of 10,000UA. At day 4: two doses to reach 40,000UA. From day 5 to Day 7: single dose of 25,00UA. Dose of 50,000 UA was self-administered daily by the patient from day 9 up to day 71.

Reporting group values	Placebo	LAIS® Frühblüher sublingual drops	Total
Number of subjects	6	15	21
Age categorical			
Adults 18-64 years			
Units: Subjects			
Adults (18-64 years)	6	15	21
Age continuous			
Units: years			
arithmetic mean	40.66	36	
standard deviation	± 15.12	± 13.08	-
Gender categorical			
Male and Female			
Units: Subjects			
Female	1	9	10
Male	5	6	11

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat (ITT) efficacy population (ITT-set) included all randomised patients who received at least one dose of study treatment and had a record of primary safety measures on at least one day of the observation period.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol population includes all evaluable patients in the ITT population without any major protocol deviations interfering with the evaluation of the secondary endpoint.

Subject analysis set title	S-Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population includes all randomised patients
who received at least one dose of study treatment

Reporting group values	ITT	PP	S-Set
Number of subjects	21	9	21
Age categorical			
Adults 18-64 years			
Units: Subjects			
Adults (18-64 years)	21	9	21
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical			
Male and Female			
Units: Subjects			
Female	10	2	10
Male	11	7	11

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo solution was supplied in vials containing 9.0 mL of aqueous solutions containing sodium chloride, sodium hydrogen bicarbonate, glycerol and purified water having the same concentration as in the investigational product vial.

Reporting group title	LAIS® Frühblüher sublingual drops

Reporting group description:

LAIS® Frühblüher: At day 1: ultra-rush schedule of three doses to reach 17,000UA. From Day 2 to day 3: single dose of 10,000UA. At day 4: two doses to reach 40,000UA. From day 5 to Day 7: single dose of 25,00UA. Dose of 50,000 UA was self-administered daily by the patient from day 9 up to day 71.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat (ITT) efficacy population (ITT-set) included all randomised patients who received at least one dose of study treatment and had a record of primary safety measures on at least one day of the observation period.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol population includes all evaluable patients in the ITT population without any major protocol deviations interfering with the evaluation of the secondary endpoint.

Subject analysis set title	S-Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population includes all randomised patients
who received at least one dose of study treatment

Primary: Safety and clinical tolerability

End point title	Safety and clinical tolerability

End point description:

The safety and clinical tolerability of Lais® Frühblüher was assessed by the following variables:
• Solicited adverse events including local reactions at the administration site
(oropharyngeal and gastrointestinal symptoms) and systemic allergic reactions
after investigational medicinal product administration.
• Unsolicited adverse events
• Proportion of patients who reached the maximum dose
• Use of rescue medication during treatment phase
• Physical examinations and vital signs
• Laboratory investigations on blood samples (blood count, renal and liver
function parameters)
• Pulmonary functions for asthmatic patients

End point type	Primary

End point timeframe:

from January 18th, 2018 to June 21st , 2018

End point values	Placebo	LAIS® Frühblüher sublingual drops	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	15	21	
Units: number	6	15	21	

Statistical analyses

Statistical analysis title	Local and Systemic Reaction

Statistical analysis description:

Local reactions and systemic allergic reactions after medicinal product administration were considered as Solicited Adverse Events. Local reactions during updosing visits were documented in two patients. In total, six systemic allergic reactions with two symptoms have been reported by one actively treated patient (6.7% of actively treated patients). No systemic allergic reaction grade II, III or IV according to AWMF classification was reported.

Comparison groups	Placebo v LAIS® Frühblüher sublingual drops
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.5212
Method	t-test, 2-sided
Parameter estimate	Odds ratio (OR)
Point estimate	2.7576
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.12
upper limit	61.16
Variability estimate	Standard deviation

Notes:

[1] - Local reactions and systemic allergic reactions after study drug administration

Secondary: Efficacy

End point title	Efficacy

End point description:

Analysis of the secondary safety endpoints unsolicited AEs, vital sign (Summary statistics for vital signs (n, mean, SD, median, minimum, maximum, percentiles, and 95% confidence intervals) and physical examinations, safety laboratory variables, pulmonary function and use of rescue medication during treatment phase was performed in the safety population.
Moreover, Immunogenicuty and Conjunctival provocation test.

End point type	Secondary

End point timeframe:

from January 18th, 2018 to June 21st , 2018

End point values	Placebo	LAIS® Frühblüher sublingual drops	ITT	S-Set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	15	21	21
Units: Frequency	6	15	21	21

Statistical analyses

Statistical analysis title	Immunogenicity IgE

Statistical analysis description:

Immunogenicity analyses:
Exploratory variables corresponding to the immunogenicity endpoints (at V1 and V6) compared the two treatment groups (ITT-set) regarding production of birch pollen specific IgE, (at V1 and V6 and change from V1). All patients had to have a birch pollen specific IgE serum level ≥ 0.7 kU/L at screening visit V1 to meet the inclusion criteria.

Comparison groups	LAIS® Frühblüher sublingual drops v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.032 [3]
Method	t-test, 2-sided

Notes:

[2] - At V1, mean concentration of specific IgE was higher in the placebo group (22.322 kU/L) than in the active group (19.971 kU/L). In the placebo group, the mean concentration increased at V6 to 26.153 kU/L, while in the verum group increased at V6 to 45.369 kU/L. Placebo ΔV6-V1 was 3.832 kU/L and active ΔV6-V1 was 25.398 kU/L.This increase resulted in a statistical significance p=0.001. The mean CAP class increased from 3.33 to 3.60 in placebo group and from 3.50to 4.21 in active group.
[3] - Placebo ΔV6-V1 was 3.832 kU/L and Lais® Frühblüher ΔV6-V1 was 25.398 kU/L.

Statistical analysis title	Immunogenicity IgA

Statistical analysis description:

Immunogenicity analyses:
Exploratory variables corresponding to the immunogenicity endpoints (at V1 and V6) compared the two treatment groups (ITT-set) regarding: Production of birch pollen specific IgA (at V1 and V6 and change from V1).

Comparison groups	LAIS® Frühblüher sublingual drops v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.157
Method	t-test, 2-sided

Notes:

[4] - At V1, the mean concentration of sIgA was 1.080 mg/L in the placebo and 1.013 mg/L in the verum group. At V6, sIgA concentrations were identical in both groups with 1.000 mg/L, showing no relevant changes in sIgA levels from V1 to V6 (Placebo ΔV6-V1: -0.080, Lais® Frühblüher ΔV6-V1: -0.013, Figure 11-4).

Statistical analysis title	Immunogenicity IgG4

Statistical analysis description:

Exploratory variables corresponding to the immunogenicity endpoints (at V1 and V6) compared the two treatment groups (ITT-set) regarding: Production of birch pollen specific IgG4 (at V1 and V6 and change from V1).

Comparison groups	LAIS® Frühblüher sublingual drops v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.482 [6]
Method	t-test, 1-sided

Notes:

[5] - At V1, the mean concentration of sIgA was 1.080 mg/L in the placebo and 1.013 mg/L in the verum group. At V6, sIgA concentrations were identical in both groups with 1.000 mg/L, showing no relevant changes in sIgA levels from V1 to V6 (Placebo ΔV6-V1: -0.080, Lais® Frühblüher ΔV6-V1: -0.013).
[6] - no relevant changes in sIgA levels from V1 to V6 : Placebo ΔV6-V1: -0.080, Lais® Frühblüher ΔV6-V1: -0.013

Statistical analysis title	Immunogenicity ratio

Statistical analysis description:

Exploratory variables corresponding to the immunogenicity endpoints (at V1 and V6) compared the two treatment groups (ITT-set) regarding: IgG4/IgE ratio. Summary statistics (n, mean, SD, median, minimum, maximum, percentiles, and 95% confidence intervals) were presented for each group.

Comparison groups	Placebo v LAIS® Frühblüher sublingual drops
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	other[7]
P-value	= 0.741 [8]
Method	t-test, 2-sided

Notes:

[7] - At V1, the sIgG4/sIgE ratio was 0.110 in the placebo and 0.033 in the Lais® Frühblüher group. At V6, the ratio was nearly unchanged in the placebo group (0.112) while in the actively treated group, the ratio decreased by 41% to 0.0196. In the placebo group,
[8] - ΔV6-V1 was 0.0019 and -0.0136 in the actively treated group

Statistical analysis title	CTP (Reactivuty Score)

Statistical analysis description:

This score was used to analyse the improvement of CPT-reactivity between V1 and V6 and to compare the improvement between actively treated and placebo patients using the following scoring system:
-2 = Worsen. of two allergen coc. steps
-1 = Worsen. of one allergen coc. steps
0 = No change
+1 = Improvement of one allergen coc. steps
+2 = Improvement of two allergen coc. steps
+3 = Improvement of three allergen coc. steps
+4 = Improvement of four allergen coc. steps.

Comparison groups	LAIS® Frühblüher sublingual drops v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.45
Method	t-test, 2-sided

Notes:

[9] - The mean CPT reactivity score (RS) at V1 was lower in the placebo group than in the Verum group. However, due to the high standard deviations in both groups, this difference may not be meaningful. ΔV6-V1 in the placebo group was 0.00 and -0.23 in the actively treated group. The change in the actively treated group showed a trend towards improvement (p=0.083). The change from V1 to V6 is higher in the verum group than in the placebo group.

Statistical analysis title	CPT (Composite Score)

Statistical analysis description:

The composite score (CS) is a combination of all severity scores at a corresponding visit and was calculated for each patient at each visit .
The clinical effects of the IMP were assessed using the Composite Score (CS) (Astvatsatourov et al. 2014). The CS was calculated for each patient at each visit. Summary statistics (n, mean, SD, median, minimum, maximum, percentiles, and 95% confidence intervals) were presented for each group.

Comparison groups	LAIS® Frühblüher sublingual drops v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.0314 [11]
Method	t-test, 2-sided

Notes:

[10] - The mean CS of the placebo group was only slightly reduced (by 7.5%) from the screening visit (0.40) to the last visit (0.37), while the CS of the Lais® Frühblüher group decreased by 19.5% from the screening visit (0.41) to the last visit (0.19). This reduction (ΔV6-V1: -0.076) was statistically significant (p=0.038). A statistical significance was not shown for the placebo group. Despite the small number of patients, the CPT data indicates clinical efficacy of Lais® Frühblüher drops.

[11] - The changes of each parameter from V1 to V6/V6b were calculated and compared between the placebo and the actively treated group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE were collected during the entire duration ot the treatment, both in escalation and in mantainance phase

Adverse event reporting additional description:

Local reactions and systemic allergic reactions after study drug administration were defined as solicited adverse events. These solicited AEs were used to assess the primary endpoint, the safety and clinical tolerability of Lais® Frühblüher treatment. Also unsolicited AEs were collected

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Overall, one unsolicited TEAE was observed in one placebo patient (16.7%)

Reporting group title	Lais® Frühblüher

Reporting group description: -

Serious adverse events	Placebo	Lais® Frühblüher	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo	Lais® Frühblüher	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	7 / 15 (46.67%)	
Investigations			
AST increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Administration site irritation	Additional description: the assessment type is not the same for all patients: 2 patients reported a total of 7 AE and the reporting was systematic for both subject. 1 patient report 1 AEs and the reporting was non systematic.		
subjects affected / exposed	0 / 6 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	8	
Administration site hypersensitivity	Additional description: the assessment type is not the same for all patients: 2 patients reported a total of 3 AEs and the reporting was systematic for both subject. 1 patient report 2 AEs and the reporting was non systematic.		
subjects affected / exposed	0 / 6 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	5	
Immune system disorders			
Seasonal allergy	Additional description: worsening of allergic birch symptoms		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Hypersensitivity	Additional description: the assessment type is not the same for all patients: 2 patients reported 1 AE (Hypersensitivity) and the reporting was non systematic for both subject. 1 patient report 6 AEs (Hypersensitivity) and the reporting was systematic.		
subjects affected / exposed	0 / 6 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	8	
Respiratory, thoracic and mediastinal disorders			
Bronchial irritation	Additional description: mild bronchial complaints		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Bronchial obstruction	Additional description: Bronchial obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	Additional description: Unclear pain in the left knee		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Influenza	Additional description: Viral infection		
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 15 (6.67%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2018	Version 3.0 : implementation of the optional study visit V6b

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

a limitation has been the small number of subject included that didn't permit the efficacy explorative evaluation

Notes: