Clinical trial results:
A multicenter, randomized, open label clinical trial for safety evaluation of an allergen immunotherapy with an accelerated dose escalation schedule using one strength of an aluminium hydroxide adsorbed allergoid preparation of birch pollen allergens in adult and pediatric patients with moderate to severe seasonal allergic rhinitis or rhinoconjunctivitis with or without bronchial asthma.

Summary

EudraCT number	2021-002317-34
Trial protocol	DE PL
Global end of trial date	29 March 2023

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	AL2101av

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-Str. 52 , Reinbek, Germany, 21465
Public contact	Clinical Development, Allergopharma GmbH & Co. KG, +49 40 727650, clinicaltrials@allergopharma.com
Scientific contact	Clinical Development, Allergopharma GmbH & Co. KG, +49 40 727650, clinicaltrials@allergopharma.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2023
Global end of trial reached?	Yes
Global end of trial date	29 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of a One strength dose escalation scheme using one strength of Allergovit Birch for allergen immunotherapy (AIT) compared to the standard escalation scheme using 2 strength of Allergovit Birch in adults, adolescents, and children with allergic rhinitis/rhinoconjunctivitis caused by birch pollen allergens with or without allergic asthma on a well-controlled level

Protection of trial subjects:

The trial 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. During the whole course of the trial, the DSMB team regularly reviewed an update of the safety data from all treated patients. After each administration of the IMP, each patient in the study was kept under supervision of a qualified and trained investigator for at least 120 min. Safety evaluation during supervision after IMP administration consisted of: FEV1, Systolic BP, Diastolic BP, Heart rate (Pulse rate), Respiratory rate.

Background therapy:

No background therapy was generally planned in this trial. 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 trial 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, 2021) to control their asthma. Any asthma medication had to be documented as concomitant medication. Restricted medication and nonpermitted medications were clearly defined in the trial protocol.

Evidence for comparator:

There was no comparator used in this trial.

Abbreviations used in this document: AE=Adverse event, AIT=Allergen immunotherapy, BP=Blood pressure, bpm=Beats per minute, DSMB=Data Safety Monitoring Board, FEV1=Forced expiratory volume in 1 second, GINA=Global Initiative for Asthma, ICF=Informed consent form, IgE = Immunoglobulin E, IgG=Immunoglobulin G, IMP=Investigational medicinal product, MedDRA=Medical Dictionary for Regulatory Activities, RBC=Red blood cells, TEAE=Treatment-emergent adverse event, TU=Therapeutic units, WAO=World Allergy Organization, y=year

Actual start date of recruitment	16 March 2022
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	Poland: 206
Country: Number of subjects enrolled	Germany: 39
Worldwide total number of subjects	245
EEA total number of subjects	245

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)	69
Adolescents (12-17 years)	63
Adults (18-64 years)	113
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 245 patients were screened for eligibility; of these 201 patients were randomized and 200 patients (87 adults, 51 adolescents, and 62 children) were actually treated with at least one dose of IMP (103 in the One Strength group and 97 in the Standard group).

Pre-assignment

Screening details:

Trial patients (outpatients) were included if they were suffering from immunoglobulin (Ig)E-mediated moderate to severe allergic rhinitis or rhinoconjunctivitis, with or without allergic asthma, triggered by house dust mite (HDM) allergens documented by skin prick test (SPT) wheal for HDM and specific IgE value of ≥ 0.70 kU/L to HDM.

Period 1

Period 1 title	Treatment (Overall trial period) (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 randomized and treated into the One Strength group (accelerated dose escalation) received 3 injections with increasing doses of only strength B of Allergovit Birch (10 000 TU/mL), followed by 2 injections with the maximum recommended dose.

Arm type	Experimental
Investigational medicinal product name	Allergovit Fagales (100% Birch)
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 birch pollen allergens. IMP is available in 2 concentrations (A: 1 000 TU/ml and B: 10 000 TU/ml). In the One Strength group only strength B was used for 3 dose escalation injections (0.1ml, 0.3ml and 0.6ml), followed by 2 maintenance injections of the maximum recommended dose (0.6ml of strength B: 10 000TU).

Arm title	Standard

Arm description:

Patients randomized and treated into the Standard group (standard dose escalation) received 7 injections with increasing doses of two strengths of Allergovit Birch (strength A: 1 000 TU/mL; strength B: 10 000 TU/mL), followed by 2 injections of the maximum recommended dose.
Note: 98 patients were randomized into the Standard group, but one patient withdraw consent before first treatment.

Arm type	Active comparator
Investigational medicinal product name	Allergovit Fagales (100% Birch)
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 birch pollen allergens. IMP is available in 2 concentrations (A: 1 000 TU/ml and B: 10 000 TU/ml). In the standard group both concentrations were used for 7 dose escalation injections (0.1ml, 0.2ml, 0.4ml, 0.8ml of strength A and 0.15ml, 0.3ml,

0.6ml of strength B), followed by 2 maintenance injections of the maximum recommended dose (0.6ml of strength B: 10 000TU).

Number of subjects in period 1[1]	One Strength	Standard
Started	103	97
Completed	96	92
Not completed	7	5
Consent withdrawn by subject	1	1
Physician decision	1	-
Adverse event, non-fatal	3	2
Other reason(s)	1	1
Sponsor/DSMB Desicion	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of patients enrolled worldwide includes screening failures (i.e. patients that signed the informed consent form, but were not randomized; N=44) and patients that were randomized, but never treated (N= 1). The number of patients in the baseline period equals the number of patients who were actually treated with IMP (= number of patients in the safety set, which was used for all analyses of this trial).

Baseline characteristics

Reporting groups	
Reporting group title	One Strength
Reporting group description:	
Patients randomized and treated into the One Strength group (accelerated dose escalation) received 3 injections with increasing doses of only strength B of Allergovit Birch (10 000 TU/mL), followed by 2 injections with the maximum recommended dose.	
Reporting group title	Standard
Reporting group description:	
Patients randomized and treated into the Standard group (standard dose escalation) received 7 injections with increasing doses of two strengths of Allergovit Birch (strength A: 1 000 TU/mL; strength B: 10 000 TU/mL), followed by 2 injections of the maximum recommended dose. Note: 98 patients were randomized into the Standard group, but one patient withdraw consent before first treatment.	

Reporting group values	One Strength	Standard	Total
Number of subjects	103	97	200
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	31	31	62
Adolescents (12-17 years)	25	26	51
Adults (18-64 years)	47	40	87
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	22.6	21.7	
standard deviation	± 14.8	± 14.6	-
Gender categorical Units: Subjects			
Female	49	42	91
Male	54	55	109

Subject analysis sets	
Subject analysis set title	Adults (18 to ≤ 65 years), One Strength
Subject analysis set type	Safety analysis
Subject analysis set description:	
Adults (18 to ≤ 65 years) treated according to the One Strength dose escalation scheme	
Subject analysis set title	Adults (18 to ≤ 65 years), Standard
Subject analysis set type	Safety analysis
Subject analysis set description:	
Adults (18 to ≤ 65 years) treated according to the Standard dose escalation scheme	
Subject analysis set title	Adolescents (12 to < 18 years), One Strength

Subject analysis set type	Safety analysis
Subject analysis set description:	
Adolescents (12 to < 18 years) treated according to the One Strength dose escalation scheme	
Subject analysis set title	Adolescents (12 to < 18 years), Standard
Subject analysis set type	Safety analysis
Subject analysis set description:	
Adolescents (12 to < 18 years) treated according to the Standard dose escalation scheme	
Subject analysis set title	Children (5 to < 12 years), One Strength
Subject analysis set type	Safety analysis
Subject analysis set description:	
Children (5 to < 12 years) treated according to the One Strength dose escalation scheme	
Subject analysis set title	Children (5 to < 12 years), Standard
Subject analysis set type	Safety analysis
Subject analysis set description:	
Children (5 to < 12 years) treated according to the Standard dose escalation scheme	

Reporting group values	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard	Adolescents (12 to < 18 years), One Strength
Number of subjects	47	40	25
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	25
Adults (18-64 years)	47	40	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	36.2	37.2	14.2
standard deviation	± 11.1	± 9.4	± 1.4
Gender categorical Units: Subjects			
Female	19	20	17
Male	28	20	8

Reporting group values	Adolescents (12 to < 18 years), Standard	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard
Number of subjects	26	31	31
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	31	31

Adolescents (12-17 years)	26	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	14.2	8.7	7.9
standard deviation	± 1.4	± 2.0	± 1.7
Gender categorical			
Units: Subjects			
Female	10	13	12
Male	16	18	10

End points

End points reporting groups

Reporting group title	One Strength

Reporting group description:

Patients randomized and treated into the One Strength group (accelerated dose escalation) received 3 injections with increasing doses of only strength B of Allergovit Birch (10 000 TU/mL), followed by 2 injections with the maximum recommended dose.

Reporting group title	Standard

Reporting group description:

Patients randomized and treated into the Standard group (standard dose escalation) received 7 injections with increasing doses of two strengths of Allergovit Birch (strength A: 1 000 TU/mL; strength B: 10 000 TU/mL), followed by 2 injections of the maximum recommended dose.
Note: 98 patients were randomized into the Standard group, but one patient withdraw consent before first treatment.

Subject analysis set title	Adults (18 to ≤ 65 years), One Strength
Subject analysis set type	Safety analysis

Subject analysis set description:

Adults (18 to ≤ 65 years) treated according to the One Strength dose escalation scheme

Subject analysis set title	Adults (18 to ≤ 65 years), Standard
Subject analysis set type	Safety analysis

Subject analysis set description:

Adults (18 to ≤ 65 years) treated according to the Standard dose escalation scheme

Subject analysis set title	Adolescents (12 to < 18 years), One Strength
Subject analysis set type	Safety analysis

Subject analysis set description:

Adolescents (12 to < 18 years) treated according to the One Strength dose escalation scheme

Subject analysis set title	Adolescents (12 to < 18 years), Standard
Subject analysis set type	Safety analysis

Subject analysis set description:

Adolescents (12 to < 18 years) treated according to the Standard dose escalation scheme

Subject analysis set title	Children (5 to < 12 years), One Strength
Subject analysis set type	Safety analysis

Subject analysis set description:

Children (5 to < 12 years) treated according to the One Strength dose escalation scheme

Subject analysis set title	Children (5 to < 12 years), Standard
Subject analysis set type	Safety analysis

Subject analysis set description:

Children (5 to < 12 years) treated according to the Standard dose escalation scheme

Primary: Treatment Emergent Adverse Events (TEAEs)

End point title	Treatment Emergent Adverse Events (TEAEs)[1]

End point description:

Number, incidence, time of onset, type and intensity of AEs and serious adverse events (SAE). An adverse event (AE) was defined as any untoward medical occurrence in a patient 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 use of trial medication until and including final visit or premature termination visit.
Results in the table below summarize the number of patients affected by one or more events events (TEAEs).

End point type	Primary

End point timeframe:

Between first IMP injection and the final visit. Approximately 9 weeks for patients randomized to One Strength (accelerated dose escalation) and approximately 13 weeks for patients randomized to Standard (standard dose escalation).

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 trial with descriptive results evaluation. Descriptive evaluation of group differences. CI for the difference (One Strength - Standard): exact 95%-confidence intervals for the difference in proportions of patients with events (%).

End point values	One Strength	Standard	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	103	97	47	40
Units: Patients with at least one event of				
TEAEs	68	54	30	18
TEAEs related to IMP	50	31	24	8
serious TEAEs	1	0	1	0
serious TEAEs related to IMP	0	0	0	0
TEAEs leading to dose reduction	13	4	10	2
TEAEs leading to discontinuation	3	2	2	1
Local reactions related to IMP	47	31	22	8
Systemic allergic reactions related to IMP	3	1	1	0
Other type of events related to IMP	5	3	2	3
TEAEs related to IMP with intensity mild	49	30	24	8
TEAEs related to IMP with intensity moderate	8	3	5	2
TEAEs related to IMP with intensity severe	0	0	0	0

End point values	Adolescents (12 to < 18 years), One Strength	Adolescents (12 to < 18 years), Standard	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	26	31	31
Units: Patients with at least one event of				
TEAEs	16	15	22	21
TEAEs related to IMP	15	11	11	12
serious TEAEs	0	0	0	0
serious TEAEs related to IMP	0	0	0	0
TEAEs leading to dose reduction	1	0	2	3
TEAEs leading to discontinuation	1	0	0	0
Local reactions related to IMP	14	11	11	12
Systemic allergic reactions related to IMP	1	0	1	1
Other type of events related to IMP	1	0	2	1
TEAEs related to IMP with intensity mild	14	10	11	12
TEAEs related to IMP with intensity moderate	2	1	1	1

TEAEs related to IMP with intensity severe	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Systemic allergic reactions according to the WAO grading system

End point title	Systemic allergic reactions according to the WAO grading system[2]

End point description:

Incidence and intensity of systemic allergic reactions after injections according to the WAO grading system.

End point type	Primary

End point timeframe:

Between first IMP injection and the final visit. Approximately 9 weeks for patients randomized to One Strength (accelerated dose escalation) and approximately 13 weeks for patients randomized to Standard (standard dose escalation).

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: This was a safety trial with descriptive results evaluation. Descriptive evaluation of group differences. CI for the difference (One Strength - Standard): exact 95%-confidence intervals for the difference in proportions of patients with events (%).

End point values	One Strength	Standard	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	103	97	47	40
Units: Systemic TEAEs related to IMP				
Grade 1	2	5	1	0
Grade 2	1	1	0	0
Grade 3, 4 and 5	0	0	0	0

End point values	Adolescents (12 to < 18 years), One Strength	Adolescents (12 to < 18 years), Standard	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	26	31	31
Units: Systemic TEAEs related to IMP				
Grade 1	0	0	1	5
Grade 2	1	0	0	1
Grade 3, 4 and 5	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: TEAEs related to IMP - Time to onset

End point title	TEAEs related to IMP - Time to onset

End point description:

Onset of IMP-related TEAEs after IMP injection.

End point type	Secondary

End point timeframe:

Between first IMP injection and the final visit. Approximately 9 weeks for patients randomized to One Strength (accelerated dose escalation) and approximately 13 weeks for patients randomized to Standard (standard dose escalation).

End point values	One Strength	Standard	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	103	97	47	40
Units: Number of TEAEs related to IMP				
<= 30 min	15	12	5	1
> 30 min and <= 2 h	32	23	10	0
> 2 h and <= 6 h	60	33	33	16
> 6 h and <= 24 h	91	85	57	19
> 24 h	13	18	5	5

End point values	Adolescents (12 to < 18 years), One Strength	Adolescents (12 to < 18 years), Standard	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	26	31	31
Units: Number of TEAEs related to IMP				
<= 30 min	2	1	8	10
> 30 min and <= 2 h	16	0	6	23
> 2 h and <= 6 h	16	3	11	14
> 6 h and <= 24 h	21	26	13	40
> 24 h	8	5	0	8

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability assessed by Patient

End point title	Tolerability assessed by Patient

End point description:

Assessment of the overall tolerability using a 5-point Likert scale. Table shows the number of patients in tolerability category (1=Very Bad, 2=Bad, 3= Average, 4=Good, 5=Very good) assessed by the patient.

End point type	Secondary

End point timeframe:

Between first IMP injection and the final visit. Approximately 9 weeks for patients randomized to One Strength (accelerated dose escalation) and approximately 13 weeks for patients randomized to Standard (standard dose escalation).

End point values	One Strength	Standard	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	103	97	47	40
Units: Number of patients				
Very Bad	0	0	1	0
Bad	0	1	1	0
Average	3	0	0	3
Good	13	7	8	4
Very good	85	86	36	33

End point values	Adolescents (12 to < 18 years), One Strength	Adolescents (12 to < 18 years), Standard	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	26	31	31
Units: Number of patients				
Very Bad	1	0	0	0
Bad	0	0	0	0
Average	0	0	0	0
Good	2	2	3	1
Very good	22	24	27	29

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability assessed by Investigator

End point title	Tolerability assessed by Investigator

End point description:

Assessment of the overall tolerability using a 5-point Likert scale. Table shows the number of patients in tolerability category (1=Very Bad, 2=Bad, 3= Average, 4=Good, 5=Very good) assessed by the investigator.

End point type	Secondary

End point timeframe:

Between first IMP injection and the final visit. Approximately 9 weeks for patients randomized to One

Strength (accelerated dose escalation) and approximately 13 weeks for patients randomized to Standard (standard dose escalation).

End point values	One Strength	Standard	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	103	97	47	40
Units: Number of patients				
Very bad	0	0	0	0
Bad	2	1	2	1
Average	2	1	1	1
Good	4	2	2	0
Very good	93	90	42	36

End point values	Adolescents (12 to < 18 years), One Strength	Adolescents (12 to < 18 years), Standard	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	26	31	31
Units: Number of patients				
Very bad	0	0	0	0
Bad	0	0	0	0
Average	1	0	0	0
Good	1	1	1	1
Very good	22	25	29	29

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic allergic reactions related to IMP - Time to onset

End point title	Systemic allergic reactions related to IMP - Time to onset

End point description:

Onset of IMP-related TEAEs after IMP injection.

End point type	Secondary

End point timeframe:

Between first IMP injection and the final visit. Approximately 9 weeks for patients randomized to One Strength (accelerated dose escalation) and approximately 13 weeks for patients randomized to Standard (standard dose escalation).

End point values	One Strength	Standard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	97		
Units: Number of TEAEs related to IMP				
<= 30 min	0	1		
> 30 min and <= 2 h	0	2		
> 2 h and <= 6 h	1	1		
> 6 h and <= 24 h	1	2		
> 24 h	1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Immunological profile (Treatment-induced change in birch specific IgG4)

End point title	Immunological profile (Treatment-induced change in birch specific IgG4)

End point description:

Changes in the immunological profile of birch-specific IgG4 provides 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 for all patients (adults, adolescents and children), during the course of the trial, the median levels of IgG4 specific for Birch pollen (Betula verrucosa) increased notably over time in both treatment groups [p-values < 0.0001 between baseline and final visit, for all age groups].

End point type	Other pre-specified

End point timeframe:

To determine the immunological profile, blood was taken at baseline visit and final visit/premature termination of the study.

End point values	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard	Adolescents (12 to < 18 years), One Strength	Adolescents (12 to < 18 years), Standard
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	40	25	26
Units: mg/L				
median (full range (min-max))	2.490 (-0.32 to 29.35)	2.460 (-0.15 to 19.26)	4.075 (0.01 to 24.24)	3.780 (0.17 to 14.62)

End point values	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	31		
Units: mg/L				
median (full range (min-max))	6.355 (-0.01 to 25.84)	6.830 (0.37 to 19.10)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The collection of adverse events starts at the day of the patient's signature on the patient informed consent form and is performed until and including the final visit or premature termination visit.

Adverse event reporting additional description:

Results are shown for the safety set (SAF), which includes all patients treated at least with one dose of IMP. Only TEAES (Treatment-emergent Adverse Events) are shown. PT of Non-serious TEAEs are listed, if at least one age group is above the frequency treshold of 2%.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Adults (18 to ≤ 65 years), One Strength

Reporting group description:

Patients treated according to the One Strength dose escalation scheme (One strength group). Patients in the One Strength group received 3 injections with increasing doses of only strength B of Allergovit Birch (10000 TU/mL), followed by 2 injections with the individual maximum recommended dose.

Reporting group title	Adults (18 to ≤ 65 years), Standard

Reporting group description:

Patients treated according to the Standard dose escalation scheme (Standard group). Patients in the Standard group received 7 injections with increasing doses of two strengths of Allergovit Birch (strength A: 1000 TU/mL; strength B: 10000 TU/mL), followed by 2 injections with the maximum recommended dose.

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

Reporting group description:

Patients treated according to the One Strength dose escalation scheme (One strength group). Patients in the One Strength group received 3 injections with increasing doses of only strength B of Allergovit Birch (10000 TU/mL), followed by 2 injections with the individual maximum recommended dose.

Reporting group title	Adolescents (12 to < 18 years), Standard

Reporting group description:

Patients treated according to the Standard dose escalation scheme (Standard group). Patients in the Standard group received 7 injections with increasing doses of two strengths of Allergovit Birch (strength A: 1000 TU/mL; strength B: 10000 TU/mL), followed by 2 injections with the maximum recommended dose.

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

Reporting group description:

Patients treated according to the One Strength dose escalation scheme (One strength group). Patients in the One Strength group received 3 injections with increasing doses of only strength B of Allergovit Birch (10000 TU/mL), followed by 2 injections with the individual maximum recommended dose.

Reporting group title	Children (5 to < 12 years), Standard

Reporting group description:

Patients treated according to the Standard dose escalation scheme (Standard group). Patients in the Standard group received 7 injections with increasing doses of two strengths of Allergovit Birch (strength A: 1000 TU/mL; strength B: 10000 TU/mL), followed by 2 injections with the maximum recommended dose.

Serious adverse events	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard	Adolescents (12 to < 18 years), One Strength
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)	0 / 40 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Immune system disorders			
Food allergy	Additional description: One patient (1.0%) in the One Strength group experienced one treatment-emergent SAE. The SAE was classified as other type of event and was not related to IMP.		
subjects affected / exposed	1 / 47 (2.13%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Adolescents (12 to < 18 years), Standard	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Immune system disorders			
Food allergy	Additional description: One patient (1.0%) in the One Strength group experienced one treatment-emergent SAE. The SAE was classified as other type of event and was not related to IMP.		
subjects affected / exposed	0 / 26 (0.00%)	0 / 31 (0.00%)	0 / 31 (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

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Adults (18 to ≤ 65 years), One Strength	Adults (18 to ≤ 65 years), Standard	Adolescents (12 to < 18 years), One Strength
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 47 (63.83%)	18 / 40 (45.00%)	16 / 25 (64.00%)
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	1 / 47 (2.13%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Headache			

subjects affected / exposed	6 / 47 (12.77%)	7 / 40 (17.50%)	1 / 25 (4.00%)
occurrences (all)	14	11	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	8 / 47 (17.02%)	2 / 40 (5.00%)	4 / 25 (16.00%)
occurrences (all)	22	2	10
Injection site oedema			
subjects affected / exposed	3 / 47 (6.38%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	5	2	0
Injection site pain			
subjects affected / exposed	7 / 47 (14.89%)	1 / 40 (2.50%)	5 / 25 (20.00%)
occurrences (all)	10	1	6
Injection site pruritus			
subjects affected / exposed	11 / 47 (23.40%)	5 / 40 (12.50%)	7 / 25 (28.00%)
occurrences (all)	30	10	18
Injection site urticaria			
subjects affected / exposed	0 / 47 (0.00%)	0 / 40 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Injection site swelling			
subjects affected / exposed	17 / 47 (36.17%)	5 / 40 (12.50%)	12 / 25 (48.00%)
occurrences (all)	37	18	23
Pyrexia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 47 (0.00%)	2 / 40 (5.00%)	0 / 25 (0.00%)
occurrences (all)	0	5	0
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 47 (0.00%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			

subjects affected / exposed	0 / 47 (0.00%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 47 (2.13%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 47 (4.26%)	0 / 40 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 47 (2.13%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 47 (2.13%)	1 / 40 (2.50%)	2 / 25 (8.00%)
occurrences (all)	1	3	2
Nasal pruritus			
subjects affected / exposed	2 / 47 (4.26%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	2	2	0
Sneezing			
subjects affected / exposed	2 / 47 (4.26%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 47 (2.13%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 47 (6.38%)	7 / 40 (17.50%)	5 / 25 (20.00%)
occurrences (all)	6	8	5
Rhinitis			

subjects affected / exposed	0 / 47 (0.00%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 40 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	2 / 47 (4.26%)	1 / 40 (2.50%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
Viral infection			
subjects affected / exposed	1 / 47 (2.13%)	1 / 40 (2.50%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
COVID-19			
subjects affected / exposed	0 / 47 (0.00%)	2 / 40 (5.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Ear infection			
subjects affected / exposed	2 / 47 (4.26%)	0 / 40 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Adolescents (12 to < 18 years), Standard	Children (5 to < 12 years), One Strength	Children (5 to < 12 years), Standard
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 26 (57.69%)	22 / 31 (70.97%)	21 / 31 (67.74%)
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	0 / 26 (0.00%)	3 / 31 (9.68%)	3 / 31 (9.68%)
occurrences (all)	0	6	3
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 26 (19.23%)	5 / 31 (16.13%)	6 / 31 (19.35%)
occurrences (all)	20	7	6
General disorders and administration site conditions			

Injection site erythema			
subjects affected / exposed	0 / 26 (0.00%)	2 / 31 (6.45%)	7 / 31 (22.58%)
occurrences (all)	0	7	9
Injection site oedema			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	1	1	2
Injection site pain			
subjects affected / exposed	5 / 26 (19.23%)	3 / 31 (9.68%)	3 / 31 (9.68%)
occurrences (all)	5	3	8
Injection site pruritus			
subjects affected / exposed	5 / 26 (19.23%)	2 / 31 (6.45%)	8 / 31 (25.81%)
occurrences (all)	15	5	15
Injection site urticaria			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	2 / 31 (6.45%)
occurrences (all)	0	2	9
Injection site swelling			
subjects affected / exposed	5 / 26 (19.23%)	8 / 31 (25.81%)	11 / 31 (35.48%)
occurrences (all)	13	17	22
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 31 (9.68%)	2 / 31 (6.45%)
occurrences (all)	0	3	2
Fatigue			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	0	2	5
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	2 / 31 (6.45%)
occurrences (all)	0	1	4
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 31 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Abdominal pain			

subjects affected / exposed	2 / 26 (7.69%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
Nausea			
subjects affected / exposed	1 / 26 (3.85%)	0 / 31 (0.00%)	2 / 31 (6.45%)
occurrences (all)	3	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 26 (3.85%)	4 / 31 (12.90%)	7 / 31 (22.58%)
occurrences (all)	1	11	16
Oropharyngeal pain			
subjects affected / exposed	1 / 26 (3.85%)	2 / 31 (6.45%)	2 / 31 (6.45%)
occurrences (all)	1	2	2
Rhinorrhoea			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Nasal pruritus			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	0	1	3
Sneezing			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 26 (0.00%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	3
Pruritus			
subjects affected / exposed	1 / 26 (3.85%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	1	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 26 (15.38%)	2 / 31 (6.45%)	5 / 31 (16.13%)
occurrences (all)	7	2	14
Rhinitis			
subjects affected / exposed	3 / 26 (11.54%)	2 / 31 (6.45%)	3 / 31 (9.68%)
occurrences (all)	3	2	6
Bronchitis			

subjects affected / exposed	0 / 26 (0.00%)	2 / 31 (6.45%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	2 / 31 (6.45%)	2 / 31 (6.45%)
occurrences (all)	0	3	4
Gastroenteritis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
Pharyngitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Viral infection			
subjects affected / exposed	1 / 26 (3.85%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	1	2	1
COVID-19			
subjects affected / exposed	0 / 26 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1

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