Clinical trial results:
A multicenter, randomized, open-label clinical trial to evaluate safety and tolerability of a year-round initiation of specific immunotherapy with an aluminum hydroxide adsorbed allergoid preparation of 6-grasses in patients with moderate to severe seasonal rhinitis or rhinoconjunctivitis with or without controlled asthma

Summary

EudraCT number	2015-002409-13
Trial protocol	DE
Global end of trial date	15 February 2017

Results information

Result version number	v1 (current)
This version publication date	26 October 2018
First version publication date	26 October 2018

Trial information

Trial identification

Sponsor protocol code	AL1501AV

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, 0049 40427650,
Scientific contact	Clinical Trials Information, Allergopharma GmbH & Co. KG, 0049 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	07 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study consisted of 2 treatment groups (Group A and Group B). Subjects in Group A started dose escalation without any time constraints relative to the pollen season and subjects in Group B after the pollen season. Other than the starting time for dose escalation and the number of subjects, there were no differences in the subject population or dosing schedule between the groups.

1) The main objective of this therapeutic phase IIIb trial was to evaluate the safety and tolerability of a year-round initiation start of immunotherapy with Allergovit® 6-grasses in patients with rhinitis or rhinoconjunctivitis, caused by grasses, with or without controlled allergic asthma compared to a standard therapy.

2) Evaluate the a possible influence (masking of adverse events) of a symptomatic co-medication during intra seasonal therapy.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that 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 every week.

For subjects who received a vaccination against viral or bacterial pathogens or for other reasons, there was a provision in the study protocol for a period of time between the vaccination and the start of the immunotherapy.

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

Background therapy:

Medication for the treatment of rhinitis and rhinoconjunctivitis was permitted and had to be documented as concomitant medication.

Subjects with bronchial asthma who required regular basic treatment of their allergic asthma had to be treated as recommended by GINA (GINA, 2015) to control their asthma. However, the in- and exclusion criteria had to be strictly followed. The start of additional asthma medication was not permitted during the duration of the trial.

Evidence for comparator:

Abbreviations used in this document:

AE=Adverse event
AIT=Allergen immunotherapy
DSMB=Data Safety Monitoring Board
ICF=Informed consent form
IMP=Investigational medicinal product
MedDRA=Medical Dictionary for Regulatory Activities
NIA=National Institute on Aging

PEF=Peak flow measurement
P. pratense= Phleum pratense
T=Treatment (as in T1 =Treatment visit 1, etc.)
TEAE=Treatment-emergent adverse event
TU/mL=Therapeutic units per mL
WAO=World Allergy Organization

Actual start date of recruitment	26 January 2016
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	Germany: 240
Worldwide total number of subjects	240
EEA total number of subjects	240

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	240
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 314 adult male and female subjects (18-64 y)] were screened for eligibility; 240 subjects were randomised to treatment, according to the exclusion and inclusion criteria.

Pre-assignment

Screening details:

Screened and randomised to treatment according to the exclusion and inclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Subjects started treatment without any time constraints relative to the pollen season.

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:

The IMP is an aluminium hydroxide-adsorbed allergoid preparation of Allergovit® 6-grasses (TU/mL).

PEF was performed before and 30 minutes after each injection (observe respiratory symptoms and PEF value was less than 70% of predicted normal). The IMP was administered at the trial site, as slow, subcutaneous injection, under sterile measures, on the extensor side of the upper arm, above the elbow. After each administration of the IMP, patients remained under supervision for at least 30 min.

IMP strength A (1,000 TU/mL) and IMP strength B (10,000 TU/mL).
Dose escalation schedule every 7 days: 100, 200, 400, 800, 1500, 3000, 6000 TU
Maintenance 2 weeks after last dose: 6000 TU, then 4 weeks after last dose 6000 TU

The majority of subjects (> 80%) reached the maintenance dose without any dose reduction, and the number of subjects needing a dose adjustment did not relevantly differ between treatment groups.

Arm title	Group B

Arm description:

Subjects started treatment after the pollen season.

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:

The IMP is an aluminium hydroxide-adsorbed allergoid preparation of Allergovit® 6-grasses (TU/mL).

PEF was performed before and 30 minutes after each injection (observe respiratory symptoms and PEF value was less than 70% of predicted normal). The IMP was administered at the trial site, as slow,

subcutaneous injection, under sterile measures, on the extensor side of the upper arm, above the elbow. After each administration of the IMP, patients remained under supervision for at least 30 min.

IMP strength A (1,000 TU/mL) and IMP strength B (10,000 TU/mL).
Dose escalation schedule every 7 days: 100, 200, 400, 800, 1500, 3000, 6000 TU
Maintenance 2 weeks after last dose: 6000 TU, then 4 weeks after last dose 6000 TU

The majority of subjects (> 80%) reached the maintenance dose without any dose reduction, and the number of subjects needing a dose adjustment did not relevantly differ between treatment groups.

Number of subjects in period 1	Group A	Group B
Started	161	79
Completed	139	65
Not completed	22	14
Consent withdrawn by subject	4	4
Adverse event, non-fatal	10	3
Other (Travel plans)	-	3
Travel plans; Long interval btw. doses	4	-
Lost to follow-up	4	3
Incl./ Excl. criteria	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description:	
Subjects started treatment without any time constraints relative to the pollen season.	
Reporting group title	Group B
Reporting group description:	
Subjects started treatment after the pollen season.	

Reporting group values	Group A	Group B	Total
Number of subjects	161	79	240
Age categorical Units: Subjects			
Adults (18-64 years)	161	79	240
Age continuous Units: years			
arithmetic mean	32.66	33.08	
standard deviation	± 9.45	± 10.46	-
Gender categorical Units: Subjects			
Female	74	37	111
Male	87	42	129
Race Units: Subjects			
Asian	8	1	9
Black/African American	0	1	1
White	151	75	226
Other	2	2	4
Pet contact Units: Subjects			
Yes; intermittent	17	8	25
Yes; permanent	31	11	42
No	113	60	173
Smoking status Units: Subjects			
Non-smoker	113	62	175
Ex-smoker	17	4	21
Current smoker	31	13	44

Subject analysis sets	
Subject analysis set title	Group A1
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Group A1: subjects from Group A with frequent use of antisymptomatic co-medication in the 3 days immediately before and 1 day after the injection (including the date of investigational medicinal product [IMP] administration); information was based on the diary data.	
Subject analysis set title	Group A2

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Group A2: subjects from Group A without or infrequent use of antisymptomatic co-medication in the 3 days immediately before and 1 day after the injection (including the date of IMP administration); information was based on the diary data.

Reporting group values	Group A1	Group A2	
Number of subjects	34	122	
Age categorical Units: Subjects			
Adults (18-64 years)	34	122	
Age continuous Units: years			
arithmetic mean	32.91	32.59	
standard deviation	± 10.20	± 9.33	
Gender categorical Units: Subjects			
Female	22	50	
Male	12	72	
Race Units: Subjects			
Asian	2	6	
Black/African American	0	0	
White	32	114	
Other	0	2	
Pet contact Units: Subjects			
Yes; intermittent	2	15	
Yes; permanent	6	24	
No	26	83	
Smoking status Units: Subjects			
Non-smoker	24	86	
Ex-smoker	4	13	
Current smoker	6	23	

End points

End points reporting groups

Reporting group title	Group A
Reporting group description:	
Subjects started treatment without any time constraints relative to the pollen season.	
Reporting group title	Group B
Reporting group description:	
Subjects started treatment after the pollen season.	
Subject analysis set title	Group A1
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Group A1: subjects from Group A with frequent use of antisymptomatic co-medication in the 3 days immediately before and 1 day after the injection (including the date of investigational medicinal product [IMP] administration); information was based on the diary data.	
Subject analysis set title	Group A2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Group A2: subjects from Group A without or infrequent use of antisymptomatic co-medication in the 3 days immediately before and 1 day after the injection (including the date of IMP administration); information was based on the diary data.	

Primary: 1_Treatment-emergent adverse events by causal relationship

End point title	1_Treatment-emergent adverse events by causal relationship
End point description:	
When assessing the causal relationship of the AE, the following points were taken into account (according to Volume 10 Clinical Trials Guideline, Chapter II Safety Reporting). A reasonable possibility of causality to IMP implies that there is evidence for the AE, e.g. • Reasonable possibility of causality to IMP implies the definitions "reasonable possibility of causality to IMP" • Or "reasonable possibility of causality to trial procedure" implies a reasonable possibility of causal relationship between the event and the trial procedure. • Temporal occurrence suggest a causal relationship. This means that there are facts (evidence) or arguments to suggest causal relationship	
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.	

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	158[1]	73	34	122
Units: patients	108	41	24	83

Notes:

[1] - Safety set for all treatment/analyses groups

Statistical analyses

Statistical analysis title	Causality of TEAE (Treatment Group A vs B)
Comparison groups	Group A v Group B
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0777
Method	Fisher exact

Statistical analysis title	Causality of TEAE (Treatment Group A1 vs A2)
Comparison groups	Group A1 v Group A2
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8372
Method	Fisher exact

Primary: 2_Treatment-emergent adverse events by worst intensity

End point title	2_Treatment-emergent adverse events by worst intensity[2]

End point description:

AE intensity in this trial was assessed by the the investigator's clinical judgement of and based on the description 'Intensity of the AE' according to National Institute on Aging (NIA)

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.

Notes:

[2] - 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: No statistical analysis was performed. Results were evaluated descriptively.

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	158[3]	73	34	122
Units: patients				
Mild	84	32	14	69
Moderate	51	19	12	39
Severe	9	6	2	7

Notes:

[3] - Safety set for all treatment/analyses groups

Statistical analyses

No statistical analyses for this end point

Secondary: 3_Treatment-emergent adverse event anaphylactic systemic reactions according to WAO

End point title	3_Treatment-emergent adverse event anaphylactic systemic reactions according to WAO

End point description:

Any TEAE anaphylactic reactions were graded according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2010*) and were based on the organ systems involved and the severity of the reaction.

WAO grading system was used for dose modification in case of an anaphylactic reaction:
• Grade 1: reduction by 1 dose step of the last administered dose
• Grade 2: reduction by 2 dose steps of the last administered dose
For Grade 1 and Grade 2: if the first dose reduction was not tolerated, a second dose reduction by 1 dose step of the last administered dose was to be performed. No more than 2 consecutive dose reductions were allowed.

TEAE=Treatment emergent adverse event
WAO = World Allergy Organization
*Cox L, Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010; 125(3): 569-574.

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.

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	158[4]	73	34	122
Units: patients	5	2	2	3

Notes:

[4] - Safety set for all treatment/analyses groups

Statistical analyses

Statistical analysis title	TEAE syst. reaction WAO (Treatment Group A vs B)
Comparison groups	Group A v Group B
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 1
Method	Fisher exact

Statistical analysis title	TEAE syst. reaction WAO (Treatment Group A1 vs A2)
Comparison groups	Group A1 v Group A2

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2989
Method	Fisher exact

Secondary: 4_Lung function test - PEF

End point title	4_Lung function test - PEF

End point description:

Each patient had to undergo a PEF measurement before and 30 minutes after each injection to recognize pulmonary reaction early enough. If respiratory symptoms have increased before the injection or the PEF value was less than 70% of predicted normal, then the injection was postponed until the patient had reached a more stable (asthma) condition. Trial medication administration to a patient with less than 70% of predicted normal was regarded as a protocol deviation.

Results shown are representative for the study visits at the start of the study, at the end of the escalation dose (T7), at the end of the study (T13), and the final visit. Mean and median PEF results were similar between all the groups at all the time points. The number of patients contributing to the data at each of the visits, is also shown.

End point type	Secondary

End point timeframe:

30 min before and 30 min after each treatment (T) visit involving IMP administration.
Visits T1, T2, T3 ... to T13. T1 to T7 were separated by 7 days (dose escalation)
Visits T8 to T13 were separated by 2 weeks.

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	158[5]	73[6]	34[7]	122[8]
Units: L/min				
arithmetic mean (standard deviation)				
Screening	511.73 (± 111.45)	493.62 (± 100.31)	503.56 (± 101.34)	514.20 (± 115.10)
T1, before	516.04 (± 104.11)	500.58 (± 111.77)	493.38 (± 84.84)	521.97 (± 108.87)
T1, after	517.62 (± 104.29)	500.39 (± 110.91)	492.03 (± 84.86)	524.36 (± 108.92)
T7, before	523.99 (± 108.94)	503.50 (± 108.20)	498.69 (± 94.89)	530.79 (± 111.81)
T7, after	523.91 (± 107.24)	505.30 (± 108.37)	498.19 (± 88.97)	530.82 (± 110.96)
T13, before	500.00 (± 115.18)	620.00 (± 0.00)	480.00 (± 0.00)	506.67 (± 140.12)
T13, after	515.00 (± 99.83)	610.00 (± 0.00)	460.00 (± 0.00)	533.33 (± 113.72)
Final Visit	522.16 (± 110.13)	502.44 (± 112.58)	495.24 (± 90.97)	529.56 (± 114.06)

Notes:

[5] - Safety Set
T1 aft=157
T7 bfr=151

T7 aft=151
T13 bfr=4
T13 aft=4
Final=153

[6] - Safety Set
T1 aft=72
T7 bfr=68
T7 aft=67
T13 bfr=1
T13 aft=1
Final=70
[7] - Safety Set
T7 bfr=32
T7 aft=32
T13 bfr=1
T13 aft=1
Final=33
[8] - Safety Set
T1 aft=121
T7 bfr=119
T7 aft=119
T13 bfr=3
T13 aft=3
Final=120

Statistical analyses

No statistical analyses for this end point

Secondary: 5_Tolerability: Likert scale (Investigator)

End point title	5_Tolerability: Likert scale (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:

At the final visit/premature termination of the study.

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	158[9]	73	34	122
Units: patients				
Missing	5	3	1	2
Very bad	3	0	1	2
Bad	7	3	1	6
Average	14	6	5	9
Good	66	23	16	50
Very good	63	38	10	53

Notes:

[9] - Safety set for all treatment/analyses groups

Statistical analyses

Statistical analysis title	Tolerability assessments by investigator; A vs B
Comparison groups	Group A v Group B
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0923
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Tolerability assessments by investigator; A1 vs A2
Comparison groups	Group A1 v Group A2
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1454
Method	Wilcoxon (Mann-Whitney)

Secondary: 6_Tolerability: Likert scale (Patient)

End point title	6_Tolerability: Likert scale (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 patients in each tolerability category of the Likert scale, as assessed by the patient.

End point type	Secondary

End point timeframe:

At the final visit/premature termination of the study.

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	158[10]	73	34	122
Units: patients				
Missing	5	3	1	2
Very bad	3	0	2	1
Bad	6	2	1	5
Average	14	6	3	11
Good	71	32	17	54
Very good	59	30	10	49

Notes:

[10] - Safety set for all treatment/analyses groups

Statistical analyses

Statistical analysis title	Tolerability assessments by patient; A vs B
Comparison groups	Group A v Group B
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4214
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Tolerability assessments by patient; A1 vs A2
Comparison groups	Group A1 v Group A2
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2527
Method	Wilcoxon (Mann-Whitney)

Secondary: 7_Treatment-emergent adverse event local reactions

End point title	7_Treatment-emergent adverse event local reactions

End point description:

Treatment-emergent adverse event local reactions are represented by common symptoms of local reactions such as pain, tenderness, pruritus/itching, erythema/redness, in duration/swelling. The size for the symptoms erythema/redness and in duration/swelling was documented to allow adjustment of the dose accordingly. All injection site reactions > 5 cm (local reactions) had to be reported as AEs.

Most local reactions were considered mild or moderate in intensity; none were classified as serious AEs. Differences of local reactions between treatment groups were not statistically significant. All local reactions, except for 3 reactions were assessed as related to the IMP.

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.

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	158[11]	73	34	122
Units: patients	102	40	20	81

Notes:

[11] - Safety set for all treatment/analyses groups

Statistical analyses

Statistical analysis title	TEAE local reaction (Treatment Group A vs B)
Comparison groups	Group A v Group B

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1907
Method	Fisher exact

Statistical analysis title	TEAE local reaction (Treatment Group A1 vs A2
Comparison groups	Group A1 v Group A2
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4238
Method	Fisher exact

Secondary: 8_Vital signs - Heart rate

End point title	8_Vital signs - Heart rate

End point description:

Clinical chemistry, vital signs, physical examination - are summarized as one representative endpoint. Shown is the heart rate, as change to baseline between screening (baseline) and the indicated study visit.

There were no relevant differences between the treatment groups or between the subgroups; same applies to laboratory parameters.

Vital signs measured:
Arterial BP, diastolic BP, heart rate, respiratory rate

Laboratory parameters:
• Clinical chemistry: creatinine, total bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase
• Blood sugar: glucose (fasting or nonfasting; status to be assessed only for determination of eligibility of the subject for the trial)
• Hematology: differential blood cell count, hemoglobin, leukocytes, platelets
• Urinalysis: protein, glucose, blood (hemoglobin), leukocytes, beta-human chorionic gonadotropin (women of childbearing potential only).

End point type	Secondary

End point timeframe:

Vital signs: screening (baseline), before and after each IMP administration, at dose escalation; and at the final/premature termination visit.
Laboratory parameters: screening (baseline) and at the final/premature termination visit.

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	158[12]	73[13]	34[14]	122[15]
Units: bpm				
median (full range (min-max))				
T1, after	-3 (-24 to 24)	-2 (-23 to 8)	-2 (-20 to 24)	-4 (-24 to 11)
T7, before	0 (-29 to 25)	0 (-20 to 24)	1.5 (-29 to 19)	-1 (-26 to 25)

T7, after	-4 (-32 to 20)	-1 (-26 to 23)	-4 (-27 to 20)	-5 (-32 to 18)
T13, before	4 (2 to 15)	20 (20 to 20)	4 (4 to 4)	4 (2 to 15)
T13, after	-2.5 (-12 to 3)	16 (16 to 16)	-12 (-12 to -12)	2 (-7 to 3)
Final Visit	0 (-25 to 24)	1 (-22 to 29)	2 (-24 to 24)	0 (-25 to 24)

Notes:

[12] - Safety set
T1 aft=157
T7 bfr=151
T7 aft=151
T13 bfr=4
T13 aft=4
Final=153

[13] - Safety set
T1 aft=71
T7 bfr=68
T7 aft=67
T13 bfr=1
T13 aft=1
Final=70

[14] - Safety set
T1 aft=34
T7 bfr=32
T7 aft=32
T13 bfr=1
T13 aft=1
Final=33

[15] - Safety set
T1 aft=121
T7 bfr=119
T7 aft=119
T13 bfr=3
T13 aft=3
Final=120

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 9_Immunologic parameter (IgG4 for P. pratense)

End point title	9_Immunologic parameter (IgG4 for P. pratense)

End point description:

Changes in IgG4 were analyzed as an exploratory parameter. Increases in grass-pollen-specific IgG4 antibody concentrations provide valuable evidence for the immunogenic activity of the active preparations.

Mean change from baseline to the final visit in P. pratense IgG4 was similar between the treatment groups and is summarized in the table below.

End point type	Other pre-specified

End point timeframe:

At screening (baseline) and the final visit/premature termination of the study.

End point values	Group A	Group B	Group A1	Group A2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	152[16]	70	33	119
Units: mg/L				
median (full range (min-max))	2.54 (0.0 to 29.1)	2.45 (0.1 to 23.7)	1.80 (0.0 to 21.4)	2.60 (0.0 to 29.1)

Notes:

[16] - Safety set for all treatment/analyses groups

Statistical analyses

Statistical analysis title	IgG 4 level change to baseline (A vs B)
Comparison groups	Group A v Group B
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9409
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	IgG 4 level change to baseline (A1 vs A2)
Comparison groups	Group A1 v Group A2
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5237
Method	Wilcoxon (Mann-Whitney)

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.

Adverse event reporting additional description:

AEs with an onset during or after the first IMP administration were defined as TEAEs. An AE was considered as related to the IMP/trial procedure if the causal relationship of the AE was recorded as having a reasonable possibility to the IMP/trial procedure in the eCRF. Fisher Exact tests were used to investigate treatment differences.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Group A

Reporting group description:

Subjects started treatment without any time constraints relative to the pollen season.

Reporting group title	Group B

Reporting group description:

Subjects started treatment after the pollen season.

Serious adverse events	Group A	Group B	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 158 (0.63%)	0 / 73 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	1 / 158 (0.63%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group A	Group B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 158 (80.38%)	54 / 73 (73.97%)	
Nervous system disorders			

Headache			
subjects affected / exposed	63 / 158 (39.87%)	23 / 73 (31.51%)	
occurrences (all)	153	49	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	47 / 158 (29.75%)	17 / 73 (23.29%)	
occurrences (all)	122	42	
Injection site pain			
subjects affected / exposed	19 / 158 (12.03%)	7 / 73 (9.59%)	
occurrences (all)	31	15	
Injection site pruritus			
subjects affected / exposed	64 / 158 (40.51%)	32 / 73 (43.84%)	
occurrences (all)	168	95	
Injection site swelling			
subjects affected / exposed	76 / 158 (48.10%)	26 / 73 (35.62%)	
occurrences (all)	223	67	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	9 / 158 (5.70%)	1 / 73 (1.37%)	
occurrences (all)	14	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 158 (6.33%)	0 / 73 (0.00%)	
occurrences (all)	13	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 158 (5.06%)	0 / 73 (0.00%)	
occurrences (all)	10	0	
Oropharyngeal pain			
subjects affected / exposed	13 / 158 (8.23%)	2 / 73 (2.74%)	
occurrences (all)	13	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	38 / 158 (24.05%)	22 / 73 (30.14%)	
occurrences (all)	56	35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2015	Planned sample size of treated subjects changed from 160 subjects in total, to 160 subjects in Group A and 80 subjects in Group B (a total of 240 subjects). Thus, the sample size calculation and justification were updated and the randomization ratio was changed from 1:1 to 2:1 (Group A: Group B). • Evaluation of possible influence of antisymptomatic co-medication on year-round initiation of AIT was added as an objective and a corresponding safety endpoint was added. • Exclusion of subjects using AIT for ≥ 4 weeks within the previous 5 years changed to any use of AIT within the previous 5 years. • Receipt of a vaccination against viral or bacterial pathogens within 2 weeks before the start of the immunotherapy added as a restriction. • Restriction of not using any short-acting antihistamines within 2 days changed to within 3 days. • Restriction of not using any systemic anti-allergic medication within 2 days before and 1 day after IMP administration changed to within 3 days before, on the day, and 1 day after IMP administration. • Requirement to record the size of any local reactions as longest diameter in cm added. • Requirement to record all signs and symptoms leading to discomfort, as AE.
03 May 2016	• Clarification that vital signs could be measured after 5 minutes in either a supine or sitting position, not only supine. • Criterion for withdrawal of subjects changed from a subject who experienced a reaction at the injection site following the first IMP administration which was considered severe to an injection site reaction following the first administration which required a dose modification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported