Clinical trial results:
A multicentre, randomized, open label clinical trial for safety evaluation of an accelerated high dose escalation schedule with one strength for an allergen immunotherapy with an aluminium hydroxide adsorbed allergoid preparation of 6-Grasses in pediatric patients with moderate to severe seasonal rhinitis or rhinoconjunctivitis with or without asthma

Summary

EudraCT number	2018-000548-25
Trial protocol	DE ES PL
Global end of trial date	25 June 2019

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	AL1605av

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	Clinical Trials Information, Allergopharma GmbH & Co. KG, +49 40427650,
Scientific contact	Clinical Trials Information, Allergopharma GmbH & Co. KG, +49 40427650,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this therapeutic phase II trial was to evaluate the safety and tolerability of an accelerated high dose escalation schedule with one strength for allergen immunotherapy with Allergovit® 6-Grasses compared to the standard escalation schedule with two strengths. Children and adolescents with rhinitis or rhinoconjunctivitis caused by grass pollen, with or without allergic asthma on a well controlled level, will be enrolled.

The trial consisted of a dose escalation phase (T1 to T3) for the accelerated dose escalation (One Strength) or (T1 to T7) for the standard dose escalation (Standard). Maintenance treatment phase T4-T5 (One Strength) and T8-T9 (Standard), and a follow-up phase of 30 days after the last IMP (final visit [FV]). The whole treatment duration (escalation phase + maintenance phase) lasted for approx. 9 weeks and 13 weeks, respectively, for the two treatment groups. Data are presented as subgroups: children and adolescents per treatment group.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) guidance for Good Clinical Practice (GCP) and the applicable regulatory requirements.

Data Safety Monitoring Board (DSMB) was in place throughout the trial; DSMB consisted of 3 independent physicians, experienced in the field of allergy. The primary function of the DSMB was to ensure the subjects' safety. The DSMB team reviewed an update of the safety data from all treated subjects.

After each administration of the IMP, each subject in the study was kept under supervision of a qualified and trained investigator for at least 30 min (in accordance with the country-specific trial protocol: 30 min in Russia and Spain, 120 min in Germany and Poland).

Safety evaluation during supervision after IMP administration consisted of: FEV1, Systolic BP, Diastolic BP, Heart rate (Pulse rate), Respiratory rate.

Other than routine care, no specific measures were implemented for the protection of trial subjects.

Background therapy:

There was no background therapy planned in this study.

Concomitant medication was defined as any medication other than the IMP that was taken during the clinical trial. Any relevant medication taken before entering the clinical trial was considered as "previous medication". All anti-allergic medication administered in the last 2 years and other medication used during the last 6 weeks prior to enrollment to the study had to be documented at the screening visit.

Medication against rhinitis and rhinoconjunctivitis was permitted, but had to be documented as concomitant medication.

Patients with bronchial asthma who required regular basic treatment of their allergic asthma were treated as recommended by GINA (GINA, 2017) to control their asthma. Any asthma medication, including medication for seasonal asthma, that had been prescribed in the previous season had to be documented as concomitant medication. Restricted medication and nonpermitted medications were clearly defined in the study protocol.

Evidence for comparator:

There was no comparator used in this study.

Abbreviations used in this document:
AE=Adverse event
AIT=Allergen immunotherapy
BMI=Body mass index
BP=Blood pressure
bpm=Beats per minute
ICF=Informed consent form
DSMB=Data Safety Monitoring Board
FEV1=Forced expiratory volume in 1 second
ICF=Informed consent form
IgG=Immunoglobulin G
kU/L=kilo Units per Litre
IMP=Investigational medicinal product
IS=Injection site
MedDRA=Medical Dictionary for Regulatory Activities
P. pratense=Phleum pratense
RBC=Red blood cells
T=Treatment (as in T1 =Treatment visit 1, etc.)
TEAE=Treatment-emergent adverse event
TU=Therapeutic units
WAO=World Allergy Organization
y=year

Actual start date of recruitment	02 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Poland: 68
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	87
EEA total number of subjects	82

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)	50
Adolescents (12-17 years)	37
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 115 adult male and female subjects (5 to <18 y) were screened for eligibility; of these, 87 were randomised to treatment according to the exclusion and inclusion criteria.

Pre-assignment

Screening details:

Study subjects (outpatients) were included if they were suffering from immunoglobulin (Ig) E-mediated seasonal moderate to severe allergic rhinitis or rhinoconjunctivitis, with or without allergic asthma, caused by grass pollen documented by skin prick test (SPT) wheal for grass pollen and specific IgE value of ≥ 0.70 kU/L to grass pollen.

Period 1

Period 1 title	Treatment (Overall trial) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	One Strength

Arm description:

Patients randomised to the 'One Strength' dose scheme received 3 injections with one strength of the IMP (B: 10,000 therapeutic units [TU]/mL), followed by 2 injections with the maximum recommended dose. Duration of the treatment was approximately 9 weeks.

Arm type	Experimental
Investigational medicinal product name	Allergovit® 6-grasses
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IMP is an aluminium hydroxide-adsorbed allergoid preparation of 6-Grasses (Allergovit® 6-grasses)
IMP was available in two concentrations (A: 1,000 TU/mL; B: 10,000 TU/mL)

IMP was administered subcutaneously in the upper arm at increasing doses at 7-day intervals with 3 injections in the group 'accelerated dose escalation'.

IMP strength B (10,000 TU/mL) was used
Dose escalation schedule once every 7 days: (1,000; 3,000; 6,000 TU)
Maintenance 2 weeks after last dose: 6,000 TU, then 4 weeks after last dose: 6,000 TU

Patients had to demonstrate an FEV1 of at least 70% of predicted normal ranges before injection, otherwise no injection was to be given and the visit was rescheduled. If the FEV1 decreased after injection compared with the value measured before injection, the investigator checked whether an AE occurred that needed documentation and medical treatment.

In this group, 88.9% of subjects reached the 1st IMP injection of the maintenance phase without dose adjustment.

Arm title	Standard

Arm description:

Patients randomized to standard dose escalation scheme ('Standard') received 7 injections with two strengths of the IMP (A: 1,000 TU/mL; B: 10,000 TU/mL), followed by 2 injections with the maximum recommended dose. Duration of the treatment was approximately 13 weeks.

Arm type	Active comparator

Investigational medicinal product name	Allergovit® 6-grasses
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IMP is an aluminium hydroxide-adsorbed allergoid preparation of 6-Grasses (Allergovit® 6-grasses) IMP was available as (A: 1,000 TU/mL; B: 10,000 TU/mL)

IMP was administered subcutaneously in the upper arm as gradually increasing doses at 7-day intervals with 7 injections in the group 'standard dose escalation'.

Patients had to demonstrate an FEV1 of at least 70% of predicted normal ranges before injection, otherwise no injection was to be given and the visit was rescheduled. If the FEV1 decreased after injection compared with the value measured before injection, the investigator checked whether an AE occurred that needed documentation and medical treatment.

In this group, 85.7% of subjects reached the 1st IMP injection of the maintenance phase without dose adjustment.

Number of subjects in period 1	One Strength	Standard
Started	45	42
Completed	43	39
Not completed	2	3
Adverse event, non-fatal	2	3

Baseline characteristics

Reporting groups	
Reporting group title	One Strength
Reporting group description:	
Patients randomised to the 'One Strength' dose scheme received 3 injections with one strength of the IMP (B: 10,000 therapeutic units [TU]/mL), followed by 2 injections with the maximum recommended dose. Duration of the treatment was approximately 9 weeks.	
Reporting group title	Standard
Reporting group description:	
Patients randomized to standard dose escalation scheme ('Standard') received 7 injections with two strengths of the IMP (A: 1,000 TU/mL; B: 10,000 TU/mL), followed by 2 injections with the maximum recommended dose. Duration of the treatment was approximately 13 weeks.	

Reporting group values	One Strength	Standard	Total
Number of subjects	45	42	87
Age categorical Units: Subjects			
Children (5 to <12 y)	25	25	50
Adolescents (12 to <18 y)	20	17	37
Age continuous Units: years			
arithmetic mean	11.1	11.2	
standard deviation	± 2.99	± 3.20	-
Gender categorical Units: Subjects			
Female	16	16	32
Male	29	26	55
Race Units: Subjects			
White	45	42	87

Subject analysis sets	
Subject analysis set title	Children (5 to <12 y) One Strength
Subject analysis set type	Safety analysis
Subject analysis set description: Children (5 to <12 y), randomised to One Strength treatment group.	
Subject analysis set title	Children (5 to <12 y) Standard
Subject analysis set type	Safety analysis
Subject analysis set description: Children (5 to <12 y), randomised to the Standard treatment group.	
Subject analysis set title	Adolescents (12 to <18 y) One Strength
Subject analysis set type	Safety analysis
Subject analysis set description: Adolescents (12 to <18 y), randomised to the One Strength treatment group.	
Subject analysis set title	Adolescents (12 to <18 y) Standard
Subject analysis set type	Safety analysis
Subject analysis set description: Adolescents (12 to <18 y), randomised to the Standard treatment group.	

Reporting group values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength
Number of subjects	25	25	20
Age categorical Units: Subjects			
Children (5 to <12 y)			
Adolescents (12 to <18 y)			
Age continuous Units: years			
arithmetic mean	8.9	8.9	13.9
standard deviation	± 1.76	± 1.32	± 1.41
Gender categorical Units: Subjects			
Female	10	8	6
Male	15	17	14
Race Units: Subjects			
White	25	25	20

Reporting group values	Adolescents (12 to <18 y) Standard		
Number of subjects	17		
Age categorical Units: Subjects			
Children (5 to <12 y)			
Adolescents (12 to <18 y)			
Age continuous Units: years			
arithmetic mean	14.6		
standard deviation	± 1.80		
Gender categorical Units: Subjects			
Female	8		
Male	9		
Race Units: Subjects			
White	17		

End points

End points reporting groups

Reporting group title	One Strength
Reporting group description:	
Patients randomised to the 'One Strength' dose scheme received 3 injections with one strength of the IMP (B: 10,000 therapeutic units [TU]/mL), followed by 2 injections with the maximum recommended dose. Duration of the treatment was approximately 9 weeks.	
Reporting group title	Standard
Reporting group description:	
Patients randomized to standard dose escalation scheme ('Standard') received 7 injections with two strengths of the IMP (A: 1,000 TU/mL; B: 10,000 TU/mL), followed by 2 injections with the maximum recommended dose. Duration of the treatment was approximately 13 weeks.	
Subject analysis set title	Children (5 to <12 y) One Strength
Subject analysis set type	Safety analysis
Subject analysis set description:	
Children (5 to <12 y), randomised to One Strength treatment group.	
Subject analysis set title	Children (5 to <12 y) Standard
Subject analysis set type	Safety analysis
Subject analysis set description:	
Children (5 to <12 y), randomised to the Standard treatment group.	
Subject analysis set title	Adolescents (12 to <18 y) One Strength
Subject analysis set type	Safety analysis
Subject analysis set description:	
Adolescents (12 to <18 y), randomised to the One Strength treatment group.	
Subject analysis set title	Adolescents (12 to <18 y) Standard
Subject analysis set type	Safety analysis
Subject analysis set description:	
Adolescents (12 to <18 y), randomised to the Standard treatment group.	

Primary: 1_Treatment-emergent adverse events - Overall

End point title	1_Treatment-emergent adverse events - Overall[1]
End point description:	
An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP. A treatment emergent adverse event (TEAE) was defined as any AE that started or worsened after the first intake of trial medication until 30 days after the last IMP administration or trial-related procedure. Results in the table below summarize the number of subjects affected by a TEAE; the number of the respective events (n) is also shown. The TEAEs (as System Organ Class and as Preferred Term) are listed under the section 'Adverse events'.	
End point type	Primary
End point timeframe:	
Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure. Approx. 9 weeks for patients in One Strength and approx. 13 weeks for patients in Standard treatment group.	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This was a safety-focused trial. No statistical analysis was performed. Results were	

evaluated descriptively.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[2]	25[3]	20[4]	17[5]
Units: subjects				
1_Subjects with TEAE	18	16	9	8
2_Subjects with serious TEAE	0	0	1	1
3_Subjects with TEAEs related to IMP	13	10	7	6
4_Subjects with TEAE leading to discontinuation	1	1	1	0

Notes:

[2] - Safety analysis set was used for all treatment groups
1_n=59
2_n=0
3_n=21
4_n=3
[3] -
1_n=58
2_n=0
3_n=27
4_n=1
[4] -
1_n=55
2_n=1
3_n=39
4_n=1
[5] -
1_n=43
2_n=5
3_n=32
4_n=0

Statistical analyses

No statistical analyses for this end point

Primary: 2_Treatment-emergent adverse events - Maximum intensity

End point title	2_Treatment-emergent adverse events - Maximum intensity[6]

End point description:

A treatment emergent adverse event (TEAE) was defined as any AE that started or worsened after the first intake of trial medication until 30 days after the last IMP administration or trial-related procedure.

The intensity of the TEAE was assessed by the the investigator.

Mild=Transient symptoms, no interference with the patient's daily activities.
Moderate=Marked symptoms, moderate interference with the patient's daily activities.
Severe=Considerable interference with the patient's daily activities.

End point type	Primary

End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a safety-focused trial. No statistical analysis was performed. Results were evaluated descriptively.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[7]	25	20	17
Units: subjects				
Mild	13	12	5	5
Moderate	5	4	4	3
Severe	0	0	0	0

Notes:

[7] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Primary: 3_Treatment-emergent adverse events - Causal relationship (IMP-related)

End point title	3_Treatment-emergent adverse events - Causal relationship (IMP-related)[8]

End point description:

TEAEs -- causal relationship to IMP.

Results in the table below show the number of subjects with at least one TEAE related to IMP, as assessed by the investigator.
The number of the respective events (n) is also shown.
The actual number of TEAEs are listed under the section 'Adverse events'.

Most of the related TEAEs were mild in intensity in both treatment groups (>85% children and >69% adolescent).

The related TEAEs included: Injection site swelling, Injection site erythema, Injection site pruritus, Injection site pain, Injection site discomfort, Injection site oedema, FEV1 decreased, Pain in extremity, Headache, Dermatitis allergic, Somnolence, Conjunctival oedema, Rhinitis, Swelling, Cough, Rhinitis allergic, Sneezing, Urticaria, Pruritus.

End point type	Primary

End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a safety-focused trial. No statistical analysis was performed. Results were evaluated descriptively.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[9]	25[10]	20[11]	17[12]
Units: subjects				
1_Subjects with TEAEs related to IMP	13	10	7	6

2_Subjects with serious TEAEs related to IMP	0	0	1	1

Notes:

[9] - Safety analysis set was used for all treatment groups
1_n=21
2_n=0
[10] -
1_n=27
2_n=0
[11] -
1_n=39
2_n=1
[12] -
1_n=32
2_n=5

Statistical analyses

No statistical analyses for this end point

Secondary: 4_Treatment-emergent adverse event - Systemic allergic reactions according to the WAO

End point title	4_Treatment-emergent adverse event - Systemic allergic reactions according to the WAO

End point description:

Systemic allergic reaction: TEAE graded by the investigator according to the WAO grading system, which is based on the organ systems involved and the severity of the reaction.

Dose reductions for systemic reactions acc. to WAO :
• Grade 1: reduction by 1 dose step of the last applied dose.
• Grade 2: reduction by 2 dose steps of the last applied dose.

For WAO Grade 1 and WAO Grade 2: if the 1st dose reduction was not tolerated, a 2nd dose reduction by 1 dose step of the last applied dose was administered.

All systemic allergic reactions were assessed by the investigator as IMP-related.
All systemic allergic reactions had a WAO grade of 1; for children, all were non-serious; for adolescents all were serious.

Children: FEV1 decreased, Dermatitis allergic;

Adolescents: Urticaria, Conjunctival oedema, Cough, Pruritus, Rhinitis;

End point type	Secondary

End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	25	20	17
Units: Sytemic TEAEs related to IMP				
Grade 1	2	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: 5_Treatment-emergent adverse event - Local reactions at the injection site

End point title	5_Treatment-emergent adverse event - Local reactions at the injection site

End point description:

Treatment-emergent adverse event - Local reactions at the injection site

Results in the table below summarize the number of subjects affected by TEAEs 'local reactions at the injection site' (IS), that were assessed by the investigators as related to the IMP. The number of the respective events (n) is also shown.

The TEAEs 'local reactions at the injection site' were:

Children: IS erythema, IS oedema, IS pain, IS pruritus, IS swelling;
Adolescents: IS discomfort, IS erythema, IS pain, IS pruritus, IS swelling;

End point type	Secondary

End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[13]	25[14]	20[15]	17[16]
Units: subjects	10	10	6	5

Notes:

[13] - Safety analysis set was used for all treatment groups
n=16
[14] -
n=27
[15] -
n=36
[16] -
n=25

Statistical analyses

No statistical analyses for this end point

Secondary: 6_Number of subjects reaching the maintenance dose without dose adjustment due to TEAE

End point title	6_Number of subjects reaching the maintenance dose without dose adjustment due to TEAE

End point description:

Number of patients reaching the maintenance dose without dose adjustment due to TEAE.

End point type	Secondary

End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[17]	25	20	17
Units: subjects	23	21	17	15

Notes:

[17] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 7_Vital signs - Heart rate (Pulse rate)

End point title	7_Vital signs - Heart rate (Pulse rate)

End point description:

Vital signs (BP, heart rate, resp. rate) were assessed at: screening, during treatment visits / any unscheduled visit, and at the final visit.

Vital signs are summarized by a representative parameter Heart rate (Pulse rate).

Results are shown as the change from pre- to 30 min post administration of IMP on the first- (T1), last escalation dose visit (T3/T7), and last maintenance visit (T5/T9).

Laboratory parameters measured (at the Screening and Final visit):
• Clin. chem: creatinine, total bilirubin, asp. aminotransferase, ala. aminotransferase, gamma-glutamyltransferase
• Blood sugar: Glucose (fasting or non-fasting; status assessed for decision on in-/exclusion of patient)
• Hematol: differential blood cell count, hemoglobin (RBC), leukocytes, platelets
• Urinalysis: protein, glucose, blood (hemoglobin), leukocytes, beta-human chorionic gonadotropin (females of childbearing potential)

There were no clinically relevant differences seen between the treatment groups.

End point type	Secondary

End point timeframe:

At IMP treatment visits (escalation and maintenance dose phase): before and after 30, 60, 120 min administration of IMP.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[18]	25[19]	20[20]	17[21]
Units: bpm				
median (full range (min-max))				
1_T1 First escalation dose	-1.0 (-30 to 12)	-2.0 (-21 to 12)	0 (-14 to 7)	0 (-8 to 14)
2_T3/T7 Last escalation dose	-0.5 (-18 to 8)	-1.0 (-8 to 13)	-2.0 (-19 to 8)	-2 (-5 to 6)
3_T5/T9 Last maintenance dose	-0.5 (-27 to 4)	0 (-9 to 17)	2 (-2 to 6)	2 (-13 to 10)

Notes:

[18] - Safety analysis set was used for all treatment groups
1_N=25
2_N=24
3_N=24
[19] - The number of subjects contributing to the data is shown for all groups.
1_N=25
2_N=24
3_N=23
[20] -
1_N=20
2_N=19
3_N=19
[21] -
1_N=17
2_N=17
3_N=16

Statistical analyses

No statistical analyses for this end point

Secondary: 8_Lung function test - FEV1

End point title	8_Lung function test - FEV1

End point description:

Subjects had to demonstrate FEV1 of at least 70% of predicted normal ranges before IMP injection, otherwise no injection was given and the visit was rescheduled. If the FEV1 decreased after injection compared to the value measured before injection, the investigator checked if an AE had to be documented and adequate medical treatment initiated. An FEV1 decrease of ≥ 20% after injection as compared to the value measured before injection, was documented as an AE.

Results shown are representative for the study visits at the first escalation dose visit (T1), at the last escalation dose visit (T3/T7), and at the last maintenance dose visit (T5/T9); before and 30 min after injection of IMP. The number of subjects contributing to the data at each visit is also shown.

Neither for children nor for adolescents systematic differences were detected between groups.

End point type	Secondary

End point timeframe:

30 min bfr, 30, 60, 120 min aftr each treatment (T)
Accelerated dose esct: 3 visits, sep by 7 d
Standard dose esct: 7 visits, sep by 7 d
Maintenance dose: 2 visits: 2 wks after last esct. dose, 4 wks after the last maintence dose

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[22]	25[23]	20[24]	17[25]
Units: % predicted				
arithmetic mean (standard deviation)				
1_T1 First escalation visit, before IMP	102.5 (± 14.21)	98.5 (± 12.76)	102.7 (± 11.12)	103.5 (± 12.03)
2_T1_First escalation visit, 30 min after IMP	101.9 (± 14.11)	98.4 (± 12.06)	104.2 (± 12.24)	102.2 (± 11.91)
3_T3/T7 Last escalation visit, before IMP	99.5 (± 14.60)	103.4 (± 13.19)	101.2 (± 10.39)	101.8 (± 14.70)
4_T3/T7 Last escalation visit, 30 min after IMP	99.1 (± 12.96)	103.5 (± 12.60)	101.9 (± 11.13)	100.8 (± 15.49)
5_T5/T9 Last maintenace visit, before IMP	101.8 (± 15.62)	104.1 (± 13.56)	105.2 (± 14.18)	104.5 (± 13.29)
6_T5/T9 Last maintenace visit, 30 min after IMP	102.0 (± 14.88)	102.9 (± 12.35)	106.0 (± 13.35)	103.6 (± 13.89)

Notes:

[22] - Safety analysis set for all treatment groups
1_N=25
2_N=25
3_N=24
4_N=24
5_N=24
6_N=24

[23] -
1_N=25
2_N=25
3_N=24
4_N=24
5_N=23
6_N=23

[24] -
1_N=20
2_N=20
3_N=19
4_N=19
5_N=19
6_N=19

[25] -
1_N=17
2_N=17
3_N=17
4_N=17
5_N=16
6_N=16

Statistical analyses

No statistical analyses for this end point

Secondary: 9a_Tolerability: Likert scale after last dose of escalation phase (Investigator)

End point title	9a_Tolerability: Likert scale after last dose of escalation phase (Investigator)

End point description:

Assessment of the overall tolerability by the investigator using a 5-point Likert scale.
Likert scale score system: 1=Very bad; 2=Bad; 3=Average; 4=Good; 5=Very good.

Table below shows the number of subjects in each tolerability category of the Likert scale, as assessed by the investigator.

End point type	Secondary

End point timeframe:

After the last IMP administration during the dose escalation phase.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[26]	25	20	17
Units: score				
number (not applicable)				
Missing	1	1	1	0
Very Bad	0	0	0	0
Bad	0	0	0	0
Average	0	0	2	0
Good	9	3	3	2
Very Good	15	21	14	15

Notes:

[26] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 9b_Tolerability: Likert scale at the final visit (Investigator)

End point title	9b_Tolerability: Likert scale at the final visit (Investigator)

End point description:

Assessment of the overall tolerability by the investigator at the final visit, using a 5-point Likert scale. Likert scale score system: 1=Very bad; 2=Bad; 3=Average; 4=Good; 5=Very good.

Table below shows the number of subjects in each tolerability category of the Likert scale, as assessed by the investigator.

End point type	Secondary

End point timeframe:

At the final visit.
Approximately 9 weeks for patients randomized to One Strength and approximately 13 weeks for patients randomized to Standard treatment group.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[27]	25	20	17
Units: score				
number (not applicable)				
Missing	1	1	0	0
Very Bad	0	0	1	0
Bad	0	0	1	0

Average	0	0	0	0
Good	4	3	3	2
Very Good	20	21	15	15

Notes:

[27] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 10a_Tolerability: Likert scale after last dose of escalation phase (Patient)

End point title	10a_Tolerability: Likert scale after last dose of escalation phase (Patient)

End point description:

Assessment of the overall tolerability by the patient using a 5-point Likert scale.
Likert scale score system: 1=Very bad; 2=Bad; 3=Average; 4=Good; 5=Very good.

Table below shows the number of subjects in each tolerability category of the Likert scale, as assessed by the patient.

End point type	Secondary

End point timeframe:

After the last IMP administration during the dose escalation phase.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[28]	25	20	17
Units: score				
number (not applicable)				
Missing	1	1	1	0
Very Bad	0	0	0	0
Bad	0	0	0	0
Average	0	0	1	0
Good	3	3	5	1
Very Good	21	21	13	16

Notes:

[28] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 10b_Tolerability: Likert scale at the final visit (Patient)

End point title	10b_Tolerability: Likert scale at the final visit (Patient)

End point description:

Assessment of the overall tolerability by the patient at the final visit, using a 5-point Likert scale.
Likert scale score system: 1=Very bad; 2=Bad; 3=Average; 4=Good; 5=Very good.

Table below shows the number of subjects in each tolerability category of the Likert scale, as assessed

by the patient.

End point type	Secondary

End point timeframe:

At the final visit.
Approximately 9 weeks for patients randomized to One Strength and approximately 13 weeks for patients randomized to Standard treatment group.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[29]	25	20	17
Units: score				
number (not applicable)				
Missing	1	1	0	0
Very Bad	0	0	0	0
Bad	0	0	1	0
Average	0	0	1	0
Good	1	1	2	2
Very Good	23	23	16	15

Notes:

[29] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 11a_Treatment-emergent adverse events related to IMP (All) - Time to onset

End point title	11a_Treatment-emergent adverse events related to IMP (All) - Time to onset

End point description:

Results show time to onset of all IMP-related TEAEs.

End point type	Secondary

End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[30]	25	20	17
Units: TEAEs related to IMP				
≤ 30 min	3	8	5	12
> 30 min. ≤ 6 h	9	10	23	8
> 6 h ≤ 24 h	6	8	10	9
> 24 h	3	1	1	3

Notes:

[30] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 11b_Treatment-emergent adverse events related to IMP (Local) - Time to onset

End point title	11b_Treatment-emergent adverse events related to IMP (Local) - Time to onset

End point description:

Results show time to onset of all local IMP-related TEAEs.

End point type	Secondary

End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[31]	25	20	17
Units: Local TEAEs related to IMP				
≤ 30 min	3	8	5	7
> 30 min ≤ 6 h	7	10	21	8
> 6 h ≤ 24 h	4	8	9	7
> 24 h	2	1	1	3

Notes:

[31] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 11c_Treatment-emergent adverse events related to IMP (Systemic) - Time to onset

End point title	11c_Treatment-emergent adverse events related to IMP (Systemic) - Time to onset

End point description:

Results show time to onset of all systemic IMP-related TEAEs.

End point type	Secondary

End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[32]	25	20	17
Units: Systemic TEAEs related to IMP				
≤ 30 min	0	0	0	5
> 30 min ≤ 6 h	1	0	1	0
> 6 h ≤ 24 h	0	0	0	0
> 24 h	1	0	0	0

Notes:

[32] - Safety analysis set was used for all treatment groups

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 12_Immunologic parameter (IgG4 specific against grass-pollen)

End point title	12_Immunologic parameter (IgG4 specific against grass-pollen)

End point description:

According to the study inclusion criteria, all patients had IgE-mediated seasonal allergic rhinitis or rhinoconjunctivitis (with or without allergic asthma), caused by grass pollen. Changes in grass-pollens pecific IgG4 antibody concentrations provide valuable information and evidence for the immunogenic activity of the active preparation. Changes in IgG4 were analyzed as an exploratory parameter.

The results (shown as changes from baseline) indicate that the mean concentration of IgG4 against P. pratense (Timothy grass) pollen increased notably over time in both treatment groups (p-value < 0.0001).

The number of subjects contributing to the data is also shown.

End point type	Other pre-specified

End point timeframe:

To determine the immunologic parameters, blood was taken at screening (baseline) and the final visit/premature termination of the study.

End point values	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength	Adolescents (12 to <18 y) Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[33]	25[34]	20[35]	17[36]
Units: mg/l				
arithmetic mean (full range (min-max))	5.781 (0.17 to 28.97)	8.008 (0.07 to 27.96)	4.119 (0 to 21.47)	7.419 (0.18 to 28.61)

Notes:

[33] - Safety analysis set was used for all treatment groups
N=24

[34] -

N=24

[35] -
N=20

[36] -
N=17

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration or trial-related procedure.

Adverse event reporting additional description:

Results are shown for the safety analysis set.

Results show treatment emergent adverse event (TEAE): any AE that started or worsened after the first intake of trial medication until 30 days after the last IMP administration or trial-related procedure. Further clarification of AEs is in the 'Description' section for end point 1.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Children (5 to <12 y) One Strength

Reporting group description:

Children (5 to <12 y) who were randomised to the One Strength treatment.

Patients randomised to the 'accelerated dose escalation scheme' received 3 injections with One Strength (B: 10, 000 therapeutic units [TU]/mL), followed by 2 injections with the maximum recommended dose.

Duration of treatment was approximately 9 weeks.

Reporting group title	Children (5 to <12 y) Standard

Reporting group description:

Children (5 to <12 y) who were randomised to the Standard treatment.

Patient randomized to 'standard dose escalation' (Standard) received 7 injections with two strengths (A: 1,000 TU/mL; B: 10, 000 TU/mL), followed by 2 injections with the maximum recommended dose.

Duration of treatment was approximately 13 weeks.

Reporting group title	Adolescents (12 to <18 y) One Strength

Reporting group description:

Adolescents (12 to <18 y) who were randomised to the One Strength treatment.

Patients randomised to the 'accelerated dose escalation scheme' received 3 injections with One Strength (B: 10, 000 therapeutic units [TU]/mL), followed by 2 injections with the maximum recommended dose.

Duration of treatment was approximately 9 weeks.

Reporting group title	Adolescents (12 to <18 y) Standard

Reporting group description:

Adolescents (12 to <18 y) who were randomised to the Standard treatment.

Patient randomized to 'standard dose escalation' (Standard) received 7 injections with two strengths (A: 1,000 TU/mL; B: 10, 000 TU/mL), followed by 2 injections with the maximum recommended dose.

Duration of treatment was approximately 13 weeks.

Serious adverse events	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Eye disorders			
Conjunctival oedema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 20 (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			
Cough			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 20 (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
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 20 (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
Urticaria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 20 (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	Adolescents (12 to <18 y) Standard		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Eye disorders			
Conjunctival oedema			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Children (5 to <12 y) One Strength	Children (5 to <12 y) Standard	Adolescents (12 to <18 y) One Strength
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 25 (72.00%)	16 / 25 (64.00%)	8 / 20 (40.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 25 (20.00%)	1 / 25 (4.00%)	1 / 20 (5.00%)
occurrences (all)	12	1	1
Somnolence			

subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	2 / 25 (8.00%)	3 / 25 (12.00%)	3 / 20 (15.00%)
occurrences (all)	3	11	11
Injection site pruritus			
subjects affected / exposed	2 / 25 (8.00%)	3 / 25 (12.00%)	4 / 20 (20.00%)
occurrences (all)	2	3	8
Injection site swelling			
subjects affected / exposed	9 / 25 (36.00%)	8 / 25 (32.00%)	5 / 20 (25.00%)
occurrences (all)	12	11	13
Injection site pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	3 / 20 (15.00%)
occurrences (all)	0	1	3
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Injection site discomfort			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0

Cough			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	1 / 20 (5.00%)
occurrences (all)	3	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Rhinitis allergic			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Dysphonia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 25 (20.00%)	3 / 25 (12.00%)	0 / 20 (0.00%)
occurrences (all)	7	3	0
Rhinitis			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	1 / 20 (5.00%)
occurrences (all)	0	3	2
Viral infection			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	1 / 20 (5.00%)
occurrences (all)	1	2	1
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Conjunctivitis			

subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Adolescents (12 to <18 y) Standard		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 17 (41.18%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	5		
Somnolence			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	7		
Injection site pruritus			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	8		
Injection site swelling			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	10		
Injection site pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Injection site discomfort			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Eye disorders			

Eye pruritus subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Sneezing subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 1 / 17 (5.88%) 2 0 / 17 (0.00%) 0		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2019	Screening phase: postponed, treatment phase: postponed. This amendment was submitted in Germany, Poland, and Russia (all on 23 Jan 2019). There were country-specific differences in postponement time: Germany (23 Jan 2019), after trial start: screening phase: postponed by 1 month; treatment phase: postponed by 1 month. Poland (23 Jan 2019), prior to trial start: screening phase: postponed by 4 months; treatment phase: postponed by 5 months. Russia (23 Jan 2019), prior to trial start: screening phase: postponed by 4 months; treatment phase: postponed by 4 months.
24 June 2019	Substantial amendment regarding the adaptation of sample size was submitted to all Competent Authorities and Independent Ethics Committees (Germany, Poland, Russia, Spain), in September 2019. The date on which this amendment was submitted to the Competent Authorities (September 2019) is after the end of the trial (i.e. after LPLV = 25 Jun 2019). However, due to technical set-up of the EudraCT database, which would generate an error message during the validation process, the date of this substantial amendment is set here to 24-Jun-2019 (i.e. one day before the LPLV of this study).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported