Clinical trial results:
A multicenter, placebo-controlled, double-blind study to evaluate efficacy and safety of a perennial sublingual specific immunotherapy with a solution of grass pollen allergen extract in children with clinically relevant grass pollen sensitivity in comparison to a symptomatic standard treatment with add on placebo.

Summary

EudraCT number	2006-005911-82
Trial protocol	DE PL
Global end of trial date	17 August 2015

Results information

Result version number	v1 (current)
This version publication date	28 June 2017
First version publication date	28 June 2017

Trial information

Trial identification

Sponsor protocol code	AL0506st

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ALLERGOPHARMA GMBH & CO. KG.
Sponsor organisation address	Hermann-Körner-Straße 52, Reinbek, Germany, 21465
Public contact	Department of Clinical Trials, Allergopharma GmbH & Co. KG, 0049 040427650,
Scientific contact	Department of Clinical Trials, Allergopharma GmbH & Co. KG, 0049 040427650,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000337-PIP01-08
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	02 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) Obtain evidence for the safety and efficacy of sublingual immunotherapy with grass pollen allergens formulated as solution in comparison with a symptomatic standard treatment with add on placebo in a representative number of grass pollen-allergic children, suffering from allergic rhinitis/rhinoconjunctivitis with or without bronchial asthma (Global Initiative for Asthma [GINA] I and II).

2) Assess immunologic parameters during the course of the study, to obtain evidence of immunologic effects of the therapeutic vaccine.

Note:
Study participants were patients with IgE-mediated allergic disease manifested as symptoms of allergic rhinitis/rhinoconjunctivitis with or without allergic bronchial asthma (GINA I and II), triggered by grass pollen allergens.

To take into account the pollen seasons, this study took place in DE and PL between March 2008 to August 2015. The study design consisted of 3 phases: double-blind (active or placebo), open label (active) , follow-up (none).

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices guidelines, and local legal requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 February 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 133
Country: Number of subjects enrolled	Germany: 74
Worldwide total number of subjects	207
EEA total number of subjects	207

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)	182
Adolescents (12-17 years)	25
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in study centers in Germany and Poland. The screening phase was performed in two subsequent years. Phase 1 was performed from 02/2008 to 06/2008 with baseline assessment during the grass pollen season 2008 and phase 2 from 08/2008 to 05/2009 with baseline assessment during the grass pollen season of the year 2009.

Pre-assignment

Screening details:

The screening was performed according to the inclusion and exclusion criteria. In total, 573 patients were screened and 207 patients were randomised into the study. Patient screening was performed in two subsequent years.

Period 1

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

Blinding implementation details:

The packing material of the study preparations (active treatment and placebo) was of uniform and neutral design. Each package was marked as study medication, stating the study number, the year of treatment as well as name and address of the manufacturer. Labelling was in accordance with the respective national requirements for clinical study preparations. All packages were clearly labelled "For use in clinical trials".

Arms

Are arms mutually exclusive?	Yes
Arm title	Active treatment SLIT

Arm description:

Subjects received sublingual specific immunotherapy (SLIT) with grass pollen allergen extract.

Arm type	Experimental
Investigational medicinal product name	Grass pollen allergen extract
Investigational medicinal product code	
Other name	Sublingual specific immunotherapy (SLIT)
Pharmaceutical forms	Oral solution
Routes of administration	Sublingual use

Dosage and administration details:

Sublingual Specific Immunotherapy (SLIT)
Solution of grass pollen allergen extract in a water/glycerol in phosphate buffered saline.

The study medication was a mixture of grass pollen allergens in a water/glycerol solution with phosphate buffered saline and was filled into polyethylene single-dose containers. The liquid was standardised to contain a major allergen content of 40µg grasses group 5 (in house assay). The allergen extracts consisted of Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense and Poa pratensis.

Patients dispensed the liquid drop wise under the tongue, kept it there for 3 minutes and swallowed afterwards. In total up to 4 drops could be removed from the container (100% dose).

Patients were treated perennially.

Arm title	Placebo

Arm description:

Subjects received placebo.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Sublingual use

Dosage and administration details:

Sublingual Specific Immunotherapy (SLIT)
Solution of water/glycerol in phosphate buffered saline.

Patients dispensed the liquid drop-wise under the tongue, kept it there for 3 minutes and swallowed afterwards. In total up to 4 drops could be removed from the container (100% dose).

Patients were treated perennially.

Number of subjects in period 1	Active treatment SLIT	Placebo
Started	158	49
Completed	132	47
Not completed	26	2
Moved to another town	1	-
Consent withdrawn by subject	9	1
Adverse event, non-fatal	8	-
Non-compliant	3	1
In-Exclusion criteria	2	-
Drug intolerance	2	-
Lost to follow-up	1	-

Period 2

Period 2 title	Open label phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	'Active-Active' treatment

Arm description:

The open-label phase (OLP) included 3 years of open label active treatment for patients randomised to placebo and 2 years of open label active treatment for patients randomised to active treatment. In all analyses of the OLP the previously active treated patients are named ‘Active - Active’ and the previously placebo treated patients ‘Placebo - Active’.

Arm type	Experimental

Investigational medicinal product name	Grass pollen allergen extract
Investigational medicinal product code	
Other name	Sublingual specific immunotherapy (SLIT)
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Sublingual use

Dosage and administration details:

Sublingual Specific Immunotherapy (SLIT)
Solution of grass pollen allergen extract in a water/glycerol in phosphate buffered saline.

The study medication was a mixture of grass pollen allergens in a water/glycerol solution with phosphate buffered saline and was filled into polyethylene single-dose containers. The liquid was standardised to contain a major allergen content of 40µg grasses group 5 (in house assay). The allergen extracts consisted of Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense and Poa pratensis.

Patients dispensed the liquid drop wise under the tongue, kept it there for 3 minutes and swallowed afterwards. In total up to 4 drops could be removed from the container (100% dose).

Patients were treated perennially.

Arm title	'Placebo-Active' treatment

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Grass pollen allergen extract
Investigational medicinal product code	
Other name	Sublingual specific immunotherapy (SLIT)
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Sublingual use

Dosage and administration details:

Sublingual Specific Immunotherapy (SLIT)
Solution of grass pollen allergen extract in a water/glycerol in phosphate buffered saline.

The study medication was a mixture of grass pollen allergens in a water/glycerol solution with phosphate buffered saline and was filled into polyethylene single-dose containers. The liquid was standardised to contain a major allergen content of 40µg grasses group 5 (in house assay). The allergen extracts consisted of Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense and Poa pratensis.

Patients dispensed the liquid drop wise under the tongue, kept it there for 3 minutes and swallowed afterwards. In total up to 4 drops could be removed from the container (100% dose).

Patients were treated perennially.

Number of subjects in period 2[1]	'Active-Active' treatment	'Placebo-Active' treatment
Started	131	46
Completed	119	33
Not completed	12	13
Physician decision	1	-
Consent withdrawn by subject	2	6
Adverse event, non-fatal	1	4
Non-compliant	1	1
Other	4	2

Lost to follow-up	3	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Several trial subject did not continue the study after the double blind phase, in the active treatment as well as in the placebo treatment groups.

Period 3

Period 3 title	Follow-up phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	'Active-Active' treatment
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	'Placebo-Active' treatment
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3[2]	'Active-Active' treatment	'Placebo-Active' treatment
Started	85	23
Completed	76	20
Not completed	9	3
In-/Exclusion criteria	1	-
Consent withdrawn by subject	6	-
Physician decision	-	1
Non-compliant	-	1
Other	-	1
Lost to follow-up	2	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Patients entering the follow-up phase was not the same as the number completing the preceding period. The reasons for this were:
Several trial subject did not continue the study after the open label phase, in the active-active

treatment as well as in the placebo-active treatment groups.

Baseline characteristics

Reporting groups	
Reporting group title	Active treatment SLIT
Reporting group description:	
Subjects received sublingual specific immunotherapy (SLIT) with grass pollen allergen extract.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo.	

Reporting group values	Active treatment SLIT	Placebo	Total
Number of subjects	158	49	207
Age categorical Units: Subjects			
Children (2-11 years)	139	43	182
Adolescents (12-17 years)	19	6	25
Age continuous Units: years			
arithmetic mean	8.74	8.67	
standard deviation	± 2.27	± 2.32	-
Gender categorical Units: Subjects			
Female	47	14	61
Male	111	35	146
Race Units: Subjects			
African descent	0	1	1
Asian descent	0	1	1
Caucasian	157	47	204
Caucasian, African descent	1	0	1
Smoking status Units: Subjects			
Smoking	0	0	0
Non-smoking	158	49	207
Household pets Units: Subjects			
None	103	25	128
Pet(s)	55	24	79
Weight Units: kg			
arithmetic mean	31.56	29.64	
standard deviation	± 10.44	± 8.85	-
Height Units: cm			
arithmetic mean	134	133.16	
standard deviation	± 14.82	± 13.98	-

End points

End points reporting groups

Reporting group title	Active treatment SLIT
Reporting group description:	
Subjects received sublingual specific immunotherapy (SLIT) with grass pollen allergen extract.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo.	
Reporting group title	'Active-Active' treatment
Reporting group description:	
The open-label phase (OLP) included 3 years of open label active treatment for patients randomised to placebo and 2 years of open label active treatment for patients randomised to active treatment. In all analyses of the OLP the previously active treated patients are named ‘Active - Active’ and the previously placebo treated patients ‘Placebo - Active’.	
Reporting group title	'Placebo-Active' treatment
Reporting group description: -	
Reporting group title	'Active-Active' treatment
Reporting group description: -	
Reporting group title	'Placebo-Active' treatment
Reporting group description: -	

Primary: 1_01_Change of the area under the curve (AUC) of symptom and medication score (SMS) after 1 year of treatment; DBP

End point title	1_01_Change of the area under the curve (AUC) of symptom and medication score (SMS) after 1 year of treatment; DBP

End point description:

The primary endpoint of this study was the change of the AUC of the SMS from the baseline season to the season after one year of treatment.
SMS was calculated by the daily sum of symptoms and the use of anti-allergic medication documented in patients diaries during the grass pollen seasons. The grass pollen season for data analysis - was the time window of 6 weeks (42 days) with the highest pollen counts.

Symptoms to be considered were:
• Eyes (itching, tear flow, redness)
• Nose (sneezing, itching, running, blocking)
• Chest (cough, wheezing, dyspnoea)

Score (according to intensity)
0 = absent symptoms (no sign/symptom evident)
1 = mild symptoms, minimal inconvenience
2 = moderate, bothersome but tolerable symptoms
3 = severe symptoms that interfered with activities of daily living and/or sleeping

Daily medication scores were assigned as in the AMS Scoring Conventions for Allergopharma clinical studies.

AUC=Area under the curve
SMS=symptom and medication score

End point type	Primary

End point timeframe:

Baseline to 1 year after treatment.

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[1]	42[2]		
Units: score				
arithmetic mean (standard deviation)	-212.5 (± 211.8)	-97.8 (± 196.8)		

Notes:

[1] - Full analysis set; Change to baseline

[2] - Full analysis set; Change to baseline

Statistical analyses

Statistical analysis title	Change to baseline (after 1 year of treatment)

Statistical analysis description:

Change to baseline (after 1 year of treatment).

Comparison groups	Active treatment SLIT v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.004 [4]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-109.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-183.53
upper limit	-35.59
Variability estimate	Standard error of the mean
Dispersion value	37.39

Notes:

[3] - The statistical null-hypothesis of no difference between the mean changes of AUC of SMS between treatment groups was tested in a confirmatory sense with an ANOVA model adjusted by gender and year of baseline.

[4] - Superiority of active treatment over placebo after one year of SLIT was demonstrated.

Secondary: 1_03a & 03b_AUC of symptom score and AUC of medication score; DBP

End point title	1_03a & 03b_AUC of symptom score and AUC of medication score; DBP

End point description:

Change in the AUC of the score, evaluated separately by symptom score and by medication score.

Criteria for the symptom score and by medication score are summarized under the endpoint 1_01.

When the symptom score was evaluated by gender, the results were similar to the results of the FAS.

AUC=Area under the curve
FAS=Full analysis set
SMS=Symptom and medication score

End point type	Secondary

End point timeframe:

Baseline to 1 year of treatment.

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[5]	42[6]		
Units: score				
arithmetic mean (standard deviation)				
Symptom score	-126.6 (± 130.7)	-55.2 (± 144.2)		
Medication score	-85.9 (± 121.1)	-42.6 (± 106.5)		

Notes:

[5] - Full analysis set; Change to baseline

[6] - Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 1_04_AUC of rhinoconjunctivitis (RC)-SMS; DBP

End point title	1_04_AUC of rhinoconjunctivitis (RC)-SMS; DBP

End point description:

AUC of rhinoconjunctivitis (RC)-SMS

The AUC of RC-SMS (which scored only symptoms and medication related to nose and eyes) was evaluated as a secondary endpoint after one year of treatment.
Criteria for the symptom score and by medication score are summarized under the endpoint 1_01.

AUC=Area under the curve
FAS=Full analysis set
RC=Rhinoconjunctivitis
SMS=Symptom and medication score

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[7]	42[8]		
Units: score				
arithmetic mean (standard deviation)	-199.7 (± 206.1)	-83.6 (± 186)		

Notes:

[7] - Full analysis set; Change to baseline

[8] - Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 1_05_Number of well days overall; DBP

End point title	1_05_Number of well days overall; DBP

End point description:

The number of well days was defined as the number of days with symptom score ≤ 4 and medication score of 0.

When the number of well days was evaluated by subgroups gender, the results were similar to those observed for the overall number of well days.

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[9]	42[10]		
Units: day				
arithmetic mean (standard deviation)	9.3 (± 12.4)	5.1 (± 11.1)		

Notes:

[9] - Full analysis set; Change to baseline

[10] - Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 1_06_Rhinoconjunctivitis (RC) well days; DBP

End point title	1_06_Rhinoconjunctivitis (RC) well days; DBP

End point description:

The number of RC well days was defined as the number of days with RC symptom score ≤ 3 and medication score of 0.

RC=Rhinoconjunctivitis

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[11]	42[12]		
Units: day				
arithmetic mean (standard deviation)	8.6 (± 12.1)	4.3 (± 10.6)		

Notes:

[11] - Full analysis set; Change to baseline

[12] - Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 1_07_Responder analysis overall; DBP

End point title	1_07_Responder analysis overall; DBP

End point description:

Patient’s response to the study medication defined as an improvement of at least 40% in the AUC of the SMS in the season after the 1st year of treatment compared to the AUC of the SMS in the baseline season.

Shown are patients who were responders.
The number of patients 'Missing' are shown under the results table.

There were no substantial differences observed when analysing the response by gender, as compared with the FAS.

AUC=Area under the curve
FAS=Full analysis set
SMS=Symptom and medication score

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[13]	42[14]		
Units: patient	63	14		

Notes:

[13] - Full analysis set

[14] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 1_08_Conjunctival provocation test (CPT); DBP

End point title	1_08_Conjunctival provocation test (CPT); DBP

End point description:

CPT reproduces the events occurring by instilling an allergen on the ocular surface.

A lyophilized grass pollen allergen extract with a standardised activity wasreconstituted and diluted for the provocation test. The initial concentration was 5 SBU/mL. Titration was performed with increasing concentrations and the highest concentration was 5,000 SBU/mL.

Changes in specific CPT results (threshold concentration) at baseline to the end of one treatment year were evaluated in the FAS.

The evaluation of the CPT results (threshold concentration) by gender was difficult to interpret due to the small sample size in the single subgroups.

CPT=Conjunctival provocation test
FAS=Full analysis set
SBU=Standard biological units per millilitre

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132[15]	47[16]		
Units: patient				
Missing	1	1		
Improved	71	19		
Unchanged	47	20		
Worsened	13	7		

Notes:

[15] - FAS=Full analysis set

[16] - FAS=Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 1_09_Immunological profile: IgE; DBP

End point title	1_09_Immunological profile: IgE; DBP

End point description:

Immunological profile: IgE

Specific IgE, IgG1, and IgG4 values were evaluated at screening visit V I/-1, after grass pollen season in baseline year at V I/6, after three months of treatment at V I/10 and V II/12 and every study year before (V II/1 and V III/1) and at the end of the grass pollen season (V II/7 and V III/6) as well as the absolute change from screening. Median values are presented because of the wide variation of the measurements and the small sample size of the placebo population.

Immunologic changes in IgE, IgG1, and IgG4 antibody levels were also evaluated by gender. The immunologic results in the subgroup analyses were similar to the results from the FAS.

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.
V I/6 Baseline
V I/10 After 3 months of treatment
V II/1 Before grass pollen season
V II/7 At end of grass pollen season

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132[17]	47[18]		
Units: kUA/L				
median (full range (min-max))				
V I/6 Baseline	6.4 (-24.2 to 47.1)	7.6 (-5.4 to 41.7)		
V I/10 After three months of treatment	2 (-41.8 to 47.5)	0.6 (-14 to 24.2)		
V II/1 Before grass pollen season	1.3 (-30.4 to 37.7)	0 (-19 to 24.2)		
V II/7 At end of grass pollen season	1.8 (-32 to 37.7)	10.2 (-1.9 to 46.6)		

Notes:

[17] - Full analysis set; Change to baseline
V I/6 N=129
V I/10 N=129
V II/1 N=126
V II/7 N=130

[18] - Full analysis set; Change to baseline
V I/6 N=45
V I/10 N=46
V II/1 N=43
V II/7 N=46

Statistical analyses

No statistical analyses for this end point

Secondary: 1_10_Immunological profile: IgG1; DBP

End point title	1_10_Immunological profile: IgG1; DBP

End point description:

Immunological profile: IgG1

Specific IgE, IgG1, and IgG4 values were evaluated at screening visit V I/-1, after grass pollen season in baseline year at
V I/6, after three months of treatment at V I/10 and V II/12 and every study year before (V II/1 and V III/1) and at the end of the grass pollen season (V II/7 and V III/6) as well as the absolute change from screening. Median values are presented
because of the wide variation of the measurements and the small sample size of the placebo population.

Immunologic changes in IgE, IgG1, and IgG4 antibody levels were also evaluated by gender. The immunologic results in the subgroup analyses were similar to the results from the FAS.

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.
V I/6 Baseline
V I/10 After three months of treatment
V II/1 Before grass pollen season
V II/7 At end of grass pollen season

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132[19]	47[20]		
Units: µg/L				
median (full range (min-max))				
V I/6 Baseline	210 (-9387 to 9706)	188 (-740 to 6126)		
V I/10 After three months of treatment	898 (-9522 to 64821)	-18.5 (-1134 to 1792)		
V II/1 Before grass pollen season	1046 (-9522 to 84545)	-49 (-1134 to 391)		
V II/7 At end of grass pollen season	895.5 (-8762 to 105313)	107 (-718 to 4924)		

Notes:

[19] - Full analysis set; Change to baseline
V I/6 N=129
V I/10 N=129
V II/1 N=126
V II/7 N=130

[20] - Full analysis set; Change to baseline
V I/6 N=45
V I/10 N=46
V II/1 N=43
V II/7 N=46

Statistical analyses

No statistical analyses for this end point

Secondary: 1_11_Immunological profile: IgG4; DBP

End point title	1_11_Immunological profile: IgG4; DBP

End point description:

Immunological profile: IgG4

Specific IgE, IgG1, and IgG4 values were evaluated at screening visit V I/-1, after grass pollen season in baseline year at
V I/6, after three months of treatment at V I/10 and V II/12 and every study year before (V II/1 and V III/1) and at the end of the grass pollen season (V II/7 and V III/6) as well as the absolute change from screening. Median values are presented
because of the wide variation of the measurements and the small sample size of the placebo population.

Immunologic changes in IgE, IgG1, and IgG4 antibody levels were also evaluated by gender. The immunologic results in the subgroup analyses were similar to the results from the FAS.

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.
V I/6 Baseline
V I/10 After three months of treatment
V II/1 Before grass pollen season
V II/7 At end of grass pollen season

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132[21]	47[22]		
Units: µg/L				
median (full range (min-max))				
V I/6 Baseline	162 (-544 to 24673)	141 (-118 to 7206)		
V I/10 After three months of treatment	1264 (-15531 to 86331)	0 (-487 to 763)		
V II/1 Before grass pollen season	1234 (-15531 to 278808)	-1 (-1702 to 232)		
V II/7 At end of grass pollen season	1204.5 (-10799 to 187812)	96 (-1246 to 2265)		

Notes:

[21] - Full analysis set; Change to baseline
V I/6 N=129
V I/10 N=129
V II/1 N=126
V II/7 N=130

[22] - Full analysis set; Change to baseline
V I/6 N=45
V I/10 N=46
V II/1 N=43
V II/7 N=46

Statistical analyses

No statistical analyses for this end point

Secondary: 1_12a & 1_12 b_Vital signs: Diastolic blood pressure; Systolic blood pressure; DBP

End point title	1_12a & 1_12 b_Vital signs: Diastolic blood pressure; Systolic blood pressure; DBP

End point description:

Diastolic blood pressure [mmHg]; Systolic blood pressure [mmHg];

Diastolic blood pressure, Systolic blood pressure: Change to baseline

Changes in vital signs from baseline visit (V I/-1) to last visit in first treatment year (V II/7).

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.
From baseline visit (V I/-1) to last visit treatment year (V II/7).

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131[23]	46[24]		
Units: mmHg				
median (full range (min-max))				
Diastolic blood pressure	0 (-30 to 35)	0 (-22 to 25)		
Systolic blood pressure	0 (-23 to 43)	-1 (-20 to 24)		

Notes:
[23] - Safety analysis set
[24] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 1_13_Vital signs: Heart rate; DBP

End point title	1_13_Vital signs: Heart rate; DBP

End point description:

Vital signs: Heart rate (Beats per minute)

Heart rate: Change to baseline

Changes in vital signs from baseline visit (V I/-1) to last visit in first treatment year (V II/7).

bpm=Beats per minute

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.
From baseline visit (V I/-1) to last visit treatment year (V II/7).

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[25]	46[26]		
Units: bpm				
median (full range (min-max))	-2 (-36 to 53)	2 (-30 to 48)		

Notes:
[25] - Safety analysis set
[26] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 1_14_Vital signs: Respiratory rate; DBP

End point title	1_14_Vital signs: Respiratory rate; DBP

End point description:

Vital signs: Respiratory rate (breaths per min)

Changes in vital signs from baseline visit (V I/-1) to last visit in first treatment year (V II/7).

End point type	Secondary

End point timeframe:

Baseline to 1 year after treatment.
From baseline visit (V I/-1) to last visit treatment year (V II/7).

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[27]	46[28]		
Units: breaths per min				
median (full range (min-max))	0 (-22 to 24)	0 (-17 to 12)		

Notes:

[27] - Safety analysis set

[28] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 2_01_Change of the area under the curve (AUC) of symptom and medication score (SMS) after treatment; OLP

End point title	2_01_Change of the area under the curve (AUC) of symptom and medication score (SMS) after treatment; OLP

End point description:

AUC of SMS over all treatment years for the FAS population during the OLP, by treatment group.

Treatment groups:
- 'Active-Active' represents patients who received active treatment during the double-blind phase and active treatment during the open-label phase.
- 'Placebo-Active' represents patients who received placebo during the double-blind phase and active treatment during the open-label phase.

Criteria for the symptom score and by medication score are summarized under the endpoint 1_01.
The number of patients available at each time point is shown under the results table.

AUC=Area under the curve
FAS=Full analysis set
OLP=Open label phase
SMS=Symptom and medication score

End point type	Secondary

End point timeframe:

Baseline to 1st, 2nd, 3rd, 4th year after treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[29]	36[30]		
Units: score				
arithmetic mean (standard deviation)				
1st year	-213.3 (± 209.4)	-132 (± 183.7)		
2nd year	-288.5 (± 251)	-232.1 (± 202.8)		
3rd year	-350.8 (± 276.2)	-328.2 (± 207.4)		

4th year	0 (± 0)	-312.8 (± 240.5)		

Notes:

[29] - Full analysis set; Change to baseline
1st year N=118
2nd year N=115
3rd year N=110
4th year N=NA

[30] - Full analysis set; Change to baseline
1st year N=34
2nd year N=36
3rd year N=35
4th year N=26

Statistical analyses

No statistical analyses for this end point

Secondary: 2_03a_AUC of symptom score; OLP

End point title	2_03a_AUC of symptom score; OLP

End point description:

Criteria for the symptom score and medication score are summarized under the endpoint 1_01.
The number of patients available at each time point is shown under the results table.
For the treatment group 'Active-Active', 4th year, the AUC of symptom score was not performed; because the EudraCT database requires a value in the Table, this is indicated as 0 (±0).

End point type	Secondary

End point timeframe:

Baseline to 1st, 2nd, 3rd, 4th year after treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[31]	36[32]		
Units: score				
arithmetic mean (standard deviation)				
1st year	-126.2 (± 132.1)	-78.6 (± 130.6)		
2nd year	-166.6 (± 168.4)	-136.3 (± 139.4)		
3rd year	-199.6 (± 170)	-185.2 (± 152.6)		
4th year	0 (± 0)	-183.1 (± 140.6)		

Notes:

[31] - Full analysis set; Change to baseline
1st year N=118
2nd year N=115
3rd year N=110
4th year N=NA

[32] - Full analysis set; Change to baseline
1st year N=34
2nd year N=36
3rd year N=35
4th year N=26

Statistical analyses

No statistical analyses for this end point

Secondary: 2_03b_AUC of medication score; OLP

End point title	2_03b_AUC of medication score; OLP

End point description:

Criteria for the symptom score and medication score are summarized under the endpoint 1_01.
The number of patients available at each time point is shown under the results table.
For the treatment group 'Active-Active', 4th year, the AUC of medication score was not performed; because the EudraCT database requires a value in the Table, this is indicated as 0 (±0).

End point type	Secondary

End point timeframe:

Baseline to 1st, 2nd, 3rd, 4th year after treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[33]	36[34]		
Units: score				
arithmetic mean (standard deviation)				
1st year	-87.1 (± 118.3)	-53.4 (± 112.1)		
2nd year	-121.8 (± 124.3)	-95.8 (± 127.4)		
3rd year	-151.2 (± 153.2)	-143.1 (± 113.4)		
4th year	0 (± 0)	-129.7 (± 127.2)		

Notes:

[33] - Full analysis set; Change to baseline
1st year N=118
2nd year N=115
3rd year N=110
4th year N=NA
[34] - Full analysis set; Change to baseline
1st year N=34
2nd year N=36
3rd year N=35
4th year N=26

Statistical analyses

No statistical analyses for this end point

Secondary: 2_04_AUC of rhinoconjunctivitis (RC)-SMS; OLP

End point title	2_04_AUC of rhinoconjunctivitis (RC)-SMS; OLP

End point description:

AUC of rhinoconjunctivitis (RC)-SMS.

For further details please see the description for endpoint 1-04.

End point type	Secondary

End point timeframe:

Baseline to 1st, 2nd, 3rd, 4th year after treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[35]	36[36]		
Units: score				
arithmetic mean (standard deviation)				
1st year	-200.3 (± 204)	-114.7 (± 179)		
2nd year	-263.3 (± 243.6)	-220.7 (± 193.8)		
3rd year	-334.3 (± 268.9)	-297 (± 207.3)		
4th year	0 (± 0)	-266.5 (± 216.8)		

Notes:

[35] - Full analysis set; Change to baseline
1st year N=118
2nd year N=115
3rd year N=110
4th year N=NA

[36] - Full analysis set; Change to baseline
1st year N=34
2nd year N=36
3rd year N=35
4th year N=26

Statistical analyses

No statistical analyses for this end point

Secondary: 2_05_Number of well days overall; OLP

End point title	2_05_Number of well days overall; OLP

End point description:

The number of well days was defined as the number of days with symptom score ≤ 4 and medication score of 0.

End point type	Secondary

End point timeframe:

Baseline to 1st, 2nd, 3rd, 4th year after treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[37]	36[38]		
Units: day				
arithmetic mean (standard deviation)				
1st year	8.8 (± 12.1)	6.1 (± 11.6)		
2nd year	14.1 (± 13.9)	11.3 (± 15.3)		
3rd year	19.8 (± 16.2)	19.5 (± 15.3)		
4th year	0 (± 0)	22.7 (± 14.7)		

Notes:

[37] - Full analysis set; Change to baseline
1st year N=118
2nd year N=115
3rd year N=110
4th year N=NA
[38] - Full analysis set; Change to baseline
1st year N=34
2nd year N=36
3rd year N=35
4th year N=26

Statistical analyses

No statistical analyses for this end point

Secondary: 2_06_Rhinoconjunctivitis (RC) well days; OLP

End point title	2_06_Rhinoconjunctivitis (RC) well days; OLP

End point description:

The number of RC well days was defined as the number of days with RC symptom score ≤ 3 and medication score of 0.

RC=Rhinoconjunctivitis

End point type	Secondary

End point timeframe:

Baseline to 1st, 2nd, 3rd, 4th year after treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[39]	36[40]		
Units: day				
arithmetic mean (standard deviation)				
1st year	8.2 (± 11.8)	5 (± 11.3)		
2nd year	13.2 (± 13.8)	9.9 (± 15)		
3rd year	18.5 (± 16)	17.9 (± 15.9)		
4th year	0 (± 0)	20.3 (± 15.2)		

Notes:

[39] - Full analysis set; Change to baseline
1st year N=118
2nd year N=115
3rd year N=110
4th year N=NA
[40] - Full analysis set; Change to baseline
1st year N=34
2nd year N=36
3rd year N=35
4th year N=26

Statistical analyses

No statistical analyses for this end point

Secondary: 2_07_Responder analysis overall; OLP

End point title	2_07_Responder analysis overall; OLP

End point description:

A positive response to study medication was defined as at least 40% improvement of AUC of SMS from baseline to the end of treatment year.

Shown are patients who were responders by treatment year.
The number of patients 'Missing' for a particular time point evaluation are shown under the results table.
For the treatment group 'Active-Active', 4th year, the responder analysis overall was not performed; because the EudraCT database requires a value in the Table, this is indicated as 0 (±0).

End point type	Secondary

End point timeframe:

Baseline to 1st, 2nd, 3rd, 4th year after treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[41]	36[42]		
Units: patient				
1st year	59	13		
2nd year	79	24		
3rd year	81	30		
4th year	0	21		

Notes:

[41] - Full analysis set
Missing
1st y N=7
2nd y N=10
3rd y N=15
4th y N=NA
[42] - Full analysis set
Missing
1st y N=2
2nd y N=0
3rd y N=1
4th y N=10

Statistical analyses

No statistical analyses for this end point

Secondary: 2_08_Conjunctival provocation test (CPT); OLP

End point title	2_08_Conjunctival provocation test (CPT); OLP

End point description:

For details please see the description for endpoint 1-09.

End point type	Secondary

End point timeframe:

Baseline to end of 3rd year after treatment.

End point values	'Active-Active' treatment			
Subject group type	Reporting group			
Number of subjects analysed	125[43]			
Units: patient				
Missing	6			
Improved	105			
Unchanged	8			
Worsened	6			

Notes:

[43] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 2_09_Immunological profile: IgE; OLP

End point title	2_09_Immunological profile: IgE; OLP

End point description:

Number of patients in the study groups
Active-Active
V I/6 N=122
V I/10 N=122
V II/1 N=119
V II/7 N=123
V II/12 N=46
V III/1 N=40
V III/6 N=48

Placebo-Active
V I/6 N=34
V I/10 N=35
V II/1 N=33
V II/7 N=36
V II/12 N=15
V III/1 N=14
V III/6 N=17

End point type	Secondary

End point timeframe:

Baseline to visit:
V I/6 Baseline
V I/10 After 3 months of treatm
V II/1 Before grass pollen season
V II/7 At end of grass pollen season
V II/12 After 3 months of treatm
V III/1 Before grass pollen season
V III/6 At end of grass pollen season

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[44]	36[45]		
Units: kUA/L				
median (full range (min-max))				
V I/6	6.43 (-24.2 to 47.1)	10.94 (-5.4 to 41.7)		
V I/10	1.98 (-41.8 to 47.5)	1.23 (-14 to 24.2)		
V II/1	1.25 (-30.4 to 37.7)	0 (-14 to 24.2)		
V II/7	1.54 (-32 to 37.7)	11.09 (-1.6 to 46.6)		
V II/12	-1.82 (-34.8 to 26)	13.5 (-7.9 to 37.7)		
V III/1	-3.67 (-41.4 to 20.7)	2.53 (-5.9 to 35.6)		
V III/6	-0.2 (-41.4 to 31.6)	3.81 (-9.3 to 35.6)		

Notes:

[44] - Full analysis set; Change to baseline

[45] - Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 2_10_Immunological profile: IgG1; OLP

End point title	2_10_Immunological profile: IgG1; OLP

End point description:

Number of patients in the study groups
Active-Active
V I/6 N=122
V I/10 N=122
V II/1 N=119
V II/7 N=123
V II/12 N=46
V III/1 N=40
V III/6 N=48

Placebo-Active
V I/6 N=34
V I/10 N=35
V II/1 N=33
V II/7 N=36
V II/12 N=15
V III/1 N=14
V III/6 N=17

End point type	Secondary

End point timeframe:

Baseline to visit:
V I/6 Baseline
V I/10 After 3 months of treatm
V II/1 Before grass pollen season
V II/7 At end of grass pollen season
V II/12 After 3 months of treatm
V III/1 Before grass pollen season
V III/6 At end of grass pollen season

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[46]	36[47]		
Units: µg/L				
median (full range (min-max))				
V I/6	215 (-9387 to 9706)	181 (-740 to 6126)		
V I/10	911 (-9522 to 64821)	0 (-740 to 1792)		
V II/1	1054 (-9522 to 84545)	-12 (-780 to 391)		
V II/7	887 (-8762 to 105313)	128.5 (-718 to 4924)		
V II/12	850.5 (-258 to 86801)	553 (-197 to 9102)		
V III/1	598 (-242 to 56380)	549 (-62 to 13123)		
V III/6	725.5 (-4067 to 67302)	420 (-1379 to 9209)		

Notes:

[46] - Full analysis set; Change to baseline

[47] - Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 2_11_Immunological profile: IgG4; OLP

End point title	2_11_Immunological profile: IgG4; OLP

End point description:

Number of patients in the study groups
Active-Active
V I/6 N=122
V I/10 N=122
V II/1 N=119
V II/7 N=123
V II/12 N=46
V III/1 N=40
V III/6 N=48

Placebo-Active
V I/6 N=34
V I/10 N=35
V II/1 N=33
V II/7 N=36
V II/12 N=15
V III/1 N=14
V III/6 N=17

End point type	Secondary

End point timeframe:

Baseline to visit:
V I/6 Baseline
V I/10 After 3 months of treatm
V II/1 Before grass pollen season
V II/7 At end of grass pollen season
V II/12 After 3 months of treatm

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[48]	36[49]		
Units: µg/L				
median (full range (min-max))				
V I/6	164 (-544 to 24673)	148 (-118 to 7206)		
V I/10	1352 (-15531 to 86331)	0 (-283 to 763)		
V II/1	1293 (-15531 to 278808)	-1 (-1702 to 232)		
V II/7	1435 (-10799 to 187812)	119.5 (-1246 to 2265)		
V II/12	1381.5 (-53 to 158729)	195 (-181 to 9993)		
V III/1	657.5 (-47 to 117410)	492.5 (-19 to 11489)		
V III/6	1138 (-16 to 150727)	416 (-12 to 8454)		

Notes:

[48] - Full analysis set; Change to baseline

[49] - Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 2_12a_Vital signs: Diastolic blood pressure; OLP

End point title	2_12a_Vital signs: Diastolic blood pressure; OLP

End point description:

Diastolic blood pressure: change to baseline from the indicated study visits, during OLP.

OLP=Open-label phase

End point type	Secondary

End point timeframe:

Baseline to visit:
V II/7 At end of grass pollen season
V III/6
V IV/6
V V/6

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[50]	46[51]		
Units: mmHg				
median (full range (min-max))				
V II/7	0 (-30 to 35)	0 (-22 to 25)		
V III/6	2 (-36 to 30)	0 (-16 to 20)		
V IV/6	4.5 (-23 to 37)	3.5 (-18 to 25)		
V V/6	0 (0 to 0)	1 (-25 to 20)		

Notes:

[50] - Safety analysis set; change to baseline
V II/7 N=129
V III/6 N=127
V IV/6 N=122
V V/6 N=NA

[51] - Safety analysis set; change to baseline
V II/7 N=46
V III/6 N=37
V IV/6 N=36
V V/6 N=34

Statistical analyses

No statistical analyses for this end point

Secondary: 2_12b_Vital signs: Systolic blood pressure; OLP

End point title	2_12b_Vital signs: Systolic blood pressure; OLP

End point description:

Systolic blood pressure: change to baseline from the indicated study visits, during OLP.

OLP=Open-label phase

End point type	Secondary

End point timeframe:

Baseline to visit:
V II/7 At end of grass pollen season
V III/6
V IV/6
V V/6

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[52]	46[53]		
Units: mmHg				
median (full range (min-max))				
V II/7	0 (-23 to 43)	-1 (-20 to 24)		
V III/6	0 (-39 to 28)	0 (-23 to 25)		
V IV/6	5 (-39 to 37)	0.5 (-20 to 25)		
V V/6	0 (0 to 0)	5 (-15 to 21)		

Notes:

[52] - Safety analysis set; change to baseline
V II/7 N=129
V III/6 N=127
V IV/6 N=122
V V/6 N=NA
[53] - Safety analysis set; change to baseline
V II/7 N=46
V III/6 N=37
V IV/6 N=36
V V/6 N=34

Statistical analyses

No statistical analyses for this end point

Secondary: 2_13_Vital signs: Heart rate; OLP

End point title	2_13_Vital signs: Heart rate; OLP

End point description:

Vital signs: Heart rate (Beats per minute)

Change to baseline from the indicated study visits, during OLP.

bpm=Beats per minute
OLP=Open-label phase

End point type	Secondary

End point timeframe:

Baseline to visit:
V II/7 At end of grass pollen season
V III/6
V IV/6
V V/6

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[54]	46[55]		
Units: bpm				
median (full range (min-max))				
V II/7	-2 (-36 to 53)	2 (-30 to 48)		
V III/6	-2 (-36 to 35)	0 (-52 to 42)		
V IV/6	-6 (-40 to 28)	-2 (-40 to 32)		
V V/6	0 (0 to 0)	-2.5 (-40 to 28)		

Notes:

[54] - Safety analysis set; change to baseline
V II/7 N=128
V III/6 N=127
V IV/6 N=122
V V/6 N=NA
[55] - Safety analysis set; change to baseline
V II/7 N=46
V III/6 N=37
V IV/6 N=36
V V/6 N=34

Statistical analyses

No statistical analyses for this end point

Secondary: 2_14_Vital signs: Respiratory rate; OLP

End point title	2_14_Vital signs: Respiratory rate; OLP

End point description:

Vital signs: Respiratory rate (breaths per min)

Change to baseline from the indicated study visits, during OLP.

bpm=Beats per minute
OLP=Open-label phase

End point type	Secondary

End point timeframe:

Baseline to visit:
V II/7 At end of grass pollen season
V III/6
V IV/6
V V/6

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[56]	46[57]		
Units: breaths per min				
median (full range (min-max))				
V II/7	0 (-22 to 24)	0 (-17 to 12)		
V III/6	0 (-18 to 18)	0 (-16 to 6)		
V IV/6	-1 (-23 to 18)	0 (-18 to 10)		
V V/6	0 (0 to 0)	0 (-17 to 18)		

Notes:

[56] - Safety analysis set; change to baseline
V II/7 N=126
V III/6 N=126
V IV/6 N=122
V V/6 N=NA
[57] - Safety analysis set; change to baseline
V II/7 N=46
V III/6 N=37
V IV/6 N=36
V V/6 N=34

Statistical analyses

No statistical analyses for this end point

Secondary: 3_01_Change of the area under the curve (AUC) of symptom and medication score (SMS); FU

End point title	3_01_Change of the area under the curve (AUC) of symptom and medication score (SMS); FU

End point description:

This prospective follow-up (FU) phase included patients who had previously received active treatment in the course of the clinical study. During the FU phase, no study treatments were administered to the patients (treatment-free).

For the FU phase of the study, the FU2 Full analysis set (FAS), which was a subset of the FU ALL patients, was used for the efficacy assessments and included 77 patients (Active - Active) and 23

patients (Placebo - Active) with AUC diary data available for at least 1 season during the FU.

Criteria for the symptom score and by medication score are summarized under the endpoint 1-01.
Data show results for patients in the subset FU2 Full analysis set, over the entire study years (y).

FU2 Full analysis set
Active- Active reporting group
Pbo N=0
Act y1 N=71
Act y2 N=70
Act y3 N=71
FU y1 N=34
FU y2 N=65

Placebo- Active reporting group
Pbo N=21
Act y1 N=22
Act y2 N=22
Act y3 N=18
FU y1 N=20
FU y2 N=19

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[58]	23[59]		
Units: score				
arithmetic mean (standard deviation)				
Placebo	0 (± 0)	-161.6 (± 189.1)		
Active year 1	-226.7 (± 213.6)	-231.5 (± 163.6)		
Active year 2	-285.5 (± 265.1)	-292.8 (± 193.5)		
Active year 3	-346 (± 256.3)	-296 (± 261.4)		
FU year 1	-286.8 (± 218.9)	-331.7 (± 298.4)		
FU year 2	-340.7 (± 258.3)	-288.8 (± 209.6)		

Notes:

[58] - FU2 Full Analysis Set; Change to baseline

[59] - FU2 Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_03a_AUC of symptom score; FU

End point title	3_03a_AUC of symptom score; FU

End point description:

Criteria for the symptom score score are summarized under the endpoint 1_01.
The FU2 Full analysis set (FAS), which was a subset of the FU ALL patients, was used for the efficacy

assessments is described in endpoint 3_01.

The number of patients available at each time point is shown below.

FU2 Full analysis set
Active- Active reporting group
Pbo=0
Act y1 N=71
Act y2 N=70
Act y3 N=71
FU y1 N=34
FU y2 N=65

Placebo- Active reporting group
Pbo N=21
Act y1 N=22
Act y2 N=22
Act y3 N=18
FU y1 N=20
FU y2 N=19

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[60]	23[61]		
Units: score				
arithmetic mean (standard deviation)				
Placebo	0 (± 0)	-81.1 (± 142.5)		
Active year 1	-138.9 (± 146.1)	-133.6 (± 134.4)		
Active year 2	-174.6 (± 179.4)	-178.2 (± 156.6)		
Active year 3	-210.9 (± 162.1)	-178.4 (± 162.8)		
FU year 1	-194.7 (± 132.3)	-180.6 (± 209)		
FU year 2	-208.7 (± 169.1)	-181.4 (± 142.5)		

Notes:

[60] - FU2 Full analysis set; Change to baseline

[61] - FU2 Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_03b_AUC of medication score; FU

End point title	3_03b_AUC of medication score; FU

End point description:

Criteria for the medication score are summarized under the endpoint 1_01.
The FU2 Full analysis set (FAS), which was a subset of the FU ALL patients, was used for the efficacy assessments is described in endpoint 3_01.

The number of patients available at each time point is shown below.

FU2 Full analysis set
Active- Active reporting group
Pbo=0
Act y1 N=71
Act y2 N=70
Act y3 N=71
FU y1 N=34
FU y2 N=65

Placebo- Active reporting group
Pbo N=21
Act y1 N=22
Act y2 N=22
Act y3 N=18
FU y1 N=20
FU y2 N=19

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[62]	23[63]		
Units: score				
arithmetic mean (standard deviation)				
Placebo	0 (± 0)	-80.6 (± 98.2)		
Active year 1	-87.8 (± 113.5)	-97.9 (± 86.9)		
Active year 2	-110.9 (± 121.5)	-114.6 (± 104.4)		
Active year 3	-135.1 (± 144.6)	-117.6 (± 130.5)		
FU year 1	-92 (± 130.8)	-151.2 (± 135.2)		
FU year 2	-132 (± 140.7)	-107.4 (± 125.2)		

Notes:

[62] - FU2 Full analysis set; Change to baseline

[63] - FU2 Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_04_AUC of rhinoconjunctivitis (RC)-SMS; FU

End point title	3_04_AUC of rhinoconjunctivitis (RC)-SMS; FU

End point description:

AUC of rhinoconjunctivitis (RC)-SMS.
For further details please see the description for endpoint 1_04.

The FU2 Full analysis set (FAS), which was a subset of the FU ALL patients, was used for the efficacy assessments is described in endpoint 3_01.

Criteria for the symptom score and by medication score are summarized under the endpoint 1_01.
Data show results for patients in the subset FU2 Full analysis set, over the entire study years (y).

FU2 Full analysis set
Active- Active reporting group
Pbo=0
Act y1 N=71
Act y2 N=70
Act y3 N=71
FU y1 N=34
FU y2 N=65

Placebo- Active reporting group
Pbo N=21
Act y1 N=22
Act y2 N=22
Act y3 N=18
FU y1 N=20
FU y2 N=19

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[64]	23[65]		
Units: score				
arithmetic mean (standard deviation)				
Placebo	0 (± 0)	-132 (± 182)		
Active year 1	-214.9 (± 210.3)	-202 (± 169)		
Active year 2	-265.5 (± 258)	-257.5 (± 189)		
Active year 3	-333.5 (± 250.8)	-253.7 (± 237)		
FU year 1	-263.9 (± 219.6)	-282.2 (± 287.4)		
FU year 2	-320.4 (± 256.2)	-242.5 (± 192.3)		

Notes:

[64] - FU2 Full analysis set; Change to baseline

[65] - FU2 Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_05_Number of well days, overall; FU

End point title	3_05_Number of well days, overall; FU

End point description:

The number of well days was defined as the number of days with symptom score ≤ 4 and medication score of 0.

Criteria for the symptom score and by medication score are summarized under the endpoint 1_01.
Data show results for patients in the subset FU2 Full analysis set, over the entire study years (y).

FU2 Full analysis set
Active- Active reporting group
Pbo=0
Act y1 N=71

Act y2 N=70
Act y3 N=71
FU y1 N=34
FU y2 N=65

Placebo- Active reporting group
Pbo N=21
Act y1 N=22
Act y2 N=22
Act y3 N=18
FU y1 N=20
FU y2 N=19

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[66]	23[67]		
Units: day				
arithmetic mean (standard deviation)				
Placebo	0 (± 0)	7.2 (± 13.6)		
Active year 1	10.3 (± 12.1)	10 (± 14.2)		
Active year 2	13.2 (± 14.5)	15.3 (± 14.4)		
Active year 3	19.9 (± 16.1)	20.2 (± 16.5)		
FU year 1	18.7 (± 15.4)	19.2 (± 17.5)		
FU year 2	18.7 (± 15)	15.7 (± 12)		

Notes:

[66] - FU2 Full analysis set; Change to baseline

[67] - FU2 Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_06_Rhinoconjunctivitis (RC) well days overall; FU

End point title	3_06_Rhinoconjunctivitis (RC) well days overall; FU

End point description:

The number of RC well days was defined as the number of days with RC symptom score ≤ 3 and medication score of 0.

Criteria for the medication score are summarized under the endpoint 1_01.
The FU2 Full analysis set (FAS), which was a subset of the FU ALL patients, was used for the efficacy assessments is described under the endpoint xx.

The number of patients available at each time point is shown below.

FU2 Full analysis set
Active- Active reporting group
Pbo=0
Act y1 N=71
Act y2 N=70
Act y3 N=71
FU y1 N=34
FU y2 N=65

Placebo- Active reporting group
Pbo N=21
Act y1 N=22
Act y2 N=22
Act y3 N=18
FU y1 N=20
FU y2 N=19

RC=Rhinoconjunctivitis

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[68]	23[69]		
Units: day				
arithmetic mean (standard deviation)				
Placebo	0 (± 0)	5.6 (± 13)		
Active year 1	9.6 (± 11.7)	8 (± 14)		
Active year 2	12.6 (± 14.2)	14 (± 15)		
Active year 3	19 (± 15.9)	16.9 (± 16.4)		
FU year 1	17.4 (± 15.6)	17.6 (± 17.7)		
FU year 2	17.8 (± 15.3)	13.5 (± 11.6)		

Notes:

[68] - FU2 Full analysis set; Change to baseline

[69] - FU2 Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_07_Responder analysis overall; FU

End point title	3_07_Responder analysis overall; FU

End point description:

A positive response to study medication was defined as at least 40% improvement of AUC of SMS from baseline to the end of treatment year.

Shown are patients who were responders by treatment year.
The number of patients 'Missing' for a particular time point evaluation are shown under the results table.

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[70]	23[71]		
Units: patient				
Placebo	0	9		
Active year 1	40	14		
Active year 2	46	18		
Active year 3	52	14		
FU year 1	26	16		
FU year 2	50	15		

Notes:

[70] - FU2 Full analysis set
Missing
Pbo N=Not appl
A y1 N=6
A y2 N=7
A y3 N=6
FU y1 N=43
FU y2 N=12

[71] - FU2 Full analysis set
Missing
Pbo N=2
A y1 N=1
A y2 N=1
A y3 N=5
FU y1 N=3
FU y2 N=4

Statistical analyses

No statistical analyses for this end point

Secondary: 3_08_Responder analysis (AUC of RC-SMS)

End point title	3_08_Responder analysis (AUC of RC-SMS)

End point description:

A positive response to study medication for the AUC of RC-SMS was defined as an at least 40% decrease of AUC of RC-SMS from baseline to the end of 1 treatment year.

Shown are patients who were responders by treatment year.
The number of patients 'Missing' for a particular time point evaluation are shown under the results table.

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[72]	23[73]		
Units: patient				
Placebo	0	9		
Active year 1	39	15		
Active year 2	43	16		
Active year 3	57	14		
FU year 1	25	14		

FU year 2	51	15		

Notes:

[72] - FU2 Full analysis set
Missing
Pbo N=Not appl
A y1 N=6
A y2 N=7
A y3 N=6
FU y1 N=43
FU y2 N=12

[73] - FU2 Full analysis set
Missing
Pbo N=2
A y1 N=1
A y2 N=1
A y3 N=5
FU y1 N=3
FU y2 N=4

Statistical analyses

No statistical analyses for this end point

Secondary: 3_09 _Cured allergy rate according to SMS; FU

End point title	3_09 _Cured allergy rate according to SMS; FU

End point description:

The number of patients with cured allergy was calculated according to Tribanek et al. (refr. below).
A patient was defined to be cured from his allergy if at most 1 mild symptom (or respective medication) per day in mean was present during the 42 days of the evaluation period. The analysis was performed based on the SMS as well as the RC-SMS.

Shown are patients who were responders by treatment year.
The number of patients 'Missing' for a particular time point evaluation are below.

Patients 'Missing' at the evaluation time point
Active - Active treatment group
Act y1 N=1
Act y2 N=2
Act y3 N=2
FU y1 N=42
FU y2 N=7

Pbo - Active treatment group
Act y1 N=0
Act y2 N=0
Act y3 N=4
FU y1 N=2
FU y2 N=3

#) Tribanek M; Narkus A; Haefner D; Meyer H. How to define ‘curing allergy’? Results from a subcutaneous specific immunotherapy study using a high-dose hypoallergenic grass pollen preparation. Allergy 2012;67[S96]:526).

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[74]	23[75]		
Units: patient				
Active year 1	6	2		
Active year 2	9	3		
Active year 3	20	4		
FU year 1	5	4		
FU year 2	13	1		

Notes:

[74] - FU2 Full analysis set

[75] - FU2 Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 3_10_Cured allergy according to RC-SMS

End point title	3_10_Cured allergy according to RC-SMS

End point description:

The number of patients with cured allergy was calculated according to Tribanek et al. (refr. below).
A patient was defined to be cured from his allergy if at most 1 mild symptom (or respective medication) per day in mean was present during the 42 days of the evaluation period. The analysis was performed based on the SMS as well as the RC-SMS.

Shown are patients who were responders by treatment year.
The number of patients 'Missing' for a particular time point evaluation are below.

Patients 'Missing' at the evaluation time point
Active - Active treatment group
Act y1 N=1
Act y2 N=2
Act y3 N=2
FU y1 N=42
FU y2 N=7

Pbo - Active treatment group
Act y1 N=0
Act y2 N=0
Act y3 N=4
FU y1 N=2
FU y2 N=3

#) Tribanek M; Narkus A; Haefner D; Meyer H. How to define ‘curing allergy’? Results from a subcutaneous specific immunotherapy study using a high-dose hypoallergenic grass pollen preparation. Allergy 2012;67[S96]:526).

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[76]	23[77]		
Units: patient				
Active year 1	6	3		
Active year 2	9	3		
Active year 3	24	4		
FU year 1	5	4		
FU year 2	16	1		

Notes:

[76] - FU2 Full analysis set

[77] - FU2 Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 3_11a_Vital signs: Diastolic blood pressure; FU

End point title	3_11a_Vital signs: Diastolic blood pressure; FU

End point description:

Changes in vital signs from baseline visit (V I/-1) to last visit in the FU phase were evaluated.

The number of patients who contributed result to a particular time points is shown below.

Active - Active treatment group
Active year 1 N=85
Active year 2 N=85
Active year 3v N=85
FU year 1 FUV1 N=49
FU year 1 FUV6 N=49
FU year 2 FUV1-2 N=76
FU year 2 FUV6-2 N=74

Placebo - Active treatment group
Placebo N=23
Active year 1 N=23
Active year 2 N=23
Active year 3 N=23
FU year 1 FUV1 N=22
FU year 1 FUV6 N=21
FU year 2 FUV1-2 N=21
FU year 2 FUV6-2 N=20

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85[78]	23[79]		
Units: mmHg				
median (full range (min-max))				
Placebo	0 (0 to 0)	2 (-20 to 25)		
Active year 1	0 (-24 to 30)	2 (-12 to 20)		

Active year 2	2 (-36 to 30)	7 (-7 to 25)		
Active year 3	5 (-20 to 32)	2 (-14 to 20)		
FU year 1 FUV1	5 (-20 to 32)	9.5 (-14 to 30)		
FU year 1 FUV6	5 (-20 to 39)	5 (-10 to 20)		
FU year 2 FUV1-2	5 (-25 to 32)	5 (-10 to 20)		
FU year 2 FUV6-2	6 (-20 to 32)	5.5 (-10 to 20)		

Notes:

[78] - FU All patients set; Change to baseline
Placebo result is not applicable for this treatment group
[79] - FU All patients set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_11b_Vital signs: Systolic blood pressure; FU

End point title	3_11b_Vital signs: Systolic blood pressure; FU

End point description:

Changes in vital signs from baseline visit (V I/-1) to last visit in the FU phase were evaluated.

The number of patients who contributed result to a particular time points is shown below.

Active - Active treatment group
Active year 1 N=85
Active year 2 N=85
Active year 3v N=85
FU year 1 FUV1 N=49
FU year 1 FUV6 N=49
FU year 2 FUV1-2 N=76
FU year 2 FUV6-2 N=74

Placebo - Active treatment group
Placebo N=23
Active year 1 N=23
Active year 2 N=23
Active year 3 N=23
FU year 1 FUV1 N=22
FU year 1 FUV6 N=21
FU year 2 FUV1-2 N=21
FU year 2 FUV6-2 N=20

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85[80]	23[81]		
Units: mmHg				
median (full range (min-max))				
Placebo	0 (0 to 0)	0 (-15 to 22)		
Active year 1	1 (-20 to 25)	1 (-15 to 25)		
Active year 2	1 (-20 to 28)	6 (-13 to 25)		
Active year 3	5 (-15 to 37)	5 (-15 to 21)		
FU year 1 FUV1	5 (-35 to 35)	5.5 (-5 to 25)		

FU year 1 FUV6	9 (-25 to 35)	10 (-3 to 30)		
FU year 2 FUV1-2	10 (-20 to 44)	10 (-9 to 34)		
FU year 2 FUV6-2	10 (-25 to 33)	10 (-7 to 32)		

Notes:

[80] - FU All patients set; Change to baseline
Placebo result is not applicable for this treatment group
[81] - FU All patients set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_12_Vital signs: Heart rate; FU

End point title	3_12_Vital signs: Heart rate; FU

End point description:

Changes in vital signs from baseline visit (V I/-1) to last visit in the FU phase were evaluated.

The number of patients who contributed results to a particular time points is shown below.

Active - Active treatment group
Active year 1 N=84
Active year 2 N=85
Active year 3v N=85
FU year 1 FUV1 N=49
FU year 1 FUV6 N=49
FU year 2 FUV1-2 N=76
FU year 2 FUV6-2 N=74

Placebo - Active treatment group
Placebo N=23
Active year 1 N=23
Active year 2 N=23
Active year 3 N=23
FU year 1 FUV1 N=22
FU year 1 FUV6 N=22
FU year 2 FUV1-2 N=21
FU year 2 FUV6-2 N=20

bpm=beats per minute
FU=Follow-up

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85[82]	23[83]		
Units: bpm				
median (full range (min-max))				
Placebo	0 (0 to 0)	4 (-20 to 24)		
Active year 1	-2 (-36 to 53)	1 (-23 to 42)		
Active year 2	0 (-36 to 32)	-5 (-18 to 32)		
Active year 3	-7 (-40 to 28)	-3 (-28 to 28)		
FU year 1 FUV1	-6 (-31 to 28)	-5 (-22 to 38)		
FU year 1 FUV6	-4 (-36 to 33)	-2 (-22 to 30)		

FU year 2 FUV1-2	-4 (-36 to 56)	-5 (-25 to 30)		
FU year 2 FUV6-2	-4 (-54 to 34)	-2.5 (-25 to 26)		

Notes:

[82] - FU All patients set; Change to baseline
Placebo result is not applicable for this treatment group
[83] - FU All patients set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Secondary: 3_13_Vital signs: Respiratory rate; FU

End point title	3_13_Vital signs: Respiratory rate; FU

End point description:

Vital signs: Respiratory rate (breaths per min)
Changes in vital signs from baseline visit (V I/-1) to last visit in the FU phase were evaluated.

The number of patients who contributed results to a particular time points is shown below.

Active - Active treatment group
Active year 1 N=84
Active year 2 N=85
Active year 3v N=85
FU year 1 FUV1 N=49
FU year 1 FUV6 N=49
FU year 2 FUV1-2 N=76
FU year 2 FUV6-2 N=74

Placebo - Active treatment group
Placebo N=23
Active year 1 N=23
Active year 2 N=23
Active year 3 N=23
FU year 1 FUV1 N=22
FU year 1 FUV6 N=22
FU year 2 FUV1-2 N=21
FU year 2 FUV6-2 N=20

End point type	Secondary

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85[84]	23[85]		
Units: breaths per min				
median (full range (min-max))				
Placebo	0 (0 to 0)	0 (-17 to 7)		
Active year 1	0 (-22 to 24)	0 (-16 to 6)		
Active year 2	0 (-18 to 8)	0 (-18 to 10)		
Active year 3	-1 (-23 to 14)	0 (-17 to 18)		
FU year 1 FUV1	-2 (-21 to 9)	0 (-17 to 12)		
FU year 1 FUV6	-2 (-19 to 8)	0 (-17 to 10)		

FU year 2 FUV1-2	-2 (-22 to 14)	0 (-6 to 10)		
FU year 2 FUV6-2	-2 (-23 to 11)	0 (-4 to 12)		

Notes:

[84] - FU All patients set; Change to baseline
Placebo result is not applicable for this treatment group
[85] - FU All patients set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Post-hoc: 1_02_Change of the AUC of SMS after 1 year of treatment: sensitivity analysis; DBP

End point title	1_02_Change of the AUC of SMS after 1 year of treatment: sensitivity analysis; DBP

End point description:

For sensitivity analyses, the missing SMS values were replaced by the patient's highest value of the defined time period (if not more than 25% of the values were missing). This SMS was referred to as the 'worst case' SMS and was analysed using the FAS.

Criteria for the symptom score and by medication score are summarized under the endpoint 1_01.

AUC=Area under the curve
SMS=Symptom and medication score
FAS=Full analysis set

End point type	Post-hoc

End point timeframe:

Baseline to 1 year after treatment.

End point values	Active treatment SLIT	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[86]	42[87]		
Units: score				
arithmetic mean (standard deviation)	-222 (± 212.1)	-96.7 (± 198.9)		

Notes:

[86] - Full analysis set; Change to baseline

[87] - Full analysis set; Change to baseline

Statistical analyses

Statistical analysis title	Change to baseline (after 1 year of treatment)

Statistical analysis description:

The sensitivity analysis of the AUC of the worst case SMS was repeated with the FAS.

Comparison groups	Active treatment SLIT v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	other[88]
P-value	= 0.0018
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-119.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	-194.01
upper limit	-45.43
Variability estimate	Standard error of the mean
Dispersion value	37.5517

Notes:

[88] - Because differences between treatment groups were observed for the mean baseline AUC of the SMS, further post-hoc sensitivity analyses were conducted to adjust for these unexpected baseline differences. These analyses tested the difference between the mean changes of AUC of SMS between treatment groups with an analysis of covariance (ANCOVA) model adjusted for gender, year of baseline, centre and AUC of the SMS at baseline.

Post-hoc: 2_02_Change of the area under the curve (AUC) of symptom and medication score (SMS): sensitivity analysis; OLP

End point title	2_02_Change of the area under the curve (AUC) of symptom and medication score (SMS): sensitivity analysis; OLP

End point description:

AUC of SMS over all treatment years for the FAS population during the OLP, by treatment group; sensitivity analysis.

For sensitivity analyses, missing SMS values were replaced by the patient's highest value of the defined time period (if not more than 25% of the values were missing). This SMS was referred to as the 'worst case' SMS and was analysed in the FAS.

Treatment groups:
- 'Active-Active' represents patients who received active treatment during the double-blind phase and active treatment during the open-label phase.
- 'Placebo-Active' represents patients who received placebo during the double-blind phase and active treatment during the open-label phase.

Criteria for the symptom score and by medication score are summarized under the endpoint 1_01.
The number of patients available at each time point is shown under the results table.

AUC=Area under the curve
FAS=Full analysis set
OLP=Open label phase
SMS=Symptom and medication score

End point type	Post-hoc

End point timeframe:

Baseline to 1st, 2nd, 3rd, 4th year after treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[89]	36[90]		
Units: score				
arithmetic mean (standard deviation)				
1st year	-223.9 (± 209.7)	-136.8 (± 180.2)		
2nd year	-300.9 (± 251.9)	-230.7 (± 205.3)		
3rd year	-360.6 (± 281.3)	-332.9 (± 209)		
4th year	0 (± 0)	-322.1 (± 236.4)		

Notes:

[89] - Full analysis set; Change to baseline
1st year N=118
2nd year N=115
3rd year N=110
4th year N=NA
[90] - Full analysis set; Change to baseline
1st year N=34
2nd year N=36
3rd year N=35
4th year N=26

Statistical analyses

No statistical analyses for this end point

Post-hoc: 3_02_Change of the AUC of SMS: sensitivity analysis; FU

End point title	3_02_Change of the AUC of SMS: sensitivity analysis; FU

End point description:

This prospective follow-up (FU) phase included patients who had previously received active treatment in the course of the clinical study; sensitivity analysis. For a description of the the 'sensitivity analysis', see endpoint 1_02.

The FU2 Full analysis set (FAS), which was a subset of the FU ALL patients, was used for the efficacy assessments is described in endpoint 3_01.

Criteria for the symptom score and by medication score are summarized under the endpoint 1_01.
Data show results for patients in the subset FU2 Full analysis set, over the entire study years (y).

FU2 Full analysis set
Active- Active reporting group
Pbo=0
Act y1 N=71
Act y2 N=70
Act y3 N=71
FU y1 N=34
FU y2 N=65

Placebo- Active reporting group
Pbo N=21
Act y1 N=22
Act y2 N=22
Act y3 N=18
FU y1 N=20
FU y2 N=19

End point type	Post-hoc

End point timeframe:

Baseline to 1st and 2nd pollen season, after 3 years of active treatment.

End point values	'Active-Active' treatment	'Placebo-Active' treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[91]	23[92]		
Units: score				
arithmetic mean (standard deviation)				
Placebo	0 (± 0)	-166.5 (± 185.5)		
Active year 1	-239.6 (± 214.6)	-231.9 (± 163.8)		

Active year 2	-298.9 (± 267)	-288.8 (± 190.7)		
Active year 3	-359.5 (± 260.7)	-300.1 (± 250.5)		
FU year 1	-286.5 (± 227.1)	-323.3 (± 296)		
FU year 2	-345.8 (± 261.8)	-281.9 (± 211.4)		

Notes:

[91] - FU2 Full analysis set; Change to baseline

[92] - FU2 Full analysis set; Change to baseline

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 3 years from the start of the study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	Double-blind phase: Active treatment 1st year
Reporting group description: -	
Reporting group title	Double-blind phase: Placebo 1st year
Reporting group description: -	
Reporting group title	Double-blind phase: Active treatment 2nd year
Reporting group description: -	
Reporting group title	Double-blind phase: Placebo 2nd year
Reporting group description: -	
Reporting group title	Open label phase: Active - Active treatment
Reporting group description: -	
Reporting group title	Open label phase: Placebo - Active treatment
Reporting group description: -	
Reporting group title	Follow-up phase: Active - Active treatment
Reporting group description: -	
Reporting group title	Follow-up phase: Placebo - Active treatment
Reporting group description: -	

Serious adverse events	Double-blind phase: Active treatment 1st year	Double-blind phase: Placebo 1st year	Double-blind phase: Active treatment 2nd year
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 158 (3.16%)	0 / 49 (0.00%)	1 / 52 (1.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Spinal column injury			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dysarthria			

subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hypoaesthesia facial			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurodermatitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anger			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 158 (0.63%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia chlamydial			
subjects affected / exposed	1 / 158 (0.63%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	2 / 158 (1.27%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-blind phase: Placebo 2nd year	Open label phase: Active - Active treatment	Open label phase: Placebo - Active treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)	10 / 158 (6.33%)	5 / 46 (10.87%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Spinal column injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dysarthria			

subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 22 (0.00%)	3 / 158 (1.90%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 22 (0.00%)	0 / 158 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 158 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 22 (4.55%)	0 / 158 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hypoaesthesia facial			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurodermatitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 22 (0.00%)	0 / 158 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anger			
subjects affected / exposed	0 / 22 (0.00%)	0 / 158 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia chlamydial			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 158 (1.27%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 158 (0.63%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 158 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Follow-up phase: Active - Active treatment	Follow-up phase: Placebo - Active treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Spinal column injury			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysarthria			

subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hypoaesthesia facial			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurodermatitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anger			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia chlamydial			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Double-blind phase: Active treatment 1st year	Double-blind phase: Placebo 1st year	Double-blind phase: Active treatment 2nd year
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 158 (87.97%)	39 / 49 (79.59%)	47 / 52 (90.38%)
Investigations			
Peak expiratory flow rate decreased			
subjects affected / exposed	9 / 158 (5.70%)	4 / 49 (8.16%)	3 / 52 (5.77%)
occurrences (all)	10	5	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	5 / 158 (3.16%)	1 / 49 (2.04%)	2 / 52 (3.85%)
occurrences (all)	5	1	2
Injury, poisoning and procedural			

complications			
Arthropod sting			
subjects affected / exposed	4 / 158 (2.53%)	0 / 49 (0.00%)	2 / 52 (3.85%)
occurrences (all)	4	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 158 (17.72%)	9 / 49 (18.37%)	8 / 52 (15.38%)
occurrences (all)	42	13	14
General disorders and administration site conditions			
Oral administration complication			
subjects affected / exposed	28 / 158 (17.72%)	1 / 49 (2.04%)	5 / 52 (9.62%)
occurrences (all)	35	1	5
Pyrexia			
subjects affected / exposed	14 / 158 (8.86%)	3 / 49 (6.12%)	2 / 52 (3.85%)
occurrences (all)	16	5	3
Influenza like illness			
subjects affected / exposed	3 / 158 (1.90%)	1 / 49 (2.04%)	3 / 52 (5.77%)
occurrences (all)	4	1	3
Malaise			
subjects affected / exposed	5 / 158 (3.16%)	1 / 49 (2.04%)	1 / 52 (1.92%)
occurrences (all)	6	1	2
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	16 / 158 (10.13%)	0 / 49 (0.00%)	1 / 52 (1.92%)
occurrences (all)	24	0	1
Ear pain			
subjects affected / exposed	5 / 158 (3.16%)	0 / 49 (0.00%)	2 / 52 (3.85%)
occurrences (all)	5	0	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	4 / 158 (2.53%)	5 / 49 (10.20%)	1 / 52 (1.92%)
occurrences (all)	5	8	1
Eye disorders			
Conjunctivitis			
subjects affected / exposed	5 / 158 (3.16%)	2 / 49 (4.08%)	0 / 52 (0.00%)
occurrences (all)	6	2	0
Conjunctivitis allergic			

subjects affected / exposed	9 / 158 (5.70%)	5 / 49 (10.20%)	4 / 52 (7.69%)
occurrences (all)	12	8	4
Eye pruritus			
subjects affected / exposed	22 / 158 (13.92%)	5 / 49 (10.20%)	4 / 52 (7.69%)
occurrences (all)	26	7	4
Eye allergy			
subjects affected / exposed	3 / 158 (1.90%)	0 / 49 (0.00%)	1 / 52 (1.92%)
occurrences (all)	3	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 158 (6.33%)	4 / 49 (8.16%)	2 / 52 (3.85%)
occurrences (all)	12	9	3
Abdominal pain upper			
subjects affected / exposed	17 / 158 (10.76%)	3 / 49 (6.12%)	4 / 52 (7.69%)
occurrences (all)	19	4	5
Diarrhoea			
subjects affected / exposed	13 / 158 (8.23%)	5 / 49 (10.20%)	6 / 52 (11.54%)
occurrences (all)	18	7	6
Nausea			
subjects affected / exposed	20 / 158 (12.66%)	4 / 49 (8.16%)	5 / 52 (9.62%)
occurrences (all)	23	4	6
Vomiting			
subjects affected / exposed	23 / 158 (14.56%)	4 / 49 (8.16%)	5 / 52 (9.62%)
occurrences (all)	27	6	5
Enteritis			
subjects affected / exposed	2 / 158 (1.27%)	1 / 49 (2.04%)	1 / 52 (1.92%)
occurrences (all)	2	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 158 (18.99%)	7 / 49 (14.29%)	11 / 52 (21.15%)
occurrences (all)	45	7	15
Dyspnoea			
subjects affected / exposed	12 / 158 (7.59%)	1 / 49 (2.04%)	1 / 52 (1.92%)
occurrences (all)	15	1	4
Epistaxis			

subjects affected / exposed	14 / 158 (8.86%)	4 / 49 (8.16%)	4 / 52 (7.69%)
occurrences (all)	24	7	4
Oropharyngeal pain			
subjects affected / exposed	7 / 158 (4.43%)	2 / 49 (4.08%)	7 / 52 (13.46%)
occurrences (all)	10	2	7
Sneezing			
subjects affected / exposed	4 / 158 (2.53%)	3 / 49 (6.12%)	1 / 52 (1.92%)
occurrences (all)	7	3	1
Throat irritation			
subjects affected / exposed	17 / 158 (10.76%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences (all)	30	0	0
Asthma			
subjects affected / exposed	3 / 158 (1.90%)	1 / 49 (2.04%)	2 / 52 (3.85%)
occurrences (all)	3	1	2
Rhinitis allergic			
subjects affected / exposed	3 / 158 (1.90%)	1 / 49 (2.04%)	2 / 52 (3.85%)
occurrences (all)	3	1	2
Nasal discomfort			
subjects affected / exposed	7 / 158 (4.43%)	0 / 49 (0.00%)	1 / 52 (1.92%)
occurrences (all)	7	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 158 (4.43%)	2 / 49 (4.08%)	0 / 52 (0.00%)
occurrences (all)	10	2	0
Rash			
subjects affected / exposed	7 / 158 (4.43%)	3 / 49 (6.12%)	1 / 52 (1.92%)
occurrences (all)	8	4	1
Urticaria			
subjects affected / exposed	2 / 158 (1.27%)	1 / 49 (2.04%)	1 / 52 (1.92%)
occurrences (all)	2	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 158 (8.86%)	1 / 49 (2.04%)	4 / 52 (7.69%)
occurrences (all)	15	1	4
Gastroenteritis			

subjects affected / exposed	10 / 158 (6.33%)	1 / 49 (2.04%)	4 / 52 (7.69%)
occurrences (all)	12	1	5
Nasopharyngitis			
subjects affected / exposed	46 / 158 (29.11%)	13 / 49 (26.53%)	26 / 52 (50.00%)
occurrences (all)	72	22	41
Pharyngitis			
subjects affected / exposed	18 / 158 (11.39%)	4 / 49 (8.16%)	1 / 52 (1.92%)
occurrences (all)	21	4	1
Respiratory tract infection viral			
subjects affected / exposed	7 / 158 (4.43%)	2 / 49 (4.08%)	1 / 52 (1.92%)
occurrences (all)	9	2	1
Rhinitis			
subjects affected / exposed	9 / 158 (5.70%)	4 / 49 (8.16%)	0 / 52 (0.00%)
occurrences (all)	9	4	0
Tonsillitis			
subjects affected / exposed	5 / 158 (3.16%)	6 / 49 (12.24%)	1 / 52 (1.92%)
occurrences (all)	7	6	1
Upper respiratory tract infection			
subjects affected / exposed	8 / 158 (5.06%)	4 / 49 (8.16%)	2 / 52 (3.85%)
occurrences (all)	10	5	2
Viral infection			
subjects affected / exposed	11 / 158 (6.96%)	8 / 49 (16.33%)	4 / 52 (7.69%)
occurrences (all)	11	8	5
Viral rhinitis			
subjects affected / exposed	8 / 158 (5.06%)	1 / 49 (2.04%)	2 / 52 (3.85%)
occurrences (all)	10	1	3
Gastrointestinal infection			
subjects affected / exposed	0 / 158 (0.00%)	0 / 49 (0.00%)	2 / 52 (3.85%)
occurrences (all)	0	0	3
H1N1 influenza			
subjects affected / exposed	1 / 158 (0.63%)	0 / 49 (0.00%)	3 / 52 (5.77%)
occurrences (all)	1	0	3
Influenza			
subjects affected / exposed	1 / 158 (0.63%)	0 / 49 (0.00%)	4 / 52 (7.69%)
occurrences (all)	1	0	4
Otitis media			

subjects affected / exposed	5 / 158 (3.16%)	1 / 49 (2.04%)	2 / 52 (3.85%)
occurrences (all)	5	1	2
Pseudocroup			
subjects affected / exposed	1 / 158 (0.63%)	0 / 49 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Double-blind phase: Placebo 2nd year	Open label phase: Active - Active treatment	Open label phase: Placebo - Active treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)	146 / 158 (92.41%)	37 / 46 (80.43%)
Investigations			
Peak expiratory flow rate decreased			
subjects affected / exposed	1 / 22 (4.55%)	11 / 158 (6.96%)	3 / 46 (6.52%)
occurrences (all)	1	22	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 22 (9.09%)	8 / 158 (5.06%)	3 / 46 (6.52%)
occurrences (all)	2	8	3
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 22 (0.00%)	9 / 158 (5.70%)	0 / 46 (0.00%)
occurrences (all)	0	11	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 22 (13.64%)	35 / 158 (22.15%)	14 / 46 (30.43%)
occurrences (all)	3	99	26
General disorders and administration site conditions			
Oral administration complication			
subjects affected / exposed	8 / 22 (36.36%)	31 / 158 (19.62%)	10 / 46 (21.74%)
occurrences (all)	8	37	11
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)	24 / 158 (15.19%)	2 / 46 (4.35%)
occurrences (all)	1	31	5
Influenza like illness			
subjects affected / exposed	1 / 22 (4.55%)	8 / 158 (5.06%)	1 / 46 (2.17%)
occurrences (all)	1	12	1
Malaise			

subjects affected / exposed	2 / 22 (9.09%)	10 / 158 (6.33%)	3 / 46 (6.52%)
occurrences (all)	4	14	5
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 22 (0.00%)	16 / 158 (10.13%)	2 / 46 (4.35%)
occurrences (all)	0	25	6
Ear pain			
subjects affected / exposed	0 / 22 (0.00%)	8 / 158 (5.06%)	1 / 46 (2.17%)
occurrences (all)	0	13	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 22 (4.55%)	10 / 158 (6.33%)	4 / 46 (8.70%)
occurrences (all)	1	11	4
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 22 (0.00%)	8 / 158 (5.06%)	0 / 46 (0.00%)
occurrences (all)	0	10	0
Conjunctivitis allergic			
subjects affected / exposed	3 / 22 (13.64%)	18 / 158 (11.39%)	6 / 46 (13.04%)
occurrences (all)	3	22	8
Eye pruritus			
subjects affected / exposed	4 / 22 (18.18%)	25 / 158 (15.82%)	6 / 46 (13.04%)
occurrences (all)	4	35	7
Eye allergy			
subjects affected / exposed	1 / 22 (4.55%)	5 / 158 (3.16%)	3 / 46 (6.52%)
occurrences (all)	1	6	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 22 (9.09%)	15 / 158 (9.49%)	5 / 46 (10.87%)
occurrences (all)	2	20	6
Abdominal pain upper			
subjects affected / exposed	3 / 22 (13.64%)	27 / 158 (17.09%)	6 / 46 (13.04%)
occurrences (all)	3	41	6
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	18 / 158 (11.39%)	4 / 46 (8.70%)
occurrences (all)	0	33	6
Nausea			

subjects affected / exposed	1 / 22 (4.55%)	25 / 158 (15.82%)	3 / 46 (6.52%)
occurrences (all)	1	33	9
Vomiting			
subjects affected / exposed	2 / 22 (9.09%)	31 / 158 (19.62%)	6 / 46 (13.04%)
occurrences (all)	2	40	6
Enteritis			
subjects affected / exposed	2 / 22 (9.09%)	5 / 158 (3.16%)	3 / 46 (6.52%)
occurrences (all)	2	5	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 22 (22.73%)	50 / 158 (31.65%)	11 / 46 (23.91%)
occurrences (all)	7	92	27
Dyspnoea			
subjects affected / exposed	2 / 22 (9.09%)	14 / 158 (8.86%)	3 / 46 (6.52%)
occurrences (all)	3	30	3
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	15 / 158 (9.49%)	2 / 46 (4.35%)
occurrences (all)	0	36	2
Oropharyngeal pain			
subjects affected / exposed	0 / 22 (0.00%)	17 / 158 (10.76%)	3 / 46 (6.52%)
occurrences (all)	0	30	5
Sneezing			
subjects affected / exposed	2 / 22 (9.09%)	7 / 158 (4.43%)	3 / 46 (6.52%)
occurrences (all)	2	11	3
Throat irritation			
subjects affected / exposed	3 / 22 (13.64%)	18 / 158 (11.39%)	4 / 46 (8.70%)
occurrences (all)	3	32	5
Asthma			
subjects affected / exposed	1 / 22 (4.55%)	8 / 158 (5.06%)	4 / 46 (8.70%)
occurrences (all)	2	9	8
Rhinitis allergic			
subjects affected / exposed	0 / 22 (0.00%)	11 / 158 (6.96%)	5 / 46 (10.87%)
occurrences (all)	0	12	6
Nasal discomfort			

subjects affected / exposed	0 / 22 (0.00%)	8 / 158 (5.06%)	1 / 46 (2.17%)
occurrences (all)	0	8	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 22 (4.55%)	10 / 158 (6.33%)	2 / 46 (4.35%)
occurrences (all)	1	16	3
Rash			
subjects affected / exposed	0 / 22 (0.00%)	9 / 158 (5.70%)	0 / 46 (0.00%)
occurrences (all)	0	10	0
Urticaria			
subjects affected / exposed	1 / 22 (4.55%)	4 / 158 (2.53%)	3 / 46 (6.52%)
occurrences (all)	1	4	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 22 (0.00%)	20 / 158 (12.66%)	4 / 46 (8.70%)
occurrences (all)	0	26	4
Gastroenteritis			
subjects affected / exposed	1 / 22 (4.55%)	21 / 158 (13.29%)	2 / 46 (4.35%)
occurrences (all)	1	26	2
Nasopharyngitis			
subjects affected / exposed	9 / 22 (40.91%)	74 / 158 (46.84%)	23 / 46 (50.00%)
occurrences (all)	14	200	47
Pharyngitis			
subjects affected / exposed	2 / 22 (9.09%)	32 / 158 (20.25%)	8 / 46 (17.39%)
occurrences (all)	2	40	11
Respiratory tract infection viral			
subjects affected / exposed	0 / 22 (0.00%)	8 / 158 (5.06%)	1 / 46 (2.17%)
occurrences (all)	0	10	1
Rhinitis			
subjects affected / exposed	0 / 22 (0.00%)	19 / 158 (12.03%)	1 / 46 (2.17%)
occurrences (all)	0	24	1
Tonsillitis			
subjects affected / exposed	1 / 22 (4.55%)	11 / 158 (6.96%)	2 / 46 (4.35%)
occurrences (all)	1	17	3
Upper respiratory tract infection			

subjects affected / exposed	1 / 22 (4.55%)	13 / 158 (8.23%)	5 / 46 (10.87%)
occurrences (all)	1	19	6
Viral infection			
subjects affected / exposed	1 / 22 (4.55%)	21 / 158 (13.29%)	2 / 46 (4.35%)
occurrences (all)	1	25	4
Viral rhinitis			
subjects affected / exposed	0 / 22 (0.00%)	12 / 158 (7.59%)	1 / 46 (2.17%)
occurrences (all)	0	17	1
Gastrointestinal infection			
subjects affected / exposed	0 / 22 (0.00%)	8 / 158 (5.06%)	1 / 46 (2.17%)
occurrences (all)	0	9	1
H1N1 influenza			
subjects affected / exposed	0 / 22 (0.00%)	4 / 158 (2.53%)	0 / 46 (0.00%)
occurrences (all)	0	4	0
Influenza			
subjects affected / exposed	0 / 22 (0.00%)	5 / 158 (3.16%)	1 / 46 (2.17%)
occurrences (all)	0	5	1
Otitis media			
subjects affected / exposed	0 / 22 (0.00%)	8 / 158 (5.06%)	1 / 46 (2.17%)
occurrences (all)	0	8	1
Pseudocroup			
subjects affected / exposed	1 / 22 (4.55%)	1 / 158 (0.63%)	1 / 46 (2.17%)
occurrences (all)	1	3	1

Non-serious adverse events	Follow-up phase: Active - Active treatment	Follow-up phase: Placebo - Active treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 85 (43.53%)	8 / 23 (34.78%)	
Investigations			
Peak expiratory flow rate decreased			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural			

complications			
Arthropod sting			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 85 (8.24%)	1 / 23 (4.35%)	
occurrences (all)	10	1	
General disorders and administration site conditions			
Oral administration complication			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Ear pain			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis allergic			

subjects affected / exposed	0 / 85 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Eye pruritus			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Eye allergy			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Enteritis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 85 (3.53%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Dyspnoea			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Epistaxis			

subjects affected / exposed	4 / 85 (4.71%)	0 / 23 (0.00%)	
occurrences (all)	6	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 85 (2.35%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Sneezing			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Throat irritation			
subjects affected / exposed	0 / 85 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Asthma			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Nasal discomfort			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 85 (2.35%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			

subjects affected / exposed	2 / 85 (2.35%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	14 / 85 (16.47%)	3 / 23 (13.04%)	
occurrences (all)	20	6	
Pharyngitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Rhinitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Tonsillitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Viral infection			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Viral rhinitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
H1N1 influenza			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Otitis media			

subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Pseudocroup			
subjects affected / exposed	0 / 85 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported