Clinical trial results:
Efficacy and Safety of sublingual immunotherapy with Allergoid LAIS®Birch-Alder tablets for patients with tree pollen-induced allergic rhinoconjunctivitis A Phase III study.

Summary

EudraCT number	2013-002129-43
Trial protocol	DE
Global end of trial date	17 June 2015

Results information

Result version number	v1 (current)
This version publication date	17 October 2021
First version publication date	17 October 2021

Trial information

Trial identification

Sponsor protocol code	SMART_7

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, Institut für Med. Statistik, Informatik u. Epidemiologie, +49 2214783456, informatik@imsie.de
Scientific contact	Coordinating investigator, Institut für Med. Statistik, Informatik u. Epidemiologie, +49 2214783456, informatik@imsie.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	17 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2015
Global end of trial reached?	Yes
Global end of trial date	17 June 2015
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 of sublingual immunotherapy with the allergoid LAIS® Birch-Alder tablets by the Total Combined Score (TCS) taking in account the Rhinoconjuncticitis Total Symptom Score (RTSS) of the six rhinoconjunctivitis symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes and the Total Rescue Medication Score (TRMS) for the peak of the birch pollen season.

Protection of trial subjects:

Moreover, the main procedures used to guarantee the subject’s anonymity especially during the analysis of their personal data were profoundly explained. The investigator also informed the patient of the possible risks linked to the administration of the product and the possible side effects which to his/her knowledge might occur. The patient was invited to ask questions which were answered by the responsible investigator until the patient was entirely satisfied. Before asking the patient to sign the consent form, the investigator ascertained that the patient had understood entirely and agreed to all information provided. Afterwards, a written Patient Informed Consent Form (ICF) and a Patient Information Form (which were previously approved by the leading ethics committee and notified to the local ethics committees) were handed over to the patient. Two copies of the ICF were to be dated and signed by the patient and the investigator, of which one copy was handed out to the patient. The second form was kept confidentially in the investigator’s file. The subject’s signature verified his/her agreement of participation in the trial. In agreement with the subject, the investigator informed the subject’s regular physician of his/her participation in the trial.

Background therapy:

The intake of anti-symptomatic medication appropriate to an escalation scheme:
Rescue medications :
- Antihistamine (oral)
- Additonal Levocabastine (eyedrops)
- Additional Beclomethasone (nasal)

Evidence for comparator: -

Actual start date of recruitment	04 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 235
Worldwide total number of subjects	235
EEA total number of subjects	235

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)	235
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible subjects were assigned to one of the two treatment groups using a randomization list that was generated on the basis of subject identifiers by a randomization program. It was planned that each treatment group should consist of 120 patients.

Pre-assignment

Screening details:

Female or male patients aged 18 to 75 years with a history of at least two years of tree pollen induced allergic rhinitis and/or allergic rhinoconjunctivitis with or without seasonal controlled allergic asthma.

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	Investigator, Monitor, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Placebo and verum preparations were identical except of the active substances (carbamylated, monomeric allergoids of birch and alder).

Arm title	LAIS® Birch-Alder tablets

Arm description:

LAIS® Birch-Alder tablets in a dosage of 1000 UA or placebo. Daily intake of one sublingual tablet.

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

Dosage and administration details:

Each patient was instructed to take one sublingual tablet per day, to place it under the tongue and to let it dissolve for two minutes before swallowing. During the treatment phase, the participant received either a daily dosage of 1,000 UA monomeric allergoid LAIS® Birch-Alder tablets or placebo according to the randomization-schedule.
The study foresaw an intake of IMP over 12 weeks pre-seasonally (cumulative dose of 84,000 UA) and 8weeks co-seasonally. Delays in study approvals and patients' recruitment moved forward the treatment. therefore the maximum pre-seasonally cumulative dose in the actively treated group amounted to 70,000 UA in only 25% of patients; 50% of the patients received a cumulative dose of only 63,000 UA and 25% of only 56,000 UA. Considering the early appearance of other cross reactive trees and the high number of subjects cosensitized, the pre-seasonal phase scheduled, important to switch on the therapeutic effect, can be considered absent for most subjects.

Number of subjects in period 1[1]	Placebo	LAIS® Birch-Alder tablets
Started	96	92
Completed	94	88
Not completed	2	4
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	-
lack of Compliance	-	1
Missing at V4	-	1
concomitant disease	-	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: Number of screened population is 235, while before randomization 47 subjects did not pass the screening procedures resulting as screening failure.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	LAIS® Birch-Alder tablets
Reporting group description:	
LAIS® Birch-Alder tablets in a dosage of 1000 UA or placebo. Daily intake of one sublingual tablet.	

Reporting group values	Placebo	LAIS® Birch-Alder tablets	Total
Number of subjects	96	92	188
Age categorical Units: Subjects			
Female or male adults (18 to 75) years	96	92	188
Age continuous Units: years			
arithmetic mean	46.36	46.25	
full range (min-max)	22 to 74	19 to 74	-
Gender categorical Units: Subjects			
Female	61	50	111
Male	35	42	77

Subject analysis sets	
Subject analysis set title	Safety set (S-set)/ Exposed Subjects
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all randomized subjects who have been exposed to the study medication at least once and consisted of 188 patients. Of these, 96 patients (51.1%) were assigned to the placebo-group and 92 patients (48.9%) received 1,000 UA/d	
Subject analysis set title	Intention-To-Treat-set (ITT-set)/Evaluable Subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT-set comprised all randomized subjects who met key eligibility and evaluability criteria according to the study protocol. Since the primary objective of this trial was the assessment of the efficacy of the sublingual therapy on the basis of the TCS during the peak pollen season, a complete set of diary data was the main criterion for inclusion into the ITT-set. In the case of missing data, the Last-Value-Carry-Forward-Option was applied.	
Subject analysis set title	Per-Protocol-set (PP-set)
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who met all critera in the protocol and delivered a complete data set of measurements and evaluations of the primary efficacy variable were allocated to the PP-set.	

Reporting group values	Safety set (S-set)/ Exposed Subjects	Intention-To-Treat-set (ITT-set)/Evaluable	Per-Protocol-set (PP-set)
Number of subjects	188	182	126

Age categorical Units: Subjects			
Female or male adults (18 to 75) years	188	182	126
Age continuous Units: years			
arithmetic mean	nk	nk	nk
full range (min-max)	nk to nk	nk to nk	nk to nk
Gender categorical Units: Subjects			
Female	111	106	70
Male	77	76	56

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	LAIS® Birch-Alder tablets
Reporting group description:	
LAIS® Birch-Alder tablets in a dosage of 1000 UA or placebo. Daily intake of one sublingual tablet.	
Subject analysis set title	Safety set (S-set)/ Exposed Subjects
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all randomized subjects who have been exposed to the study medication at least once and consisted of 188 patients. Of these, 96 patients (51.1%) were assigned to the placebo-group and 92 patients (48.9%) received 1,000 UA/d	
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Subject analysis set description:	
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Subject analysis set title	Per-Protocol-set (PP-set)
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who met all critera in the protocol and delivered a complete data set of measurements and evaluations of the primary efficacy variable were allocated to the PP-set.	

Primary: TCS

End point title	TCS
End point description:	
The primary objective is to assess the efficacy of sublingual immunotherapy with the allergoid LAIS® Birch-Alder tablets by the Total Combined Score (TCS) taking into account the Rhinoconjunctivitis Total Symptom Score (RTSS) of the six rhinoconjunctivitis symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) and the Total Rescue Medication Score (TRMS). As patients were screened only up to seven days before starting with drug intake, no baseline period exists.	
End point type	Primary
End point timeframe:	
Evaluation will be done for the peak of the birch pollen season, defined by those 14 consecutive days per centre with the highest local tree pollen counts, starting with “high” pollen concentrations	

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: Score				
arithmetic mean (full range (min-max))	11.75 (0.00 to 30.9)	12.4 (0.00 to 30.1)		

Statistical analyses

Statistical analysis title	daily TCS
Comparison groups	LAIS® Birch-Alder tablets v Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.594 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - the difference was statistically not significant (p=0.594)

Secondary: TCS 30D

End point title	TCS 30D

End point description:

efficacy of a sublingual immunotherapy with the allergoid LAIS® Birch-Alder tablets related to the TCS for the birch pollen season of 30 days.

End point type	Secondary

End point timeframe:

30 Days

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: score				
arithmetic mean (full range (min-max))	10.10 (0.2 to 30.0)	10.29 (0.2 to 24.5)		

Statistical analyses

Statistical analysis title	TCS 30D compare between groups
Comparison groups	Placebo v LAIS® Birch-Alder tablets
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.607
Method	Asymp. Sig. (2-tailed)

Secondary: TCS 60 days

End point title	TCS 60 days

End point description:

In the experimental design used, the efficacy of the SLIT with the Lais Birch-Alder tablets was not confirmed in this trial. Multiple deviations occurred with heavy alteration of the clinical/methodological setting and a consequent adherence of the results to the expectations based on the original

experimental model. Therefore, the conclusions of the study do not imply the product is basically ineffective when used and investigated in proper setting and experimental model.
It is assumed that a sufficient pre-seasonal period before the onset of the pollen season is necessary to permit immunotherapy the consolidation of its therapeutic action, different from common drugs and based on a progressive immunostimulation redirecting the immune system toward tolerance, before the initiation of the natural pollen exposure. In this study, the pre-seasonal phase of the treatment schedule, important to switch on the therapeutic effect, can be considered absent for most subjects.

End point type	Secondary

End point timeframe:

60 days. Assess the efficacy of a sublingual immunotherapy with the allergoid LAIS® Birch-Alder tablets related to the TCS) for the or the entire pollen season of 60 days (March and April).

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: score				
arithmetic mean (full range (min-max))	8.84 (0.1 to 26.7)	9.13 (0.5 to 22.3)		

Statistical analyses

Statistical analysis title	TCS 60D compare between groups
Comparison groups	Placebo v LAIS® Birch-Alder tablets
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.572
Method	Asymp. Sig. (2-tailed)

Secondary: Rescue medication

End point title	Rescue medication

End point description:

The use of asthma rescue medication for the tree pollen season of 60 days was assessed for asthmatic patients as a secondary parameter. For the inhalation of corticosteroids with long-acting β2-agonists (twice daily by the patients) a score of maximum nine points was calculated.

End point type	Secondary

End point timeframe:

60 days

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: score				
arithmetic mean (full range (min-max))	0.52 (0.00 to 8)	0.88 (0.00 to 9)		

Statistical analyses

Statistical analysis title	60D compare use of rescue medication.
Comparison groups	Placebo v LAIS® Birch-Alder tablets
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.567 [2]
Method	Asymp. Sig. (2-tailed)

Notes:

[2] - The difference was statistically not significant (p=0.567)

Secondary: Severity S

End point title	Severity S

End point description:

Improvement in the allergic severity S between baseline and visit V5 within the Conjunctival Provocation Test (CPT)

End point type	Secondary

End point timeframe:

between baseline and post treatment final visit V5

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: Score				
arithmetic mean (full range (min-max))	0.12 (-1.8 to 2.00)	0.16 (-1.5 to 1.9)		

Statistical analyses

Statistical analysis title	Compare Severity S

Statistical analysis description:

P-values comparing the allergic severity S between baseline and visit 5 betweent group (ITT-set)

Comparison groups	Placebo v LAIS® Birch-Alder tablets

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.497
Method	Asymp. Sig. (2-tailed)

Notes:

[3] - 1)At baseline most of the patients exhibited low reactivity to the CPT with birch pollen extract, by reacting to highest concentrated provocation solution thus preventing a fine assessment of the subsequent improvement.

2) The change in the allergic severity S in the CPT between baseline and final visit was statistically significant within each of the both treatment groups, respectively.

Secondary: CPT result score

End point title	CPT result score

End point description:

The changes of the threshold allergen concentration for a positive CPT between baseline and V5 were analyzed by means of the CPT result score. Regarding that a higher threshold for a positive CPT meant a lower allergic reactivity, a negative reaction to the CPT was rated as "0". A positive reaction at the highest threshold of 10,000 SQ/ml was rated as "1", a positive reaction at the threshold of 1,000 SQ/ml as "2" and positive reaction at the threshold of 100 SQ/ml as "3". The changes of the threshold allergen concentration for a positive CPT were allocated to the following three categories: "improved", "unchanged" or "worse" depending on wether a higher, the same or a lower allergen concentration was administered for a positive CPT at V5 compared to baseline, respectively.

End point type	Secondary

End point timeframe:

between baseline and V5

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: score				
arithmetic mean (full range (min-max))	0.60 (-2 to 3)	0.64 (-1 to 3)		

Statistical analyses

Statistical analysis title	Delta CPT between the two treatment.

Statistical analysis description:

comparing delta CPT between the two treatment

Comparison groups	Placebo v LAIS® Birch-Alder tablets
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.56 [5]
Method	Asymp. Sig. (2-tailed)

Notes:

[4] - P-value comparing delta CPT between the two treatment groups

[5] - IImprovement of the threshold allergen concentration in the CPT at V5 compared to baseline

exhibited 59.1% of the patients in the 1,000 UA/d- group and 53.2% of the patients in the placebo group. However, difference was statistically not significant.

Secondary: Well Days

End point title	Well Days

End point description:

The “well days” were defined as days of the entire tree pollen season with a maximum symptom score of 2 and no use of rescue medication according to Dahl (2006) and Durham (2006). The number of well days ranged between 0 and 59 days in both treatment groups.

End point type	Secondary

End point timeframe:

60 Days

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: days				
arithmetic mean (full range (min-max))	17.7 (0.00 to 59)	16.59 (0.00 to 59)		

Statistical analyses

Statistical analysis title	Well Days Compare

Statistical analysis description:

Well Days Compared between the two treatment groups

Comparison groups	LAIS® Birch-Alder tablets v Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 842 [6]
Method	Asymp. Sig. (2-tailed)

Notes:

[6] - The difference between the two treatment groups was statistically not significant

Secondary: IgG4

End point title	IgG4

End point description:

Delta birch pollen-specific IgG4 (mg/l) V0 – V5.

End point type	Secondary

End point timeframe:

Blood sampling for the measurement of birch pollen specific IgG4 was performed at V0 and V5

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: mg/ml				
arithmetic mean (full range (min-max))	-0.11 (-6.11 to 4.44)	-0.06 (-3.45 to 1.44)		

Statistical analyses

Statistical analysis title	IgG4 between the two treatment groups
Comparison groups	Placebo v LAIS® Birch-Alder tablets
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.531 [8]
Method	Asymp. Sig. (2-tailed)

Notes:

[7] - P-value comparing delta birch pollen specific IgG4 between the two treatment groups

[8] - Comparing borh treatment groups, the difference in IgG4-concentration was statistically not significant (p=0.531)

Secondary: RQLQ

End point title	RQLQ

End point description:

The patients were asked to fill in the RQLQ at V1 and V5. With this questionnaire, the problems that adults with rhinoconjunctivitis experienced during the study were measured. It had 28 questions in seven domains: activity limitations sleep impairment, non-nasal/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotional problems. This was done by using a 7-point scale from 0 (not troubled) to 6 (extremely troubled).

End point type	Secondary

End point timeframe:

RQLQ at V1 and V5

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: score				
arithmetic mean (full range (min-max))	-0.30 (-4 to 4)	-0.52 (-3 to 2)		

Statistical analyses

Statistical analysis title	global score RQLQ between the two treatment
Comparison groups	Placebo v LAIS® Birch-Alder tablets

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.484 [9]
Method	Asymp. Sig. (2-tailed)

Notes:

[9] - There was no statistical significance between the both treatment groups (p=0.484)

Secondary: Rhinitis Control Assessment Test (RCAT)

End point title	Rhinitis Control Assessment Test (RCAT)

End point description:

The rhinitis symptom control was compared between both treatment groups using the RCAT at V5. The RCAT encompassed 6 items (nasal congestion, sneezing, watery eyes, the sleep disruption, activity limitation caused by symptoms as well as a self-evaluation of the symptom control) and the responses were measured on a 5-point Likert-type scale. Thereby, the RCAT scores ranged from 6 to 30. Higher scores indicated better rhinitis control.

End point type	Secondary

End point timeframe:

RCAT at V5.

End point values	Placebo	LAIS® Birch-Alder tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: Score				
arithmetic mean (full range (min-max))	14.32 (6 to 25)	13.79 (6 to 25)		

Statistical analyses

Statistical analysis title	RCAT score at V5 between the two treatment groups
Comparison groups	LAIS® Birch-Alder tablets v Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.545 [10]
Method	Asymp. Sig. (2-tailed)

Notes:

[10] - The difference between the two treatment groups was statistically not significant (p=0.545)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

Of 188 patients in the safety analysis set, 65 patients reported a total number of 129 treatment emergent adverse events (TEAEs) which occured between V1 and V5 during the intake of study medication. No fatality or anaphylactic reaction occurred which would have required the use of epinephrine.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	nk

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	LAIS® Birch-Alder tablets

Reporting group description:

LAIS® Birch-Alder tablets in a dosage of 1000 UA or placebo. Daily intake of one sublingual tablet.

Serious adverse events	Placebo	LAIS® Birch-Alder tablets	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: The SAE was reported due to the intention of the patient to go to the hospital. At the hospital, the patient received an intraveneous infusion against pain but hospitalization was not neccessary. The investigator judged that there was no relation to		
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (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	Placebo	LAIS® Birch-Alder tablets	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 96 (35.42%)	31 / 92 (33.70%)	
Surgical and medical procedures			

Meniscus operation			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Local swelling			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Discomfort			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Rhinitis atrophic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Sneezing			
subjects affected / exposed	2 / 96 (2.08%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Wheezing			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Nasal discomfort			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Cough			

subjects affected / exposed	1 / 96 (1.04%)	1 / 92 (1.09%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Nasal inflammation			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Asthma			
subjects affected / exposed	1 / 96 (1.04%)	1 / 92 (1.09%)	
occurrences (all)	1	1	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	2 / 96 (2.08%)	3 / 92 (3.26%)	
occurrences (all)	2	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 96 (2.08%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Peak expiratory flow rate decreased			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 96 (3.13%)	4 / 92 (4.35%)	
occurrences (all)	3	7	
Hypertonia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Thrombocytopenia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pruritus			
subjects affected / exposed	2 / 96 (2.08%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Eye pain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Ocular discomfort			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Eye inflammation			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Renal and urinary disorders			

Cystitis noninfective			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 96 (4.17%)	2 / 92 (2.17%)	
occurrences (all)	4	2	
Myosclerosis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Muscle tightness			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 96 (1.04%)	1 / 92 (1.09%)	
occurrences (all)	1	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 96 (3.13%)	2 / 92 (2.17%)	
occurrences (all)	3	2	
Viral infection			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	5 / 96 (5.21%)	9 / 92 (9.78%)	
occurrences (all)	5	9	
Pharyngitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	
Sinusitis			

subjects affected / exposed	2 / 96 (2.08%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 96 (0.00%)	3 / 92 (3.26%)	
occurrences (all)	0	3	
Tonsillitis bacterial			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 96 (0.00%)	1 / 92 (1.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	1 / 96 (1.04%)	0 / 92 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2014	Originally, the study was planned to last from November 2013 to the end of April 2014, consisting of the screening visit V0, five visits (V1-V5) during the treatment period, and one post-seasonal termination visit (V6). The intake of study medication (verum or placebo) was planned to last 20 weeks There was one substantial amendment of the study protocol version 3.0 prior to the start of the trial concerning the conduct of the study resulting in study protocol version 3.1. Due to a delay, the initiations of the investigator sites started in December instead of November 2013. Therefore the initially planned study duration of 20 weeks was shortened to 84 ± 14 days (12 ± 2 weeks). Visit 6 was cancelled and the intervals between V1 and V4 (56 ± 7 days) as well as V1 and V5 (84 ± 14 days) were newly determined. Diaries and rescue medication were handed out at visit V3 instead of visit V4. Visit 5 was defined as the termination visit at the end of the tree pollen season, containing all parameters to be checked from the former visit 6.
28 March 2014	A second substantial amendment of the study protocol was necessary due to the delayed start of the trial in combination with an expected early birch pollen season in 2014 based on the mild winter 2013/14. This amendment resulted in study protocol version 3.2. Instead of time intervals between V1 and V4 as well as V1 and V5, respectively, calendar weeks were determined for V4 (week 10 to 12, 10.03.2014 - 21.03.2014) and V5 (week 18 to 19, 28.04.2014 - 09.05.2014). Therefore, the study terminated at the latest in May 2014. Due to an unforeseen shortage of CPT-allergen solution announced in early January 2014 by the manufacturer ALK-Abello, the CPT at V3 was optional depending on sufficient allergen solution available
03 December 2014	In versions 3.0 to 3.2 of the study protocol it was planned to assess the TCS for the peak 30 days of the birch pollen season with a pollen count of at least "moderate" (stage 2 according to Deutscher Wetterdienst Medizin-Meteorologie). However, this 30 day peak was identical with the entire birch pollen season from end of March till end of April in Germany in 2014. Since the peak birch pollen season in 2014 lasted 14 days in all areas of Germany with a constant high pollen concentration (stage 3 according to Deutscher Wetterdienst Medizin-Meteorologie),it was decided in the blind review meeting to finally evaluate the primary efficacy variable for those 14 consecutive days at the centre with the highest local birch pollen counts (amendment 3 resulting in study protocol version 3.3). We specified the peak of the birch pollen season as 14 consecutive days with a "high" pollen count and used three analysis periods to distinguish between the peak of the birch pollen season and the entire season: Therefore, the TCS for the birch pollen season of 30 days as well as the RTSS, the six individual symptom scores of the RTSS and the TRMS for the peak birch pollen season of 14 days were evaluated as secondary parameters.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported