



Clinical trial results:

Open label phase II multicenter clinical trial to evaluate safety during accelerated dose escalation of an allergoid birch pollen preparation in patients with IgE mediated allergic rhinitis or rhinoconjunctivitis with or without controlled bronchial asthma

Summary

EudraCT number	2015-005400-28
Trial protocol	DE
Global end of trial date	20 February 2017

Results information

Result version number	v1 (current)
This version publication date	21 February 2019
First version publication date	21 February 2019

Trial information

Trial identification

Sponsor protocol code	AL1502AV
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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	02 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and tolerability of an accelerated dose escalation scheme with Allergovit birch in patients with seasonal allergic rhinitis or rhinoconjunctivitis caused by birch pollen with or without controlled bronchial asthma (acc. to the Global Initiative for Asthma [GINA] 2015).

Efficacy exploratory immunological parameters:

Evaluate the change of total specific IgG and specific IgG4 for Betula verrucosa between screening visit and final visit.

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.

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

Background therapy:

Concomitant medication was defined as any medication other than the IMP that was taken during the clinical trial. All concomitant medications and procedures were reported in the eCRF, stating the indication, dosage and start and end date of therapy. Any changes in concomitant medications were documented and checked against the study inclusion and exclusion criteria.

Evidence for comparator:

Abbreviations used in this document:

AE=Adverse event

AIT=Allergen immunotherapy

DSMB=Data Safety Monitoring Board

bpm=Beats per minute

ICF=Informed consent form

IMP=Investigational medicinal product

MedDRA=Medical Dictionary for Regulatory Activities

PEF=Peak flow measurement

T=Treatment (as in T1 =Treatment visit 1, etc.)

TU=Therapeutic units

WAO=World Allergy Organization

Actual start date of recruitment	27 June 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: 130
Worldwide total number of subjects	130
EEA total number of subjects	130

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)	130
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 175 adult male and female subjects (18-64 y) were screened for eligibility; 130 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	Accelerated dose escalation

Arm description:

Patient randomized to accelerated dose escalation with 4 injections were treated over a period of up to 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Allergovit® Birch
Investigational medicinal product code	
Other name	Birch pollen allergoid
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® Birch, provided in two stock concentrations (1000 TU/mL, 10,000TU/mL); injected volume was between 0.1 and 0.6 mL (depending on the stock concentration used). The foreseen scheme could be adjusted according to the well-being of the patient and could be lower than the max dose (6000 TU).

PEF and vital signs were measured before and after each injection. 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 120 min (accelerated dose escalation) and 30 min (standard dose escalation).

Accelerated dose escalation scheme every 7 days (injection number): 200 (1), 600 (2), 2000 (3), 6000 (4) TU.

Maintenance every 2 weeks after last dose: 6000 (5), 6000 (6) TU.

Arm title	Standard dose escalation
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Arm description:

Patients randomized to standard dose escalation with 7 injections were treated for up to 15 weeks.

Arm type	Experimental
Investigational medicinal product name	Allergovit® Birch
Investigational medicinal product code	
Other name	Birch pollen allergoid
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® Birch, provided in two stock concentrations (1000 TU/mL, 10,000TU/mL); injected volume was between 0.1 and 0.6 mL (depending on the stock concentration used). The foreseen scheme could be adjusted according to the

well-being of the patient and could be lower than the max dose (6000 TU).

PEF and vital signs were measured before and after each injection. 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 120 min (accelerated dose escalation) and 30 min (standard dose escalation).

Standard dose escalation scheme every 7 days (injection number): 100 (1), 200 (2), 400 (3), 800 (4), 1500 (5), 3000 (6), 6000 (7) TU.

Maintenance every 2 weeks after last dose: 6000 (8), 6000 (9) TU.

Number of subjects in period 1	Accelerated dose escalation	Standard dose escalation
Started	63	67
Completed	61	64
Not completed	2	3
Consent withdrawn by subject	-	1
Study visit not kept according to schedule	-	1
Adverse event, non-fatal	1	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Accelerated dose escalation
Reporting group description:	
Patient randomized to accelerated dose escalation with 4 injections were treated over a period of up to 12 weeks.	
Reporting group title	Standard dose escalation
Reporting group description:	
Patients randomized to standard dose escalation with 7 injections were treated for up to 15 weeks.	

Reporting group values	Accelerated dose escalation	Standard dose escalation	Total
Number of subjects	63	67	130
Age categorical			
Units: Subjects			
Adults (18-64 years)	63	67	130
Age continuous			
Units: years			
arithmetic mean	36.4	37.1	-
standard deviation	± 11.8	± 13.5	-
Gender categorical			
Units: Subjects			
Female	34	40	74
Male	29	27	56
Race			
Units: Subjects			
Caucasian	63	66	129
Asian	0	1	1
Smoking status			
Units: Subjects			
Non-smoker	41	54	95
Ex-smoker	13	7	20
Current smoker	9	6	15
Body mass index			
Units: kg/m ²			
arithmetic mean	25.05	25.47	-
standard deviation	± 4.34	± 5.08	-
Skin prick test (SPT)			
To assess the patient's eligibility following inclusion criteria, a routine SPT at screening visit was performed to assess the allergy status of the patient to birch pollen (<i>Betula verrucosa</i>). A negative control (NaCl) and a positive control (Histamine Dihydrochloride (0.1 %)) were performed in parallel.			
Data represent the median wheal diameter of the prick in millimeters (mm).			
Units: mm			
median	9.00	9.00	-
full range (min-max)	4.0 to 19.0	5.0 to 31.0	-

End points

End points reporting groups

Reporting group title	Accelerated dose escalation
Reporting group description:	
Patient randomized to accelerated dose escalation with 4 injections were treated over a period of up to 12 weeks.	
Reporting group title	Standard dose escalation
Reporting group description:	
Patients randomized to standard dose escalation with 7 injections were treated for up to 15 weeks.	

Primary: 1_Treatment-emergent adverse events: causal relationship

End point title	1_Treatment-emergent adverse events: causal relationship ^[1]
End point description:	
Results shown represent the number of patients with AEs that were assessed by the investigator as related to IMP.	
When assessing the causality of an AE, the investigator had 2 options:	
<ul style="list-style-type: none">• Related to IMP• Not related to IMP	
The causality of an AE was suggested to be related, if:	
<ul style="list-style-type: none">• The AE occurred in a causal temporal relationship to IMP administration• The localization of the AE implied a causal relationship to IMP administration	
The results shown below reflect the number of patients and the numbers of AEs assessed by the investigator as related to the IMP.	
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; up to 12 wks for patients in accelerated dose escalation and up to 15 wks for patients in 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 and tolerability trial. Thus, no hypotheses for the final analysis were formulated and the data were analyzed descriptively. This is in line with the ICH E9 guideline.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[2]	67 ^[3]		
Units: patients	36	39		

Notes:

[2] - Safety Set

Number of AEs assessed by the investigator as related to IMP N=238

[3] - Safety Set

Number of AEs assessed by the investigator as related to IMP N=167

Statistical analyses

No statistical analyses for this end point

Primary: 2_Treatment-emergent adverse events: worst intensity

End point title	2_Treatment-emergent adverse events: worst intensity ^[4]
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End point description:

Results shown represent the number of patients with AEs of intensities defined below.
AE intensity in this trial was assessed by the the investigator's clinical judgement.

AE intensity:

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.

The results shown below reflect the number of patients with AEs by intensity, as assessed by the investigator.

End point type	Primary
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End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration; up to 12 wks for patients in accelerated dose escalation and up to 15 wks for patients in standard dose escalation.

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 and tolerability trial. Thus, no hypotheses for the final analysis were formulated and the data were analyzed descriptively. This is in line with the ICH E9 guideline.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[5]	67 ^[6]		
Units: patients				
Mild	23	31		
Moderate	25	22		
Severe	3	0		

Notes:

[5] - Safety Set

[6] - Safety Set

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
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End point description:

An AE was defined as a systemic reaction, if the type of event in the AE section of the eCRF was assessed as "anaphylactic reaction acc. WAO grade" and the WAO grade was documented as '1', '2', '3', '4', or '5'.

Anaphylactic reactions are graded based on organ systems involved and severity according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System. The WAO grading of anaphylactic reactions included in this trial is a modified WAO grading.

The results shown below reflect the number of patients and the numbers of AEs, assessed by the investigator as treatment-emergent AEs (anaphylactic systemic reactions) according to WAO.

End point type	Secondary
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End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration; up to 12 wks for patients in accelerated dose escalation and up to 15 wks for patients in standard dose escalation.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[7]	67 ^[8]		
Units: patients				
Overall	4	2		
During dose escalation phase	3	2		
During maintenance phase	1	0		

Notes:

[7] - Safety Set

Number of events

Overall N=4

Escalation phase N=3

Maintenance phase N=1

[8] - Safety Set

Number of events

Overall N=3

Escalation phase N=3

Maintenance phase N=0

Statistical analyses

No statistical analyses for this end point

Secondary: 4_Lung function test: PEF

End point title	4_Lung function test: PEF
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End point description:

PEF measurements were performed as part of safety measures. The visit and the injection were rescheduled if a patient did not demonstrate PEF of $\geq 70\%$ of predicted normal prior to the injection.

PEF was determined at all study visits as follows.

Accelerated dose escalation scheme: before, and 15, 30, 60, 120 min after injection

Standard dose escalation scheme: before, and 15, 30 min after injection

PEF results were similar at all study visits in both groups.

Results shown below are representative for the study visits: first injection day (T1) before, end of injection (after 30 min standard or after 120 min accelerated dose escalation phase); last injection day (T9 Standard dose and T9 accelerated dose, before and after 30 min standard and before or after 120 min accelerated dose escalation phase).

The mean and median PEF results were similar between the treatment groups at all the time points.

The number of patients contributing to the data at each data point is shown.

End point type	Secondary
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End point timeframe:

PEF was measured at the screening visit, during treatment, any additional visits, and final visit, at times specified below under the heading 'Description'.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[9]	67 ^[10]		
Units: % of predicted normal				
arithmetic mean (standard deviation)				
First day (before injection)	99.4 (± 13.6)	100.3 (± 12.8)		
First day (after injection)	99.9 (± 13.3)	100.3 (± 13.1)		
Last day (before injection)	99.4 (± 14.2)	99.2 (± 14.0)		
Last day (after injection)	99.9 (± 13.3)	98.9 (± 13.8)		

Notes:

[9] - Safety Set

1st d bfr=63

1st d 120 min aft=63

Lst d bfr=59

Lst d 120 min aft=59

[10] - Safety Set

1st d bfr=67

1st d 30 min aft=66

Lst d bfr=64

Lst d 30 min aft=64

Statistical analyses

No statistical analyses for this end point

Secondary: 5_Tolerability: Likert scale (Investigator)

End point title	5_Tolerability: Likert scale (Investigator)
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End point description:

At the final visit, the tolerability was assessed by the investigator using a 5 point Likert scale, as defined below.

Likert scale score system: 1=Very bad; 2=Bad; 3=Average; 4=Good; 5=Very good.

The values represent the number of patients, according to the investigators' assessment.

End point type	Secondary
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End point timeframe:

At the final visit.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[11]	67		
Units: patients				
Very bad	1	1		
Bad	3	0		
Average	3	2		
Good	35	30		
Very good	20	33		
Missing	1	1		

Notes:

[11] - Safety Set used for analysis for both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 6_Tolerability: Likert scale (Patient)

End point title	6_Tolerability: Likert scale (Patient)
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End point description:

At the final visit, the tolerability was assessed by the patient using a 5 point Likert scale, as defined below.

Likert scale score system: 1=Very bad; 2=Bad; 3=Average; 4=Good; 5=Very good.

The values represent the number of patients, according to the patient's own assessment.

End point type	Secondary
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End point timeframe:

At the final visit.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[12]	67		
Units: patients				
Very bad	0	1		
Bad	4	1		
Average	5	1		
Good	31	29		
Very good	22	34		
Missing	1	1		

Notes:

[12] - Safety Set used for analysis for both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 7_Treatment-emergent adverse events: local reactions

End point title	7_Treatment-emergent adverse events: local reactions
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End point description:

Local reactions (AEs) at the injection site > 5 cm or leading to distinct discomfort interfering with the patient's daily activities.

Results shown represent the number of patients with AEs, characterized as local reactions at injection site and related to IMP.

The AEs were: Injection site swelling, Injection site erythema, Injection site pruritus, Injection site pain, Injection site warmth, Discomfort, Injection site anaesthesia, Injection site haematoma, Injection site hypoaesthesia, Injection site induration, Injection site paraesthesia, Injection site rash, Injection site reaction, Injection site urticaria.

End point type	Secondary
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End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration; up to 12 wks for patients in accelerated dose escalation and up to 15 wks for patients in standard dose escalation.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[13]	67		
Units: patients				
Overall	34	38		
Mild	15	29		
Moderate	17	9		
Severe	2	0		

Notes:

[13] - Safety set used for analysis for both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 8_Small local reactions not considered as AE

End point title	8_Small local reactions not considered as AE
End point description:	
Number of patients with or without any small local reactions (≥ 2.5 cm and ≤ 5 cm) that were not considered as AEs.	
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; up to 12 wks for patients in accelerated dose escalation and up to 15 wks for patients in standard dose escalation.	

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[14]	67		
Units: patients				
No	48	59		
Yes	15	8		

Notes:

[14] - Safety Set used for analysis for both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 9_Vital signs - Heart rate

End point title	9_Vital signs - Heart rate
End point description:	
Clinical chemistry, vital signs, physical examination - are summarized in one representative endpoint. Shown is the heart rate; the time points are as described for the end point 6.	

The number of patients contributing to the data at each data point is shown.

There were no relevant differences between the treatment groups for vital signs and for 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 non fasting; status to be assessed only for determination of eligibility of the subject for the trial)
- Hematology: differential blood cell count, hemoglobin, leukocytes, platelets
- Urine analysis: protein, glucose, blood (hemoglobin), leukocytes, beta-human chorionic gonadotropin (women of childbearing potential only).

End point type	Secondary
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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	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[15]	67 ^[16]		
Units: bpm				
median (full range (min-max))				
First day (before injection)	73.0 (50 to 100)	73.0 (46 to 106)		
First day (30 or 120 min after injection)	70 (52 to 86)	72 (47 to 97)		
Last day (before injection)	74 (57 to 93)	73.5 (59 to 99)		
Last day (30 or 120 min after injection)	70 (57 to 86)	70.5 (61 to 101)		
Final visit	71.0 (56 to 99)	71.5 (56 to 109)		

Notes:

[15] - Safety Set

1st d bfr=63

1st d 120 min aft=63

Lst d bfr=59

Lst d 120 min aft=59

Final d=62

[16] - Safety Set

1st d bfr=67

1st d 30 min aft=66

Lst d bfr=64

Lst d 30 min aft=64

Final d=66

Statistical analyses

No statistical analyses for this end point

Secondary: 10_Number of patients reaching the maintenance dose without dose adjustment

End point title	10_Number of patients reaching the maintenance dose without dose adjustment
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End point description:

Number of patients reaching 1st injection of the planned maintenance dose without or with dose reductions.

End point type	Secondary
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End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration; up to 12 wks for patients in accelerated dose escalation and up to 15 wks for patients in standard dose escalation.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[17]	67		
Units: patients				
Without dose reduction	50	60		
With 1 dose reduction	9	5		
Not reach maintenance dose	4	2		

Notes:

[17] - Safety Set used for analysis for both treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 11_Treatment-emergent adverse events: leading to dose reduction

End point title	11_Treatment-emergent adverse events: leading to dose reduction
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End point description:

Results shown represent the number of patients with AEs that led to dose reduction.

The AEs were: Eye swelling, Injection site erythema, Injection site pain, Injection site pruritus, Injection site swelling, Hypersensitivity, Rhinitis.

End point type	Secondary
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End point timeframe:

Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration; up to 12 wks for patients in accelerated dose escalation and up to 15 wks for patients in standard dose escalation.

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[18]	67 ^[19]		
Units: patients	10	2		

Notes:

[18] - Safety Set

AEs leading to leading to dose reduction N=30

[19] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: 12_Treatment-emergent adverse events: premature trial discontinuation

End point title	12_Treatment-emergent adverse events: premature trial discontinuation
End point description:	
Results shown represent the number of patients with AEs that led to premature trial discontinuation.	
The AEs were: Injection site erythema, Injection site swelling.	
End point type	Secondary
End point timeframe:	
Between the signature date of the ICF and the final visit, until approx. 30 days after the last IMP administration; up to 12 wks for patients in accelerated dose escalation and up to 15 wks for patients in standard dose escalation.	

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[20]	67 ^[21]		
Units: patients	1	0		

Notes:

[20] - Safety Set

AEs leading to premature trial discontinuation N=2

[21] - Safety Set

AEs leading to premature trial discontinuation N=0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 13_Immunologic parameter total specific IgG (Betula verrucosa)

End point title	13_Immunologic parameter total specific IgG (Betula verrucosa)
End point description:	
Exploratory immunological parameter.	
The change of specific total IgG and specific IgG for Betula verrucosa was determined between the screening visit (baseline) and the final visit of the study.	
End point type	Other pre-specified
End point timeframe:	
At screening (baseline) and at the final visit/premature termination of the study.	

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62 ^[22]	65		
Units: mg/L				
median (full range (min-max))	5.00 (-1.4 to 41.4)	5.60 (-3.7 to 24.9)		

Notes:

[22] - Exploratory Immunological Parameters Set was used for evaluation of both treatment groups

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 14_Immunologic parameter total specific IgG4 (Betula verrucosa)

End point title	14_Immunologic parameter total specific IgG4 (Betula verrucosa)
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End point description:

Exploratory immunological parameter.

The change of specific total IgG and specific IgG4 for Betula verrucosa was determined between the screening visit and the final visit of the study.

End point type	Other pre-specified
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End point timeframe:

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

End point values	Accelerated dose escalation	Standard dose escalation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62 ^[23]	65		
Units: mg/L				
median (full range (min-max))	1.52 (0.0 to 28.1)	1.66 (-0.1 to 12.8)		

Notes:

[23] - Exploratory Immunological Parameters Set was used for evaluation of both treatment groups

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Accelerated dose escalation
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Reporting group description:

Patient randomized to accelerated dose escalation with 4 injections were treated over a period of up to 12 weeks.

AEs with onset during or after 1st administration of trial medication were defined as treatment-emergent.

Reporting group title	Standard dose escalation
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Reporting group description:

Patients randomized to standard dose escalation with 7 injections were treated for up to 15 weeks.

AEs with onset during or after 1st administration of trial medication were defined as treatment-emergent.

Serious adverse events	Accelerated dose escalation	Standard dose escalation	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Accelerated dose escalation	Standard dose escalation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 63 (80.95%)	53 / 67 (79.10%)	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 63 (30.16%)	19 / 67 (28.36%)	
occurrences (all)	37	39	
General disorders and administration site conditions			

Injection site erythema subjects affected / exposed occurrences (all)	23 / 63 (36.51%) 67	18 / 67 (26.87%) 37	
Injection site pain subjects affected / exposed occurrences (all)	8 / 63 (12.70%) 12	6 / 67 (8.96%) 6	
Injection site pruritus subjects affected / exposed occurrences (all)	17 / 63 (26.98%) 59	20 / 67 (29.85%) 51	
Injection site swelling subjects affected / exposed occurrences (all)	27 / 63 (42.86%) 79	23 / 67 (34.33%) 59	
Injection site warmth subjects affected / exposed occurrences (all)	3 / 63 (4.76%) 7	7 / 67 (10.45%) 9	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 63 (4.76%) 3	2 / 67 (2.99%) 2	
Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 63 (9.52%) 9	6 / 67 (8.96%) 7	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 63 (0.00%) 0	4 / 67 (5.97%) 4	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	22 / 63 (34.92%) 26	21 / 67 (31.34%) 27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2016	<p>In the protocol version final 1.0 dated 15th January 2016; two trial parts were originally planned.</p> <p>During the first trial part from May 2016 – December 2016 adult patients were planned to be enrolled. In December 2016, an interim analysis of the data obtained within in the dose escalation phase of the first trial part had been planned. It should have been decided, whether the second trial part enrolling additional adults and also adolescents or children could be performed. The sponsor decided to waive then 2nd trial part in adolescents and children due to changes in the product strategy, despite no safety concerns obtained from the first part of the study. The protocol was amended accordingly, describing the trial conduct in adults only.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported