



Clinical trial results:

Efficacy and Safety of sublingual immunotherapy with Allergoid LAIS® Grass tablets for patients with grass pollen-induced allergic rhinoconjunctivitis, a phase III study

Summary

EudraCT number	2012-004916-79
Trial protocol	DE
Global end of trial date	08 September 2014

Results information

Result version number	v1 (current)
This version publication date	21 April 2022
First version publication date	21 April 2022

Trial information

Trial identification

Sponsor protocol code	SMART_10
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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	Head of Scientific Department, Head of Scientific Department, +39 02581981,
Scientific contact	Head of Scientific Department, Head of Scientific Department, +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	03 September 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 September 2014
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®Grass tablets by the total combined score (TCS) taking in 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) for the peak of the grass pollen season.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles which have their origins in the Declaration of Helsinki. Thus the Declaration of Helsinki, the GCP (Good Clinical Practice) guidelines (Committee of Proprietary Medicinal Products/ International Conference on Harmonization, CPMP/ICH/135/95) as well as the requirements of national drug and data protection laws and other applicable regulatory requirements have been strictly followed throughout the entire process. A copy of The Declaration of Helsinki and the ICH/GCP guidelines were included in each Investigator's file (see Reference List). In conformity with the ICH guidelines, patients participating in the study were covered by the clinical trial insurance for test subjects. The insurance policy was issued by Allianz Global Corporate & Speciality AG, Königinstr. 28, 80802 Munich, policy number: DEL 004158130.

Background therapy:

The intake of anti-symptomatic medication appropriate to an escalation scheme was documented daily in a patient diary and evaluated afterwards using a score.

It was recommended to the patients to start the treatment of the seasonally allergic symptoms with oral antihistamines (step 1 - 1 X 10 mg). In the case of ongoing eye symptoms additional Levocabastine eye drops (step 2 - 2 x 1 drop per eye) were recommended. If the nasal symptoms were not alleviated, nasal corticosteroids (Beclomethasone) (step 3 - 2 x 0.05 mg/per nostril) could be applied.

Evidence for comparator: -

Actual start date of recruitment	10 December 2013
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	Germany: 157
Worldwide total number of subjects	157
EEA total number of subjects	157

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)	157
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial has been conducted in Germany. It was planned to recruit 200 patients in total, with 100 participants in each treatment group. A total number of 157 patients were recruited and screened for inclusion and exclusion criteria; 90 eligible patients were randomized and included into the statistical analyses.

Pre-assignment

Screening details:

90 patients were randomized at V1. 2 patients were excluded as per protocol violation. Both patients were in the placebo group and treated only for a short time. Therefore 88 patients performed V2. Patients (Pt) drop-out: 1Pt following V2 - 1Pt at V3 - 2Pt at V4 - 3Pt at V5. Finally, 81 patients finished the study.

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	Investigator, Monitor, Data analyst, Subject

Blinding implementation details:

Sealed envelopes, one for each randomization code, contained the declaration of the corresponding treatment and were deposited at the study centre.

The sealed envelopes were only to be opened upon any patient-related event which required unblinding even if knowledge of the kind of treatment might have influenced the management of this event.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

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

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:

Independent of the assigned treatment group, the patients ingested one sublingual tablet per day. The participants were instructed to place the tablet under the tongue and to let it dissolve for two minutes before swallowing. The first application on day 0 was performed under supervision of the investigator and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and was self-administered by the patient.

Arm title	LAIS® Grass Tablets
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Arm description:

The active ingredients of 1,000 UA-LAIS®Grass sublingual tablets were carbamylated, monomeric allergoids consisting of timothy grass (*Phleum pratense*), common meadow grass (*Poa pratensis*) and meadow soft grass (*Holcus lanatus*) in equal parts. Excipients were lactose, microcrystalline cellulosa, silica dioxide and magnesium stearate for each tablet

Arm type	Experimental
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Investigational medicinal product name	LAIS® Grass 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 participants were instructed to place the tablet under the tongue and to let it dissolve for two minutes before swallowing. The first application on day 0 was performed under supervision of the investigator and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and was self-administered by the patient.

Number of subjects in period 1^[1]	Placebo	LAIS® Grass Tablets
Started	44	46
Completed	37	44
Not completed	7	2
Lack of Compliance	1	-
Consent withdrawn by subject	4	1
Adverse event, non-fatal	-	1
Late screening failure	2	-

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: For this study, 157 patients were screened. Since 67 patients were omitted as screening failures, 90 patients were randomized into the study. No patient was lost to follow up. A total of nine patients dropped out.

Baseline characteristics

Reporting groups

Reporting group title	Grass pollen
Reporting group description: -	

Reporting group values	Grass pollen	Total	
Number of subjects	90	90	
Age categorical			
Units: Subjects			
Adults (18-75)	90	90	
Age continuous			
Units: years			
median	38.4		
full range (min-max)	18 to 69	-	
Gender categorical			
Units: Subjects			
Female	43	43	
Male	47	47	

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 90 patients. Of the 90 exposed patients, 44 patients (48.9%) were assigned to the placebo-group and 46 (51.1%) received 1,000 UA LAIS® Grass tablets per day

Subject analysis set title	Intention-To-Treat-set (ITT-set)/Evaluable Subjects
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Since the primary endpoint of this study was the TCS defined by the addition of the daily symptom and medication scores, the availability of diary data during the grass peak pollen season was the key eligibility criterion. Patients not having filled in any patient diary card were only be evaluated in the safety analysis set. Therefore, eight patients of the 90 randomized subjects were not allocated into the ITT-set. In the study protocol was determined that in the case of missing data the Last-Value-Carry-Forward-Option had to be applied. Data missing at the start of the peak pollen season had to be treated as missing data without First-Value-Carry-Backward-Option. However according to the decisions made in the blind data review meeting, for patients with missing diary data on day one of the peak pollen season (and more ahead of the start of the pollen season) and no other baseline assessment of allergy symptoms: the first available data on symptoms and medication use must be assume

Subject analysis set title	Per-Protocol-set (PP-set)
Subject analysis set type	Per protocol

Subject analysis set description:

Patients who met all criteria in the protocol and delivered a complete data set of measurements and evaluations of the primary efficacy variable were allocated to the PP-set. As mentioned in the study protocol, a maximum of two successive missing single evaluations of the Rhinoconjunctivitis Total Symptom Score (RTSS) was accepted a per protocol evaluation. Furthermore, the total number of missing single evaluations of the RTSS was not allowed to exceed 25% over the entire course of the peak pollen period.

In the blind data review meeting, it was determined that patients having started to fill in the diary card later than 22nd of May of 2014 were evaluated in the ITT analysis set. For this reason, 13 patients were not analyzed in the PP-set. Finally, 60 patients were included into the PP-set. Of these, 26 (43.3%) belonged to the placebo group and 34 patients (56.7%) were allocated into the 1,000 UA/d-group

Reporting group values	Safety set (S-set)/ Exposed Subjects	Intention-To-Treat- set (ITT- set)/Evaluable	Per-Protocol-set (PP- set)
Number of subjects	90	82	60
Age categorical Units: Subjects			
Adults (18-75)	90	82	60
Age continuous Units: years			
median	38.4	38.621	38.16
full range (min-max)	18 to 69	18 to 69	18 to 69
Gender categorical Units: Subjects			
Female	43	40	30
Male	47	42	30

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo and verum preparations were identical except of the active substances (carbamylated, monomeric allergoids of grass)	
Reporting group title	LAIS® Grass Tablets
Reporting group description: The active ingredients of 1,000 UA-LAIS®Grass sublingual tablets were carbamylated, monomeric allergoids consisting of timothy grass (<i>Phleum pratense</i>), common meadow grass (<i>Poa pratensis</i>) and meadow soft grass (<i>Holcus lanatus</i>) in equal parts. Excipients were lactose, microcrystalline cellulosa, silica dioxide and magnesium stearate for each 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 90 patients. Of the 90 exposed patients, 44 patients (48.9%) were assigned to the placebo-group and 46 (51.1%) received 1,000 UA LAIS® Grass tablets per day	
Subject analysis set title	Intention-To-Treat-set (ITT-set)/Evaluable Subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description: Since the primary endpoint of this study was the TCS defined by the addition of the daily symptom and medication scores, the availability of diary data during the grass peak pollen season was the key eligibility criterion. Patients not having filled in any patient diary card were only be evaluated in the safety analysis set. Therefore, eight patients of the 90 randomized subjects were not allocated into the ITT-set. In the study protocol was determined that in the case of missing data the Last-Value-Carry-Forward-Option had to be applied. Data missing at the start of the peak pollen season had to be treated as missing data without First-Value-Carry-Backward-Option. However according to the decisions made in the blind data review meeting, for patients with missing diary data on day one of the peak pollen season (and more ahead of the start of the pollen season) and no other baseline assessment of allergy symptoms: the first available data on symptoms and medication use must be assume	
Subject analysis set title	Per-Protocol-set (PP-set)
Subject analysis set type	Per protocol
Subject analysis set description: Patients who met all criteria in the protocol and delivered a complete data set of measurements and evaluations of the primary efficacy variable were allocated to the PP-set. As mentioned in the study protocol, a maximum of two successive missing single evaluations of the Rhinoconjunctivitis Total Symptom Score (RTSS) was accepted a per protocol evaluation. Furthermore, the total number of missing single evaluations of the RTSS was not allowed to exceed 25% over the entire course of the peak pollen period. In the blind data review meeting, it was determined that patients having started to fill in the diary card later than 22nd of May of 2014 were evaluated in the ITT analysis set. For this reason, 13 patients were not analyzed in the PP-set. Finally, 60 patients were included into the PP-set. Of these, 26 (43.3%) belonged to the placebo group and 34 patients (56.7%) were allocated into the 1,000 UA/d-group	

Primary: TCS 30D Efficacy

End point title	TCS 30D Efficacy
End point description: The primary parameter was the assessment of the efficacy of the sublingual immunotherapy with the allergoid LAIS®Grass tablets via a Total Combined Score (TCS) taking into account a Rhinoconjunctivitis Total Symptom Score (RTSS) and a Total Rescue Medication Score (TRMS) for the peak of the grass pollen season. The peak pollen season was defined by those 30 consecutive days per centre with the highest local grass pollen counts, starting with at least "moderate" pollen in the nearest pollen count station in that region.	
End point type	Primary
End point timeframe: Grass pollen season of 30 days	

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)	10.04 (± 6.683)	9.16 (± 6.995)		

Statistical analyses

Statistical analysis title	TCS 30D compare between groups
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Statistical analysis description:

From all individual daily TCS-values a treatment-dependent mean daily TCS for each day of the peak pollen season of 30 days were calculated.

The result of the clinical study was considered as clinically meaningful if a reduction in the actively treated group compared with the placebo group of at least 30 % of the TCS AND a reduction of either the RTSS and/or TRMS of 30% was demonstrated AND a clinically meaningful improvement of QoL occurred during the peak pollen season.

Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.449
Method	Asymp. Sig. (2-tailed)

Notes:

[1] - A statistically significant difference between the actively treated group and the placebo group was not demonstrated.

The individual mean daily TCS ranged from 0.47 to 23.10 in the placebo group and from 0.07 to 34.07 in the 1,000 UA/d-group. Therefore, a benefit for actively treated patients could not be demonstrated though the TCS for these patients was lower in the first 2 weeks of the pollen peak compared to the placebo patients.

Secondary: Rhino-conjunctivitis Symptom Score (RSS) 30D

End point title	Rhino-conjunctivitis Symptom Score (RSS) 30D
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End point description:

The daily mean score for "itchy eyes" was 0.98 in the placebo group and 0.84 in the actively treated group (p = 0.300). The daily mean score for "itchy nose" was 0.83 in the placebo group and 0.89 in the 1,000 UA/d-group (p = 0.845). For the symptom "rhinorrhea" the daily mean score in the placebo group amounted to 0.90 versus 0.83 in the 1,000 UA/d-group (p = 0.632). The daily mean score for "sneezing" was 0.91 in the placebo group and 0.96 in the 1,000 UA/d-group (p = 0.791). The symptom "watery eyes" had a daily mean score of 0.71 in the placebo group versus 0.50 in the actively treated group (p = 0.106). The mean score for "nasal congestion" was 0.78 in the placebo versus 0.86 in the 1,000 UA/d-group (p = 0.605). None of these differences between the two treatment groups were statistically significant.

End point type	Secondary
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End point timeframe:

Peak Grass Pollen Season of 30 Days

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: score				
arithmetic mean (standard deviation)				
Itchy eyes daily mean 30 days	0.98 (± 0.661)	0.84 (± 0.674)		
Itchy nose daily mean 30 days	0.83 (± 0.601)	0.89 (± 0.674)		
Rhinorrhea daily mean 30 days	0.90 (± 0.647)	0.83 (± 0.667)		
Sneezing daily mean 30 days	0.91 (± 0.647)	0.96 (± 0.652)		
Watery eyes daily mean 30 days	0.71 (± 0.642)	0.50 (± 0.566)		
Nasal congestion daily mean 30 days	0.78 (± 0.685)	0.86 (± 0.748)		

Statistical analyses

Statistical analysis title	Itchy eyes daily mean 30 days
Comparison groups	LAIS® Grass Tablets v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Itchy nose daily mean 30 days
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.845
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Rhinorrhea daily mean 30 days
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.632
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Sneezing daily mean 30 days
Comparison groups	Placebo v LAIS® Grass Tablets

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.791
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Watery eyes daily mean 30 days
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Nasal congestion daily mean 30 days
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.605
Method	Asymp. Sig. (2-tailed)

Secondary: Rhino-conjunctivitis Symptom Score (RSS) 60D

End point title	Rhino-conjunctivitis Symptom Score (RSS) 60D
End point description:	
<p>For the entire grass pollen season of 60 days, the daily mean score for "itchy eyes" was 0.70 in the placebo group and 0.48 in the actively treated group ($p = 0.300$). The daily mean score for "itchy nose" was 0.64 in the placebo group and 0.57 in the 1,000 UA/d-group ($p = 0.802$). For the symptom "rhinorrhea" the daily mean score in the placebo group amounted to 0.68 versus 0.55 in the 1,000 UA/d-group ($p = 0.885$). The daily mean score for "sneezing" was 0.73 in the placebo group and 0.78 in the 1,000 UA/d-group ($p = 0.762$). The symptom "watery eyes" had a daily mean score of 0.49 in the placebo group versus 0.22 in the actively treated group ($p = 0.250$). The mean score for "nasal congestion" was 0.59 in the placebo versus 0.51 in the 1,000 UA/d-group ($p = 0.491$). None of these differences between the two treatment groups were statistically significant</p>	
End point type	Secondary
End point timeframe:	
the Peak Grass Pollen Season of the Entire Season of 60 Days.	

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)				
Itchy eyes Daily mean 60 days	0.70 (± 0.500)	0.71 (± 0.528)		
Itchy nose Daily mean 60 days	0.64 (± 0.495)	0.69 (± 0.568)		
Rhinorrhea Daily mean 60 days	0.68 (± 0.496)	0.67 (± 0.543)		
Sneezing Daily mean 60 days	0.73 (± 0.500)	0.78 (± 0.552)		
Watery eyes Daily mean 60 days	0.49 (± 0.444)	0.40 (± 0.463)		
Nasal congestion Daily mean 60 days	0.59 (± 0.532)	0.68 (± 0.603)		

Statistical analyses

Statistical analysis title	Itchy eyes Daily mean 60 days
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Itchy nose Daily mean 60 days
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.802
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Rhinorrhea Daily mean 60 days
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.885
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Sneezing Daily mean 60 days
Comparison groups	Placebo v LAIS® Grass Tablets

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.762
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Watery eyes Daily mean 60 days
Comparison groups	LAIS® Grass Tablets v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	Nasal congestion daily mean 60 days
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.491
Method	Asymp. Sig. (2-tailed)

Secondary: TCS Entire Grass Pollen Season of 60 Days (ITT-set)

End point title	TCS Entire Grass Pollen Season of 60 Days (ITT-set)
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End point description:

The daily mean TCS for the 60 day period was 7.34 in the placebo group and 7.24 in the actively treated group. This difference was not statistically significant ($p = 0.727$). In the placebo group, minimum TCS was 0.98 and maximum was 20.35. In the actively treated group, minimum TCS was 0.05 and maximum was 31.23 .

The course of the daily mean TCS in the pollen season of 60 days was similar in the actively treated group compared to the placebo group (Figure 11.1).

End point type	Secondary
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End point timeframe:

Entire Grass Pollen Season of 60 Days

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: score				
arithmetic mean (standard deviation)	7.34 (\pm 5.157)	7.24 (\pm 6.192)		

Statistical analyses

Statistical analysis title	TCS 60D
Comparison groups	LAIS® Grass Tablets v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.727
Method	Asymp. Sig. (2-tailed)

Notes:

[2] - The course of the daily mean TCS in the pollen season of 60 days was similar in the actively treated group compared to the placebo group

Secondary: RTSS for the Entire Grass Pollen Season (ITT-set)

End point title	RTSS for the Entire Grass Pollen Season (ITT-set)
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End point description:

The daily mean RTSS for the entire grass pollen season of 60 days amounted to 3.83 in the placebo group versus 3.84 in the 1,000 UA/d-group. The difference between the two groups was statistically not significant ($p = 0.791$). The daily RTSS ranged from 0.28 points to 10.28 points in the placebo group and from 0.05 to 14.73 points in the 1,000 UA/d-group

End point type	Secondary
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End point timeframe:

Entire grass pollen season of 60 days.

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)	3.83 (\pm 2.303)	3.84 (\pm 2.801)		

Statistical analyses

Statistical analysis title	RTSS Entire Grass Pollen Season (ITT-set)
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Statistical analysis description:

The daily mean RTSS for the entire grass pollen season of 60 days amounted to 3.83 in the placebo group versus 3.84 in the 1,000 UA/d-group. The difference between the two groups was statistically not significant ($p = 0.791$). The daily RTSS ranged from 0.28 points to 10.28 points in the placebo group and from 0.05 to 14.73 points in the 1,000 UA/d-group.

Comparison groups	Placebo v LAIS® Grass Tablets
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Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.791
Method	Asymp. Sig. (2-tailed)

Secondary: TRMS Entire Grass Pollen Season (ITT-set)

End point title	TRMS Entire Grass Pollen Season (ITT-set)
End point description: The daily mean TRMS for the entire grass pollen season of 60 days was 3.51 in the placebo group and 3.40 in the 1,000 UA/d-group without a statistically significant difference (p = 0.612). The score ranged from 0 to 14.98 points in the placebo group and from 0 to 16.50 points in the 1,000 UA/d-group.	
End point type	Secondary
End point timeframe: Entire Grass Pollen Season 60days	

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)	3.51 (± 3.482)	3.40 (± 4.074)		

Statistical analyses

Statistical analysis title	TRMS 60D
Comparison groups	LAIS® Grass Tablets v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.612
Method	Asymp. Sig. (2-tailed)

Secondary: Reduction of RSS and RCAT

End point title	Reduction of RSS and RCAT
End point description: The mean retrospective RTSS for the preceeding pollen season 2013 was 13.13 for the placebo and 13.39 for the 1,000 UA/day group. During the entire pollen season 2014 the RTSS decreased to 3.83 in the placebo and 3.84 in the 1,000 UA/d group. For both treatment groups, the difference between the retrospective RTSS and the RTSS was statistically significant (p<0.001) Comparing the difference of the retrospective RTSS of the year 2013 and the RTSS of 2014 between the two treatment groups, stastical significance was not detected (p = 0.809) The rhinitis symptom control was compared between both treatment groups using RCAT at V6. the RCAT scores ranged from 6 to 30. Higher scores indicated better rhinitis control.	

In the placebo group, the mean RCAT score was 19.18 compared to 20.48 in the 1,000 UA/d-group demonstrating similar rhinitis control in both groups (Table 14.1.4.4.1). The difference between the two treatment groups was statistically not significant (p=0.165)

End point type	Secondary
End point timeframe:	
pollen season 2013 - pollen season 2014 : At V0 a retrospective RTSS for the preceding grass pollen season 2013 was evaluated for comparison with the RTSS for the upcoming pollen season 2014.	

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)				
RTSS D(2013-2014)	9.30 (± 2.886)	9.55 (± 2.810)		
RCAT	19.18 (± 3.618)	20.48 (± 3.274)		

Statistical analyses

Statistical analysis title	RTSS D(2013-2014)
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.809
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	RCAT
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
Method	Asymp. Sig. (2-tailed)

Secondary: Allergic Severity S

End point title	Allergic Severity S
End point description:	

Regarding the conjunctival provocation test, there was a distinct improvement in the allergic severity S between baseline and V4 in each of the two treatment groups, respectively. In the placebo group the allergic severity S improved from 0.58 at baseline to 0.15 at V4. This improvement within the placebo group was statistically significant (p < 0.05). In the 1,000 UA/d-group the allergic severity S improved from 0.40 at baseline to 0.04 at V4. However, this improvement was not statistically significant (p =

0.234).

Comparing the placebo group with the 1,000 UA/d-group, the difference in delta allergic severity S (baseline to V4) was not statistically significant ($p = 0.201$)

End point type	Secondary
End point timeframe: etwween Baseline and Visit V4	

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)	0.15 (± 0.705)	0.04 (± 0.564)		

Statistical analyses

Statistical analysis title	Allergic Severity S D(Baseline-V4)
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.201
Method	Asymp. Sig. (2-tailed)

Secondary: Threshold Allergen Concentration

End point title	Threshold Allergen Concentration
End point description: The CPT was considered positive if the response was stage 2 or higher. The test was finished after a positive result and no further allergen solutions were applied. Regarding that a higher threshold for a positive CPT meant a lower allergic reactivity, a negative reaction in the CPT was labeled as "0". A positive reaction at the highest threshold of 10,000 SQ-E/ml was labeled as "1", a positive reaction at the threshold of 1,000 SQ-E/ml as "2" and positive reaction at the threshold of 100 SQ-E/ml as "3". CPT result score: 0 = no reaction at any allergen concentration 1 = positive reaction at 10,000 SQ-E/ml 2 = positive reaction at 1,000 SQ-E/ml 3 = positive reaction at 100 SQ-E/ml The CPT result score represented the basis for the calculation of the change of the threshold allergen concentration for a positive response within the CPT between baseline and V4.	
End point type	Secondary
End point timeframe: From Baseline to V4	

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)	0.37 (± 1.125)	0.11 (± 0.970)		

Statistical analyses

Statistical analysis title	CPT Results between the Two Groups (ITT-set)
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Statistical analysis description:

The change of the threshold allergen concentration for a positive CPT was numerally described by means of the CPT result score. In the placebo group, the score decreased from 1.50 at baseline to 1.12 at visit 4. The difference was 0.37. In the 1,000 UA/d-group, the CPT result score declined from 1.23 at baseline to 1.11 at visit 4. The difference was 0.11. The decrease in the CPT result score between baseline and visit 4 in each treatment group was statistically not significant

Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.237
Method	Asymp. Sig. (2-tailed)

Notes:

[3] - Comparing the difference of the CPT result score between baseline and visit 4 between the two treatment groups, this was also not statistically significant (p=0.237)

Secondary: Redness of the Eye

End point title	Redness of the Eye
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End point description:

Previous to the provocation, the status of the eye was documented by photography and used as baseline. Afterwards, one eye of the patient was challenged with the test solution containing grass allergens while the other eye was treated with control solution. 10 minutes after applying each of the solutions, photographs of the eyes were taken again. This procedure was continued until a CPT response of stage 2 had occurred. The redness of the conjunctiva of each patient was rated by two independent observers using the following scale.

In analogy to allergic severity S, the redness of the eye was depicted by a composite score (CS)

End point type	Secondary
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End point timeframe:

From baseline to V4

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)				
Delta Th(Red) Baseline V4	-0.04 (± 1.224)	-0.41 (± 1.500)		
Delta CS bl-V4	0.04 (± 0.776)	-0.11 (± 0.365)		

Statistical analyses

Statistical analysis title	Delta Th(Red) Baseline V4
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Statistical analysis description:

Redness of the eye was assessed by a central observer. At baseline, the threshold score of the redness of the eye was 1.53 in the placebo and 1.05 in the actively treated group. At V4, the threshold score increased to 1.63 and 1.53 in the placebo and 1,000 UA/day group, respectively. This indicated a reddening of the conjunctiva at an allergene challenge in the range of 1,000 to 10,000 SQ-E/ml in the CPT.

Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.263
Method	Asymp. Sig. (2-tailed)

Notes:

[4] - The difference between baseline and V4 was -0.04 in the placebo group and -0.41 in the actively treated group, respectively. Statistical significance was not detected neither comparing threshold at baseline and visit 4 in each treatment group nor comparing both treatment groups according to the difference of the threshold between baseline and visit 4.

Statistical analysis title	Delta CS
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Statistical analysis description:

Delta Composite Score Baseline – V4 between the two treatment groups

Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.162
Method	Asymp. Sig. (2-tailed)

Notes:

[5] - The mean composite score (CS) changed from 0.35 at baseline to 0.36 at visit 4 in the placebo group. In the actively treated group, the mean CS increased from 0.20 at baseline to 0.30 at visit 4. These changes were not statistically significant. Comparing delta CS baseline – visit 4 between the two treatment groups, this was also not statistically significant.

Secondary: Well Days

End point title	Well Days
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End point description:

The number of well days defined as days with a maximum symptom score of 2 and no rescue medication use. Well Days Mean within 60 Days was compared between the 2 Treatment Groups

End point type	Secondary
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End point timeframe:

Entire Grass Pollen Season of 60 Days

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)				
Mean Number of Well days	27.32 (± 16.369)	25.77 (± 17.619)		

Statistical analyses

Statistical analysis title	Well Days Compare between Groups
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.593
Method	Asymp. Sig. (2-tailed)

Notes:

[6] - The number of well days defined as days with a maximum symptom score of 2 and no rescue medication use ranged between 0 and 56 days in the placebo group and 0 to 60 days in the 1,000 UA/day group. The mean number of well days was 27.32 in the placebo group and 25.77 in the actively treated group. The difference between the two treatment groups was statistically not significant (p = 0.593)

Secondary: IgG4

End point title	IgG4
End point description:	Blood sampling for the measurement of grass pollen specific IgG4 was performed before and after treatment. Delta Grass Pollen Specific IgG4 was compared between the Two Treatment Groups.
End point type	Secondary
End point timeframe:	Entire grass pollen season of 60 days

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)				
Delta IgG4	-0.01 (± 0.338)	-0.04 (± 0.265)		

Statistical analyses

Statistical analysis title	Delta IgG4 before and after treatment
Comparison groups	LAIS® Grass Tablets v Placebo

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627
Method	Asymp. Sig. (2-tailed)

Secondary: Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

End point title	Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)
End point description: The patients were asked to fill in the RQLQ at V1, V5, V6 and V7. With this questionnaire, the problems which 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.	
End point type	Secondary
End point timeframe: From V1 to V7	

End point values	Placebo	LAIS® Grass Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Score				
arithmetic mean (standard deviation)				
RQLQ Score V1	1.04 (± 0)	0.80 (± 0)		
RQLQ Score V5	1.44 (± 1.263)	1.22 (± 0.948)		
RQLQ Score V6	1.78 (± 1.051)	1.58 (± 1.093)		
RQLQ Score V7	0.43 (± 1.135)	0.63 (± 1.176)		

Statistical analyses

Statistical analysis title	RQLQ Comparing the Global Score V1
Statistical analysis description: The global score considering all subscores of the seven domains was calculated at V1. Comparing both treatment groups, there was no statistical significance. Similarly, the subscores of the seven domains exhibited neither statistically significant differences nor numerical differences (i.e. more than 0.5 points) with clinical relevance between the treatment groups.	
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.791
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	RQLQ Comparing the Global Score V5
Statistical analysis description:	
The global score considering all subscores of the seven domains was calculated at V5. Comparing both treatment groups, there was no statistical significance. Similarly, the subscores of the seven domains exhibited neither statistically significant differences nor numerical differences (i.e. more than 0.5 points) with clinical relevance between the treatment groups.	
Comparison groups	LAIS® Grass Tablets v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	RQLQ Comparing the Global Score V6
Statistical analysis description:	
The global score considering all subscores of the seven domains was calculated at V6. Comparing both treatment groups, there was no statistical significance. Similarly, the subscores of the seven domains exhibited neither statistically significant differences nor numerical differences (i.e. more than 0.5 points) with clinical relevance between the treatment groups.	
Comparison groups	Placebo v LAIS® Grass Tablets
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.281
Method	Asymp. Sig. (2-tailed)

Statistical analysis title	RQLQ Comparing the Global Score V7
Statistical analysis description:	
The global score considering all subscores of the seven domains was calculated at V7 Comparing both treatment groups, there was no statistical significance. Similarly, the subscores of the seven domains exhibited neither statistically significant differences nor numerical differences (i.e. more than 0.5 points) with clinical relevance between the treatment groups.	
Comparison groups	LAIS® Grass Tablets v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.281
Method	Asymp. Sig. (2-tailed)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

observation period between V1 and V7.

Adverse event reporting additional description:

37 patients reported a total number of 61 treatment emergent adverse events (TEAEs) which occurred during the observation period between V1 and V7. Two serious adverse events were reported, which were not related to the intake of study medication. Neither fatality nor anaphylactic reaction which would have required the use of epinephrine occurred.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	safety-set
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Reporting group description: -

Serious adverse events	safety-set		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 90 (2.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident	Additional description: road traffic accident with traumatic brain injuries		
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	safety-set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 90 (41.11%)		

Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Surgical and medical procedures			
Cerumen removal			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Nasal dryness			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Cough			

subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Asthma			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Psychiatric disorders			
Mental disorder due to a general condition			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Investigations			
Laboratory test abnormal			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Sports injury			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Craniocerebral injury			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

Skull fractured base subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 90 (3.33%) 3		
Eye disorders Eye pruritus subjects affected / exposed occurrences (all) Eye inflammation subjects affected / exposed occurrences (all) Conjunctivitis allergic subjects affected / exposed occurrences (all) Ocular hyperaemia subjects affected / exposed occurrences (all) Blepharitis subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2 2 / 90 (2.22%) 2 2 / 90 (2.22%) 2 1 / 90 (1.11%) 1 1 / 90 (1.11%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Paresthesia oral subjects affected / exposed occurrences (all) Tongue coated subjects affected / exposed occurrences (all) Oral pruritus subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1 1 / 90 (1.11%) 1 1 / 90 (1.11%) 1 1 / 90 (1.11%) 1		
Skin and subcutaneous tissue disorders			

<p>Eczema</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Rash</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Musculoskeletal and connective tissue disorders</p> <p>Foot deformity</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Infections and infestations</p> <p>Chlamydial infection</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>3 / 90 (3.33%)</p> <p>occurrences (all)</p> <p>6</p> <p>Conjunctivitis bacterial</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p> <p>Tonsillitis</p> <p>subjects affected / exposed</p> <p>1 / 90 (1.11%)</p> <p>occurrences (all)</p> <p>1</p> <p>Sinusitis</p> <p>subjects affected / exposed</p> <p>2 / 90 (2.22%)</p> <p>occurrences (all)</p> <p>2</p> <p>Otitis externa</p>			

subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2013	Changes implemented by reason of deficiency letter of PEI
19 June 2013	Postponement of study
20 November 2013	Component resolved diagnostics in allergy diagnostics (RAST) was implemented
07 May 2014	Adaptation of the visit schedule required to the extension of the inclusion period,

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.

The need to amend the trial from pre-seasonal treatment phase of 20 weeks to pre-/co-seasonal treatment with 9 to 12 weeks. The overall duration of the intake of study medication still was 20 weeks.

Notes: