



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 patients with moderate to severe seasonal rhinitis or rhinoconjunctivitis with or without asthma

Summary

EudraCT number	2017-000754-19
Trial protocol	DE ES PL
Global end of trial date	31 May 2018

Results information

Result version number	v1 (current)
This version publication date	03 May 2019
First version publication date	03 May 2019

Trial information

Trial identification

Sponsor protocol code	AL1602av
-----------------------	----------

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	11 February 2019
Is this the analysis of the primary completion data?	No
<hr/>	
Global end of trial reached?	Yes
Global end of trial date	31 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of an accelerated high dose escalation schedule using one strength allergen immunotherapy with Allergovit® 6-Grasses compared with the standard escalation schedule using two strengths. Adults subjects with rhinitis or rhinoconjunctivitis caused by grass pollen, with or without allergic asthma on a well controlled level were enrolled into the study.

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.

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 mins 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, 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 should 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 had to be treated as recommended by GINA (GINA, 2017) to control their asthma. However, the in- and exclusion criteria had to be strictly followed. 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
IMP=Investigational medicinal product
MedDRA=Medical Dictionary for Regulatory Activities
P. pratense=Phleum pratense
T=Treatment (as in T1 =Treatment visit 1, etc.)
TEAE=Treatment-emergent adverse event
TU=Therapeutic units
WAO=World Allergy Organization

Actual start date of recruitment	04 October 2017
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: 19
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Spain: 6
Worldwide total number of subjects	87
EEA total number of subjects	74

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)	86
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 129 adult male and female subjects (18-65 y) were screened for eligibility; of these, 87 were randomised to treatment, according to the exclusion and inclusion criteria. One subject discontinued the study this subject prior to any IMP administration, due to 'flue-like' symptoms.

Pre-assignment

Screening details:

Study subjects (outpatients) were included if they were suffering from immunoglobulin (Ig) E mediated seasonal allergic rhinitis or rhinoconjunctivitis, with or without allergic asthma, caused by grass pollen documented by skin prick test (SPT) wheal for grass pollen.

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	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. The duration of treatment was approximately 9 weeks.

One subject in the 'One Strength' dose scheme discontinued the study due to 'flue-like' symptoms; this subject did not receive any IMP and was excluded from the overall analysis.

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 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 as 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: 1000, 3000, 6000 TU

Maintenance 2 weeks after last dose: 6000 TU, then 4 weeks after last dose 6000 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, 80% of subjects reached the 1st IMP injection of the maintenance phase without dose adjustment.

Arm title	Standard
-----------	----------

Arm description:

Patient randomized to standard dose escalation scheme ('Standard') received 7 injections with two strengths of the IMP (A: 1000 TU/mL; B: 10 000 TU/mL), followed by 2 injections with the maximum recommended dose. The duration of treatment was approximately 13 weeks.

Two subjects randomized to the 'Standard' dose scheme, due to allocation error actually received the IMP of the 'One Strength' scheme. Thus, data and results of these two subjects were part of the 'One Strength' scheme analyses.

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:

The 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'.

IMP strengths A and B were used.

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

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, 95% of subjects reached the 1st IMP injection of the maintenance phase without dose adjustment.

Number of subjects in period 1	One Strength	Standard
Started	46	41
Completed	38	39
Not completed	8	2
Consent withdrawn by subject	2	1
Adverse event, non-fatal	3	-
Flue-like symptoms, before any IMP administration	1	-
Treatment allocation error	2	-
Protocol deviation	-	1

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. The duration of treatment was approximately 9 weeks.

One subject in the 'One Strength' dose scheme discontinued the study due to 'flue-like' symptoms; this subject did not receive any IMP and was excluded from the overall analysis.

Reporting group title	Standard
-----------------------	----------

Reporting group description:

Patient randomized to standard dose escalation scheme ('Standard') received 7 injections with two strengths of the IMP (A: 1000 TU/mL; B: 10 000 TU/mL), followed by 2 injections with the maximum recommended dose. The duration of treatment was approximately 13 weeks.

Two subject randomized to the 'Standard' dose scheme, due to allocation error actually received the IMP of the 'One Strength' scheme. Thus, data and results of these two subjects were part of the 'One Strength' scheme analyses.

Reporting group values	One Strength	Standard	Total
Number of subjects	46	41	87
Age categorical Units: Subjects			
Adults (18-64 years)	46	40	86
From 65-84 years	0	1	1
Age continuous Units: years			
arithmetic mean	32.98	36.05	
standard deviation	± 9.48	± 12.21	-
Gender categorical Units: Subjects			
Female	19	20	39
Male	27	21	48
Smoking status Units: Subjects			
Never	37	31	68
Ex-smoker	6	4	10
Current smoker	3	6	9
Ethnicity Units: Subjects			
American Indian or Alaskan Native	1	0	1
Asian	0	1	1
White	45	40	85
BMI Units: kg/m2			
median	24.74	23.89	
full range (min-max)	18.73 to 35.92	17.93 to 43.52	-

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. The duration of treatment was approximately 9 weeks.

One subject in the 'One Strength' dose scheme discontinued the study due to 'flue-like' symptoms; this subject did not receive any IMP and was excluded from the overall analysis.

Reporting group title	Standard
-----------------------	----------

Reporting group description:

Patient randomized to standard dose escalation scheme ('Standard') received 7 injections with two strengths of the IMP (A: 1000 TU/mL; B: 10 000 TU/mL), followed by 2 injections with the maximum recommended dose. The duration of treatment was approximately 13 weeks.

Two subject randomized to the 'Standard' dose scheme, due to allocation error actually received the IMP of the 'One Strength' scheme. Thus, data and results of these two subjects were part of the 'One Strength' scheme analyses.

Primary: 1_Treatment-emergent adverse events - Overall

End point title	1_Treatment-emergent adverse events - Overall ^[1]
-----------------	--

End point description:

TEAE was defined as any untoward medical occurrence in a patient or clinical investigation subject who received the IMP. The TEAEs did not necessarily have to have a causal relationship with this treatment. A TEAE 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.

Results in the table below summarize the number of subjects affected by a TEAE; the number of the respective events 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.

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	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[2]	41 ^[3]		
Units: subjects				
1_Subjects with TEAE	37	35		
2_Subjects with serious TEAE	1	0		
3_Subjects with TEAEs related to IMP	27	20		
4_Subjects with TEAE leading to discontinuation	2	0		

Notes:

[2] - Safety set

1_TEAEs N=200

2_TEAEs N=2

3_TEAEs N=129
4_TEAEs N=2

[3] - Safety set
1_TEAEs N=244
2_TEAEs N=0
3_TEAEs N=132
4_TEAEs 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 ^[4]
-----------------	--

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:

[4] - 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	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[5]	41		
Units: subjects				
Mild	22	24		
Moderate	13	11		
Severe	2	0		

Notes:

[5] - Safety set was used for the analyses of both treatment groups

Statistical analyses

No statistical analyses for this end point

Primary: 3_Treatment-emergent adverse events - Causal relationship

End point title	3_Treatment-emergent adverse events - Causal relationship ^[6]
-----------------	--

End point description:

TEAEs, assessed as related to IMP.

Relatedness of TEAEs to the IMP was assessed by the the investigator.

Most of the related TEAEs were mild in intensity (85% in the accelerated escalation dose and 91% in the standard escalation dose group). The TEAEs included Injection site swelling, Injection site erythema, Injection site pruritus, Injection site pain, Injection site warmth, Injection site haemorrhage, FEV1 decrease, and Headache and are listed under the section 'Adverse events'.

Results in the table below summarize the number of subjects affected by an TEAEs or serious TEAEs related to IMP; the number of the respective events is also shown.

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	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[7]	41 ^[8]		
Units: subjects				
Subjects with adverse events	27	20		
Subjects with serious adverse events	1	0		

Notes:

[7] - Safety set was used for the analyses of both treatment groups

Number of events

AE=127

SAE=2

[8] - Number of events

AE=132

SAE=0

Statistical analyses

No statistical analyses for this end point

Secondary: 5_Treatment-emergent adverse event - Systemic allergic reactions according to WAO

End point title	5_Treatment-emergent adverse event - Systemic allergic reactions according to WAO
-----------------	---

End point description:

A systemic allergic reaction was defined as an AE graded by the investigator according to the WAO grading system that is based on the organ systems involved and the severity of the reaction (Cox et al 2010)*.

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.

The systemic allergic reaction AEs were: Tachycardia, Eye pruritus, Malaise, Rhinitis, FEV1 decreased, Restlessness, Asthma, Dyspnoea, Rhinorrhoea, Throat tightness, Erythema.

All systemic allergic reactions were assessed by the investigator as non-serious

*Cox L, Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010; 125(3): 569-57

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	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[9]	41		
Units: subjects				
Grade 1	2	1		
Grade 2	3	0		

Notes:

[9] - Safety set was used for the analyses of both treatment groups

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 treatment-emergent adverse event.

In the 'accelerated dose escalation' group, 5 patients did not reach the maintenance phase without dose adjustment due to a TEAE: 3 had TEAEs leading to dose reduction and 2 patients terminated the trial prematurely due to 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	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[10]	41		
Units: subjects	40	39		

Notes:

[10] - Safety set was used for the analyses of both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 7_Vital signs - Heart rate

End point title	7_Vital signs - Heart rate
-----------------	----------------------------

End point description:

Clinical chemistry, vital signs, and physical examination are summarized by a representative parameter 'Heart rate'.

Results are shown as the change (at 30 min) from pre-IMP administration on the first (T1), last (T3/T7)

escalation dose visit and the last maintenance (M2) visit.

Vital signs measured:

Arterial BP, diastolic BP, heart rate, respiratory rate

Laboratory parameters measured (at the screening visit and Final visit):

- Clinical chemistry: creatinine, total bilirubin, aspartate, liver enzymes aminotransferase, alanine aminotransferase, gamma-glutamyltransferase
- Blood sugar: Glucose (fasting or non-fasting; status assessed for decision on in-/exclusion of patient)
- Hematology: differential blood cell count, hemoglobin, leukocytes, platelets
- Urinalysis: protein, glucose, blood (hemoglobin), leukocytes, beta-human chorionic gonadotropin (women of childbearing potential).

There were no clinical relevant differences noted 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	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[11]	41 ^[12]		
Units: bpm				
median (full range (min-max))				
T1 visit 30 min after	-2 (-19 to 12)	0 (-21 to 12)		
T3/T7 visit after	-2 (-28 to 21)	-2 (-20 to 9)		
M2 visit 30 min after	-4 (-23 to 38)	-3 (-22 to 9)		

Notes:

[11] - Safety set

Patients contributing data

T1 aft N=45

T3 aft N=38

M2 aft N=38

[12] - Safety set

Patients contributing data

T1 aft N=41

T7 aft N=41

M2 aft N=39

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 injection, otherwise no injection was to be 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 $\geq 20\%$ 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 start (screening), at the end of the escalation dose (T3/T7), at the end of the maintenance dose (M2), and at the final visit (30 days after the last IMP injection). At all time points, the mean and median results for FEV1 were similar. There were no trends or systematic differences in changes of FEV1 from baseline during the trial between or

within the treatment groups. The number of patients contributing to the data at each visits is also shown.

End point type	Secondary
End point timeframe:	
30 min bfr, 30, 60, 120 min aftr each treatment (T)	
Accelerated dose escalat: 3 visits, separtd by 7 d	
Standard dose escalat: 7 visits, separtd by 7 d	
Maintenance dose: 2 visits separated by 2 wk; 2 wk after escalat	
Final visit: 30 d after last IMP	

End point values	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[13]	41 ^[14]		
Units: % predicted				
arithmetic mean (standard deviation)				
Screening	102.9 (± 12.53)	100.2 (± 11.90)		
T3/T7 before	103.8 (± 14.44)	98.6 (± 12.54)		
T3/T7 30 min after	101.8 (± 15.84)	98.9 (± 13.58)		
M2 before	103.7 (± 13.38)	100.5 (± 15.57)		
M2 30 min after	103.4 (± 13.37)	102.0 (± 21.53)		
Final visit	102.3 (± 13.79)	96.6 (± 12.23)		

Notes:

[13] - Safety set

Scrng=45

T3 bfr=38

T3 aft=37

M2 bfr=38

M2 aft=38

Final=42

[14] - Safety set

Scrng=41

T7 bfr=41

T7 aft=40

M2 bfr=39

M2 aft=39

Final=40

Statistical analyses

No statistical analyses for this end point

Secondary: 9_Tolerability: Likert scale after escalation dose phase (Investigator)

End point title	9_Tolerability: Likert scale after escalation dose 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 escalation dose phase (T3/T7 visit) and at the Final visit.	

End point values	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38 ^[15]	38		
Units: score				
Missing (T3/T7 visit)	7	3		
Very Bad (T3/T7 visit)	0	0		
Bad (T3/T7 visit)	0	0		
Average (T3/T7 visit)	4	0		
Good (T3/T7 visit)	11	9		
Very Good (T3/T7 visit)	23	29		

Notes:

[15] - Safety set was used for the analyses of both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 9a_Tolerability: Likert scale Final visit (Investigator)

End point title	9a_Tolerability: Likert scale Final visit (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 escalation dose phase and at the Final visit.	

End point values	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[16]	40		
Units: score				
Missing (Final visit)	0	1		
Very Bad (Final visit)	1	0		
Bad (Final visit)	2	0		
Average (Final visit)	3	0		
Good (Final visit)	11	8		
Very Good (Final visit)	28	32		

Notes:

[16] - Safety set was used for the analyses of both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 10_Tolerability: Likert scale after escalation dose phase (Subject)

End point title	10_Tolerability: Likert scale after escalation dose phase (Subject)
-----------------	---

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 subject.

End point type	Secondary
----------------	-----------

End point timeframe:

After the last IMP administration during the escalation dose phase (T3/T7 visit) and at the Final visit.

End point values	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38 ^[17]	38		
Units: score				
Missing (T3/T7 visit)	7	3		
Very Bad (T3/T7 visit)	0	0		
Bad (T3/T7 visit)	0	0		
Average (T3/T7 visit)	3	1		
Good (T3/T7 visit)	17	14		
Very Good (T3/T7 visit)	18	23		

Notes:

[17] - Safety set was used for the analyses of both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 10a_Tolerability: Likert scale Final visit (Subject)

End point title	10a_Tolerability: Likert scale Final visit (Subject)
-----------------	--

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 subject.

End point type	Secondary
----------------	-----------

End point timeframe:

After the last IMP administration during the escalation dose phase (T3/T7 visit) and at the Final visit.

End point values	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[18]	40		
Units: score				
Missing (Final visit)	0	1		
Very Bad (Final visit)	0	0		
Bad (Final visit)	3	0		
Average (Final visit)	3	1		
Good (Final visit)	15	15		
Very Good (Final visit)	24	24		

Notes:

[18] - Safety set was used for the analyses of both treatment groups

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 11_Immunologic parameter (IgG4 specific against grass-pollen from P. pratense)

End point title	11_Immunologic parameter (IgG4 specific against grass-pollen from P. pratense)
-----------------	--

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

In particular, the results indicate that the mean change from baseline to the final visit in IgG4 against the pollen from P. pratense (Timothy-grass) was similar between the treatment groups and is summarized in the table below.

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	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42 ^[19]	40		
Units: mg/l				
arithmetic mean (full range (min-max))	5.229 (-0.45 to 28.88)	5.311 (0.00 to 28.81)		

Notes:

[19] - Safety set was used for the analyses of both treatment groups

Statistical analyses

No statistical analyses for this end point

Post-hoc: 4_Treatment-emergent adverse events related to IMP - Time to onset

End point title	4_Treatment-emergent adverse events related to IMP - Time to onset
-----------------	--

End point description:

End point type	Post-hoc
----------------	----------

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	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[20]	41 ^[21]		
Units: TEAEs related to IMP				
≤ 30 min	23	22		
> 30 min, ≤ 6 h	56	50		
> 6 h, ≤ 24 h	36	46		
> 24 h	14	14		

Notes:

[20] - Safety set
TEAE related to IMP
N=129

[21] - Safety set
TEAE related to IMP
N=132

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 set.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20.0
--------------------	------

Reporting groups

Reporting group title	One Strength
-----------------------	--------------

Reporting group description:

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	Standard
-----------------------	----------

Reporting group description:

Patient randomized to 'standard dose escalation' (Standard) received 7 injections with two strengths (A: 1000 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	One Strength	Standard	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)	0 / 41 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	1 / 45 (2.22%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site swelling			
subjects affected / exposed	1 / 45 (2.22%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 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	One Strength	Standard	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 45 (82.22%)	35 / 41 (85.37%)	
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	2 / 45 (4.44%)	6 / 41 (14.63%)	
occurrences (all)	3	7	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 45 (20.00%)	10 / 41 (24.39%)	
occurrences (all)	15	20	
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	21 / 45 (46.67%)	14 / 41 (34.15%)	
occurrences (all)	49	38	
Injection site erythema			
subjects affected / exposed	13 / 45 (28.89%)	15 / 41 (36.59%)	
occurrences (all)	28	51	
Injection site pruritus			
subjects affected / exposed	14 / 45 (31.11%)	7 / 41 (17.07%)	
occurrences (all)	24	26	
Injection site pain			
subjects affected / exposed	2 / 45 (4.44%)	3 / 41 (7.32%)	
occurrences (all)	2	7	
Injection site warmth			
subjects affected / exposed	3 / 45 (6.67%)	0 / 41 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 45 (2.22%)	3 / 41 (7.32%)	
occurrences (all)	2	6	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 45 (13.33%)	9 / 41 (21.95%)	
occurrences (all)	9	14	
Upper respiratory tract infection			

subjects affected / exposed	3 / 45 (6.67%)	3 / 41 (7.32%)	
occurrences (all)	3	3	

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