



Clinical trial results:

Double-blind phase IV multicentre clinical trial to evaluate and compare specific and non specific effects of SCIT by use of an Environmental Challenge Chamber after treatment with Allergovit® grasses or Allergovit® birch in patients with grass and birch pollen allergy

Summary

EudraCT number	2013-003095-12
Trial protocol	DE
Global end of trial date	26 November 2015

Results information

Result version number	v1 (current)
This version publication date	31 March 2017
First version publication date	31 March 2017
Summary attachment (see zip file)	AL1303AV_Lay Summary_final English (AL1303AV_Lay Summary_final English 2016-10-10 (AL05).pdf) AL1303AV_Lay Summary_final German (AL1303AV_Lay Summary_final German 2016-10-11 (AL05).pdf)

Trial information

Trial identification

Sponsor protocol code	AL1303AV
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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	Allergopharma GmbH & Co. KG, Allergopharma GmbH & Co. KG, 0049 40727650000,
Scientific contact	Allergopharma GmbH & Co. KG, Allergopharma GmbH & Co. KG, 0049 40727650000,

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	26 November 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate a specific treatment effect of ALLERGOVIT® grasses and ALLERGOVIT® birch and to assess the superiority of their specific effects compared with their unspecific effects. The treatment groups received either ALLERGOVIT® grasses or ALLERGOVIT® birch, which mutually served as non-active comparator.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices guidelines, and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator:

The treatment groups received either ALLERGOVIT® grasses or ALLERGOVIT® birch, which mutually served as non-active comparator.

In this trial, dual allergen sensitivity (birch as well as grass pollen) were treated with either the one or the other allergen. Each allergen treatment was acting as placebo for the other by evaluating the symptoms in the ECC after exposure to either of the allergens.

ECC=Environmental Challenge Chamber

Actual start date of recruitment	03 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 95
Worldwide total number of subjects	95
EEA total number of subjects	95

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	93
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

For each of the 269 patients screened, the trial started with a Screening Visit and a telephone contact. The telephone contact (one week before pre-treatment ECC visits and before randomization) was done to confirm patient eligibility (laboratory report, new diseases or any concomitant medication changes).

ECC=Environmental Challenge Chamber

Pre-assignment

Screening details:

At screening Visit (S1), a skin prick test (SPT), immunological profile assessment, and a lung function test (peak expiratory flow [PEF]) was performed. Relevant symptoms (adj. area under the curve (AUC) of Total Nasal Symptom Score (TNSS) of at least 10) documented during the pre-treatment exposure with birch or grass pollen allergens in the ECC.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

No placebo or other active comparator solution was used as comparator in this trial. The treatment groups received either ALLERGOVIT® grasses or ALLERGOVIT® birch, which mutually served as a comparator. Both active preparations used were identical in their outer appearance to ensure blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	ALLERGOVIT® grasses

Arm description:

For each patient, the trial started with a screening Visit (S1, optional S2), a telephone contact, followed by a baseline period of at least 5 days. During this period, the baseline data for the calculation of the Primary Endpoint was surveyed in 2 ECC visits (pre-treatment ECC) with an interval of at least 5 days (ECCpre Birch and ECCpre Grass visits).

Patients were randomized according to a 1:1 allocation sequence to receive either ALLERGOVIT® grasses or ALLERGOVIT® birch during the treatment period with up to 13 injections over 36 to 44 weeks. After the treatment period, all treated patients performed 2 distinct post-treatment ECC visits (ECCpost Birch and ECCpost Grass), again with an interval of at least 5 days.

At least 5 days after the last post-treatment ECC visit, the final visit was scheduled.

Arm type	Experimental
Investigational medicinal product name	ALLERGOVIT® grasses
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ALLERGOVIT® grasses: 100% aluminium adsorbed allergoid preparation of pollen from Phleum pratense, Lolium perenne, Festuca pratensis, Holcus lanatus, Dactylis glomerata, and Poa pratensis at 1,000 and 10,000 TU/mL for subcut inject, in the upper arm by the investigator during the treatment visits.

Dosing: 2 phases: dose escalation (up titration), maintenance.

Dose escalation phase: injections with strength 1,000 TU/mL, using the dose steps: 0.1 mL, 0.2 mL, 0.4 mL and 0.8 mL, followed by injections with strength 10,000 TU/mL, using the dose steps: 0.15 mL, 0.3 mL, and 0.6 mL. At the beginning of the dose escalation phase, injections were admin at intervals of 7 d. Modifications to the dose escalation scheme were allowed when AEs occurred. Dose was increased

progressively by 1 step, when that the previous dose was tolerated well.

Maintenance phase: when max individually tolerated dose was reached, it was administered again after 2 wks, then after 4 wks, later after 6 to 8 wks.

Arm title	ALLERGOVIT® birch
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Arm description:

For each patient, the trial started with a screening Visit (S1, optional S2), a telephone contact, followed by a baseline period of at least 5 days. During this period, the baseline data for the calculation of the Primary Endpoint was surveyed in 2 ECC visits (pre-treatment ECC) with an interval of at least 5 days (ECCpre Birch and ECCpre Grass visits).

Patients were randomized according to a 1:1 allocation sequence to receive either ALLERGOVIT® grasses or ALLERGOVIT® birch during the treatment period with up to 13 injections over 36 to 44 weeks. After the treatment period, all treated patients performed 2 distinct post-treatment ECC visits (ECCpost Birch and ECCpost Grass), again with an interval of at least 5 days.

At least 5 days after the last post-treatment ECC visit, the final visit was scheduled.

Arm type	Experimental
Investigational medicinal product name	ALLERGOVIT® birch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ALLERGOVIT® birch: 100% aluminium adsorbed allergoid preparation - pollen from birch (*Betula verrucosa*) at 1 000 and 10 000 TU/mL for subcut. injection, admin. in the upper arm by the investigator during the treatment visits.

Dosing: 2 phases: dose escalation (up-titration), maintenance.

Dose escalation phase: injections with strength 1,000 TU/mL, using the dose steps: 0.1 mL, 0.2 mL, 0.4 mL and 0.8 mL, followed by injections with strength 10,000 TU/mL, using the dose steps: 0.15 mL, 0.3 mL, and 0.6 mL. At the beginning of the dose escalation phase, injections were admin at intervals of 7 d. Modifications to the dose escalation scheme were allowed when AEs occurred. Dose was increased progressively by 1 step, when that the previous dose was tolerated well.

Maintenance phase: when max individually tolerated dose was reached, it was administered again after 2 wks, then after 4 wks, later after 6 to 8 wks.

Number of subjects in period 1	ALLERGOVIT® grasses	ALLERGOVIT® birch
Started	47	48
Completed	42	45
Not completed	5	3
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	1
Pregnancy	1	2
Other, not further specified	1	-

Baseline characteristics

Reporting groups

Reporting group title	ALLERGOVIT® grasses
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Reporting group description:

For each patient, the trial started with a screening Visit (S1, optional S2), a telephone contact, followed by a baseline period of at least 5 days. During this period, the baseline data for the calculation of the Primary Endpoint was surveyed in 2 ECC visits (pre-treatment ECC) with an interval of at least 5 days (ECCpre Birch and ECCpre Grass visits).

Patients were randomized according to a 1:1 allocation sequence to receive either ALLERGOVIT® grasses or ALLERGOVIT® birch during the treatment period with up to 13 injections over 36 to 44 weeks. After the treatment period, all treated patients performed 2 distinct post-treatment ECC visits (ECCpost Birch and ECCpost Grass), again with an interval of at least 5 days.

At least 5 days after the last post-treatment ECC visit, the final visit was scheduled.

Reporting group title	ALLERGOVIT® birch
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Reporting group description:

For each patient, the trial started with a screening Visit (S1, optional S2), a telephone contact, followed by a baseline period of at least 5 days. During this period, the baseline data for the calculation of the Primary Endpoint was surveyed in 2 ECC visits (pre-treatment ECC) with an interval of at least 5 days (ECCpre Birch and ECCpre Grass visits).

Patients were randomized according to a 1:1 allocation sequence to receive either ALLERGOVIT® grasses or ALLERGOVIT® birch during the treatment period with up to 13 injections over 36 to 44 weeks. After the treatment period, all treated patients performed 2 distinct post-treatment ECC visits (ECCpost Birch and ECCpost Grass), again with an interval of at least 5 days.

At least 5 days after the last post-treatment ECC visit, the final visit was scheduled.

Reporting group values	ALLERGOVIT® grasses	ALLERGOVIT® birch	Total
Number of subjects	47	48	95
Age categorical Units: Subjects			
Adults (18-64 years)	47	46	93
From 65-84 years	0	2	2
Age continuous Units: years			
arithmetic mean	34.2	33	
standard deviation	± 9.8	± 11.2	-
Gender categorical Units: Subjects			
Female	25	28	53
Male	22	20	42
Race Units: Subjects			
Asian	3	1	4
White	42	45	87
Other	2	2	4

End points

End points reporting groups

Reporting group title	ALLERGOVIT® grasses
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Reporting group description:

For each patient, the trial started with a screening Visit (S1, optional S2), a telephone contact, followed by a baseline period of at least 5 days. During this period, the baseline data for the calculation of the Primary Endpoint was surveyed in 2 ECC visits (pre-treatment ECC) with an interval of at least 5 days (ECCpre Birch and ECCpre Grass visits).

Patients were randomized according to a 1:1 allocation sequence to receive either ALLERGOVIT® grasses or ALLERGOVIT® birch during the treatment period with up to 13 injections over 36 to 44 weeks. After the treatment period, all treated patients performed 2 distinct post-treatment ECC visits (ECCpost Birch and ECCpost Grass), again with an interval of at least 5 days.

At least 5 days after the last post-treatment ECC visit, the final visit was scheduled.

Reporting group title	ALLERGOVIT® birch
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Reporting group description:

For each patient, the trial started with a screening Visit (S1, optional S2), a telephone contact, followed by a baseline period of at least 5 days. During this period, the baseline data for the calculation of the Primary Endpoint was surveyed in 2 ECC visits (pre-treatment ECC) with an interval of at least 5 days (ECCpre Birch and ECCpre Grass visits).

Patients were randomized according to a 1:1 allocation sequence to receive either ALLERGOVIT® grasses or ALLERGOVIT® birch during the treatment period with up to 13 injections over 36 to 44 weeks. After the treatment period, all treated patients performed 2 distinct post-treatment ECC visits (ECCpost Birch and ECCpost Grass), again with an interval of at least 5 days.

At least 5 days after the last post-treatment ECC visit, the final visit was scheduled.

Subject analysis set title	ALLERGOVIT® grasses (pre grass)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects who were in the Full analysis set and received a challenge with ALLERGOVIT® grasses.

Full analysis set: according to the Intention-to-Treat (ITT) principle: all patients who received at least one dose of trial medication during the course of the trial and for whom an efficacy assessment after baseline was available.

Subject analysis set title	ALLERGOVIT® birch (pre birch)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects who were in the Full analysis set and received a challenge with ALLERGOVIT® birch.

Full analysis set: according to the Intention-to-Treat (ITT) principle: all patients who received at least one dose of trial medication during the course of the trial and for whom an efficacy assessment after baseline was available.

Subject analysis set title	ALLERGOVIT® birch (post birch)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects who were in the Full analysis set and received a challenge with ALLERGOVIT® birch.

Full analysis set: according to the Intention-to-Treat (ITT) principle: all patients who received at least one dose of trial medication during the course of the trial and for whom an efficacy assessment after baseline was available.

Subject analysis set title	ALLERGOVIT® grasses (post grass)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects who were in the Full analysis set and received a challenge with ALLERGOVIT® grasses.

Full analysis set: according to the Intention-to-Treat (ITT) principle: all patients who received at least one dose of trial medication during the course of the trial and for whom an efficacy assessment after

baseline was available.

Subject analysis set title	Combined specific treatment effect
Subject analysis set type	Full analysis

Subject analysis set description:

Combined specific treatment effect on all subjects in the full analysis set (both treatments).

Subject analysis set title	Combined unspecific treatment effect
Subject analysis set type	Full analysis

Subject analysis set description:

Combined unspecific treatment effect on all subjects in the full analysis set (both treatments).

Subject analysis set title	ALLERGOVIT® grasses treated patients; ECCpre birch
Subject analysis set type	Full analysis

Subject analysis set description:

Patients treated with ALLERGOVIT® grasses and who were exposed to birch pollen in the ECC (pre birch).

Subject analysis set title	ALLERGOVIT® grasses treated patients; ECCpost birch
Subject analysis set type	Full analysis

Subject analysis set description:

Patients treated with ALLERGOVIT® grasses and who were exposed to birch pollen in the ECC (post birch).

Subject analysis set title	ALLERGOVIT® birch treated patients; ECCpre grasses
Subject analysis set type	Full analysis

Subject analysis set description:

Patients treated with ALLERGOVIT® birch and who were exposed to grass pollen in the ECC (pre grasses).

Subject analysis set title	ALLERGOVIT® birch treated patients; ECCpost grasses
Subject analysis set type	Full analysis

Subject analysis set description:

Patients treated with ALLERGOVIT® birch and who were exposed to grass pollen in the ECC (post grasses).

Subject analysis set title	Specific treatment effect of ALLERGOVIT® grasses
Subject analysis set type	Full analysis

Subject analysis set description:

Specific treatment effect of ALLERGOVIT® grasses

Subject analysis set title	Unspecific treatment effect of ALLERGOVIT® grasses
Subject analysis set type	Full analysis

Subject analysis set description:

Unspecific treatment effect of ALLERGOVIT® grasses.

Subject analysis set title	Specific treatment effect of ALLERGOVIT® birch
Subject analysis set type	Full analysis

Subject analysis set description:

Specific treatment effect of ALLERGOVIT® birch

Subject analysis set title	Unspecific treatment effect of ALLERGOVIT® birch
Subject analysis set type	Full analysis

Subject analysis set description:

Unspecific treatment effect of ALLERGOVIT® birch.

Subject analysis set title	Birch pollen season: ALLERGOVIT® grasses
Subject analysis set type	Full analysis

Subject analysis set description:

Patients treated with ALLERGOVIT® grasses, self-assessed during the birch pollen season.

Subject analysis set title	Grass pollen season: ALLERGOVIT® grasses
Subject analysis set type	Full analysis

Subject analysis set description:

Patients treated with ALLERGOVIT® grasses, self-assessed during the grass pollen season.

Subject analysis set title	Birch pollen season: ALLERGOVIT® birch
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients treated with ALLERGOVIT® birch, self-assessed during the birch pollen season.	
Subject analysis set title	Grass pollen season: ALLERGOVIT® birch
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients treated with ALLERGOVIT® birch, self-assessed during the grass pollen season.	

Primary: 1a_Specific treatment effect on TNSS; adjusted AUC: ALLERGOVIT® grasses

End point title	1a_Specific treatment effect on TNSS; adjusted AUC: ALLERGOVIT® grasses
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End point description:

Specific treatment effect of ALLERGOVIT® grasses defined as change of the adjusted AUC of TNSS, as measured during an exposure to grass pollen in the ECC between baseline (ECCpre) and after end of treatment (ECCpost), for patients treated with ALLERGOVIT® grasses (ECCpost grass minus ECCpre grass).

TNSS is the sum of scores, taken for the following symptoms: nasal congestion, rhinorrhea, nasal itching, and sneezing at each time point. Results are based on a 4-point scale score (0 to 3): 0=no symptoms; 1=mild symptoms that were easily tolerated; 2=awareness of symptoms, which were bothersome but tolerable; 3=severe symptoms that were hard to tolerate and interfered with daily activity.

AUC=Area under the curve
ECC=Environmental challenge chamber
TNSS=Total nasal symptom score

End point type	Primary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® grasses (pre grass)	ALLERGOVIT® grasses (post grass)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46 ^[1]	40 ^[2]		
Units: score				
arithmetic mean (standard deviation)	34.8 (± 11.98)	20.28 (± 12.76)		

Notes:

[1] - Full analysis set

[2] - Full analysis set

Statistical analyses

Statistical analysis title	ECCpost grass - ECCpre grass
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Statistical analysis description:

Comparison refers to the adjusted AUC of TNSS for subjects challenged with grass pollen and represents the change between ECCpost grass (end of treatment) - ECCpre grass (baseline).

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 40.

Comparison groups	ALLERGOVIT® grasses (pre grass) v ALLERGOVIT® grasses (post grass)
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-13.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.56
upper limit	-9.54

Notes:

[3] - Test for a specific treatment effect of ALLERGOVIT® grasses.

Repeated measurement model to test the specific treatment effect in the ALLERGOVIT® grasses group, between the ECCpost - ECCpre visits. Values refer to the adjusted AUC of TNSS.

Primary: 1b_Specific treatment effect on TNSS; adjusted AUC: ALLERGOVIT® birch

End point title	1b_Specific treatment effect on TNSS; adjusted AUC: ALLERGOVIT® birch
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End point description:

Specific treatment effect of ALLERGOVIT® birch defined as change of the adjusted AUC of TNSS, as measured during an exposure to birch pollen in the ECC between baseline (ECCpre) and after end of treatment (ECCpost), for patients treated with ALLERGOVIT® birch (ECCpost birch minus ECCpre birch).

TNSS is the sum of scores, taken for the following symptoms: nasal congestion, rhinorrhea, nasal itching, and sneezing at each time point. Results are based on a 4-point scale score (0 to 3): 0=no symptoms; 1=mild symptoms that were easily tolerated; 2=awareness of symptoms, which were bothersome but tolerable; 3=severe symptoms that were hard to tolerate and interfered with daily activity.

AUC=Area under the curve
ECC=Environmental challenge chamber
TNSS=Total nasal symptom score

End point type	Primary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® birch (pre birch)	ALLERGOVIT® birch (post birch)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48 ^[4]	43 ^[5]		
Units: score				
arithmetic mean (standard deviation)	23.31 (± 11.45)	14.35 (± 10.6)		

Notes:

[4] - Full analysis set

Statistical analyses

Statistical analysis title	ECCpost birch - ECCpre birch
Statistical analysis description:	
Comparison refers to the adjusted AUC of TNSS for subjects challenged with birch pollen and represents the change between ECCpost birch (end of treatment) - ECCpre birch (baseline).	
The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 43.	
Comparison groups	ALLERGOVIT® birch (pre birch) v ALLERGOVIT® birch (post birch)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-9.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.13
upper limit	-5.5

Notes:

[6] - Test for a specific treatment effect of ALLERGOVIT® birch.

Repeated measurement model to test the specific treatment effect in the ALLERGOVIT® birch group, between the ECCpost - ECCpre visits. Values refer to the adjusted AUC of TNSS.

Secondary: 2_Specific treatment effect of SCIT compared with unspecific treatment effect of SCIT for both treatments

End point title	2_Specific treatment effect of SCIT compared with unspecific treatment effect of SCIT for both treatments
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End point description:

Specific treatment effect of SCIT compared with the unspecific treatment effect of SCIT for both treatments on TNSS; adjusted AUC: [end of treatment - pre treatment (baseline)]

Specific treatment effect of SCIT compared with the unspecific treatment effect of SCIT for both treatments, defined as the difference of the changes of the adjusted AUC of TNSS measured during exposure to grass pollen and during exposure to birch pollen. The specific treatment effect of SCIT was defined as the combined specific treatment effect of ALLERGOVIT® grasses (ECCpost grass – ECCpre grass) and the specific treatment effect of ALLERGOVIT® birch (ECCpost birch – ECCpre birch). Whereas the unspecific treatment effect of SCIT was defined as the combined unspecific treatment effect of ALLERGOVIT® grasses (ECCpost birch – ECCpre birch) and the unspecific treatment effect of ALLERGOVIT® birch (ECCpost grass – ECCpre grass).

SCIT=Specific subcutaneous immunotherapy

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	Combined specific treatment effect	Combined unspecific treatment effect		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83 ^[7]	83 ^[8]		
Units: score				
arithmetic mean (standard deviation)	-11.61 (± 13.38)	-4.82 (± 13.05)		

Notes:

[7] - Full analysis set

[8] - Full analysis set

Statistical analyses

Statistical analysis title	Unspecific - Specific treatment effect of SCIT
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Statistical analysis description:

Unspecific treatment effect - Specific treatment effect.

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 79.

Comparison groups	Combined unspecific treatment effect v Combined specific treatment effect
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	6.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.86
upper limit	10.28

Secondary: 3a_Unspecific treatment effect of ALLERGOVIT® grasses

End point title	3a_Unspecific treatment effect of ALLERGOVIT® grasses
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End point description:

The unspecific treatment effect of ALLERGOVIT® preparations was calculated as shown below.

•Unspecific treatment effect of ALLERGOVIT® grasses: ECCpost birch – ECCpre birch, for patients given ALLERGOVIT® grasses

Results show the evaluation of the unspecific effect of ALLERGOVIT® grasses, i.e. the change of the adjusted AUC of TNSS, as measured during ECCpre Birch and ECCpost Birch for patients treated with ALLERGOVIT® grasses.

AUC=Area under the curve

ECC=Environmental challenge chamber

TNSS=Total nasal symptom score

End point type	Secondary
End point timeframe:	
Baseline (pre treatment) to end of treatment (at approximately 9 months).	

End point values	ALLERGOVIT® grasses treated patients; ECCpre birch	ALLERGOVIT® grasses treated patients; ECCpost birch		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46 ^[9]	41 ^[10]		
Units: score				
arithmetic mean (standard deviation)	23.65 (± 8.85)	19.39 (± 11.72)		

Notes:

[9] - Full analysis set

[10] - Full analysis set

Statistical analyses

Statistical analysis title	Unspecific treatment effect of ALLERGOVIT® grasses
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Statistical analysis description:

Unspecific treatment effect of ALLERGOVIT® grasses; ECCpost birch - ECCpre birch

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 41.

Comparison groups	ALLERGOVIT® grasses treated patients; ECCpre birch v ALLERGOVIT® grasses treated patients; ECCpost birch
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0702
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-3.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.92
upper limit	-0.29

Secondary: 3b_Unspecific treatment effect of ALLERGOVIT® birch

End point title	3b_Unspecific treatment effect of ALLERGOVIT® birch
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End point description:

The unspecific treatment effect of ALLERGOVIT® preparations was calculated as shown below.

•Unspecific treatment effect of ALLERGOVIT® birch: ECCpost grasses – ECCpre grasses, for patients given ALLERGOVIT® birch

Results show the evaluation of the unspecific effect of ALLERGOVIT® birch, i.e. the change of the adjusted AUC of TNSS, as measured during ECCpre grasses and ECCpost grasses for patients treated with ALLERGOVIT® birch.

AUC=Area under the curve
 ECC=Environmental challenge chamber
 TNSS=Total nasal symptom score

End point type	Secondary
End point timeframe:	
Baseline (pre treatment) to end of treatment (at approximately 9 months).	

End point values	ALLERGOVIT® birch treated patients; ECCpre grasses	ALLERGOVIT® birch treated patients; ECCpost grasses		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48 ^[11]	42 ^[12]		
Units: score				
arithmetic mean (standard deviation)	30.75 (± 11.86)	25.21 (± 13.75)		

Notes:

[11] - Full analysis set

[12] - Full analysis set

Statistical analyses

Statistical analysis title	Unspecific treatment effect of ALLERGOVIT® birch
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Statistical analysis description:

Unspecific treatment effect of ALLERGOVIT® grasses; ECCpost birch - ECCpre birch

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 42.

Comparison groups	ALLERGOVIT® birch treated patients; ECCpre grasses v ALLERGOVIT® birch treated patients; ECCpost grasses
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0074
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.79
upper limit	-1.78

Secondary: 4a_Specific compared with unspecific treatment effect of ALLERGOVIT® grasses

End point title	4a_Specific compared with unspecific treatment effect of ALLERGOVIT® grasses
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End point description:

For patients treated with ALLERGOVIT® grasses:

- Specific treatment effect of ALLERGOVIT® grasses: ECCpost grass – ECCpre grass
- Unspecific treatment effect of ALLERGOVIT® grasses: ECCpost birch – ECCpre birch

ECC=Environmental challenge chamber

End point type	Secondary
End point timeframe:	
Baseline (pre treatment) to end of treatment (at approximately 9 months).	

End point values	Specific treatment effect of ALLERGOVIT® grasses	Unspecific treatment effect of ALLERGOVIT® grasses		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40 ^[13]	41 ^[14]		
Units: score				
arithmetic mean (standard deviation)	-13.55 (± 12.55)	-3.32 (± 11.42)		

Notes:

[13] - Full analysis set

[14] - Full analysis set

Statistical analyses

Statistical analysis title	ALLERGOVIT® grasses: Unspec-Spec treatment effect
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Statistical analysis description:

ALLERGOVIT® grasses treated patients

Unspecific treatment effect - Specific treatment effect

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 40.

Comparison groups	Specific treatment effect of ALLERGOVIT® grasses v Unspecific treatment effect of ALLERGOVIT® grasses
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	10.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	15.7

Secondary: 4b_Specific compared with unspecific treatment effect of ALLERGOVIT® birch

End point title	4b_Specific compared with unspecific treatment effect of ALLERGOVIT® birch
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End point description:

For patients treated with ALLERGOVIT® birch:

- Specific treatment effect of ALLERGOVIT® birch: ECCpost birch – ECCprebirch
- Unspecific treatment effect of ALLERGOVIT® birch: ECCpost grass – ECCpre grass

ECC=Environmental challenge chamber

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	Specific treatment effect of ALLERGOVIT® birch	Unspecific treatment effect of ALLERGOVIT® birch		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43 ^[15]	42 ^[16]		
Units: score				
arithmetic mean (standard deviation)	-9.81 (± 14.01)	-6.29 (± 14.46)		

Notes:

[15] - Full analysis set

[16] - Full analysis set

Statistical analyses

Statistical analysis title	ALLERGOVIT® birch: Unspec-Spec treatment effect
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Statistical analysis description:

ALLERGOVIT® birch treated patients

Unspecific treatment effect - Specific treatment effect

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 39.

Comparison groups	Specific treatment effect of ALLERGOVIT® birch v Unspecific treatment effect of ALLERGOVIT® birch
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2374
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	7.78

Secondary: 4c_Specific compared with unspecific treatment effect: ALLERGOVIT® grasses vs ALLERGOVIT® birch

End point title	4c_Specific compared with unspecific treatment effect: ALLERGOVIT® grasses vs ALLERGOVIT® birch
End point description:	
Specific compared with unspecific treatment effect: ALLERGOVIT® grasses vs ALLERGOVIT® birch	
Specific treatment effect of ALLERGOVIT® grasses: ECCpost grass – ECCpre grass, given ALLERGOVIT® grasses; unspecific treatment effect of ALLERGOVIT® birch: ECCpost grass – ECCpre grass, given ALLERGOVIT® birch.	
End point type	Secondary
End point timeframe:	
Baseline (pre treatment) to end of treatment (at approximately 9 months).	

End point values	Specific treatment effect of ALLERGOVIT® grasses	Unspecific treatment effect of ALLERGOVIT® birch		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40 ^[17]	42 ^[18]		
Units: score				
arithmetic mean (standard deviation)	-13.55 (± 12.55)	-6.29 (± 14.46)		

Notes:

[17] - Full analysis set

[18] - Full analysis set

Statistical analyses

Statistical analysis title	Specific (Grasses) vs Unspecific (birch) effect
Statistical analysis description:	
The specific treatment effect of ALLERGOVIT® grasses (mean diff. AUC TNSS -13.55[±12.55]) was significantly (p = 0.0172) larger than the unspecific treatment effect of ALLERGOVIT® birch (mean difference in adjusted AUC TNSS -6.29 [±14.46]). Thus, superiority of the specific treatment effects of ALLERGOVIT® grasses or birch over the unspecific treatment effects of ALLERGOVIT® birch or grasses, respectively, could be shown.	
Comparison groups	Specific treatment effect of ALLERGOVIT® grasses v Unspecific treatment effect of ALLERGOVIT® birch
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0172 ^[19]
Method	t-test, 2-sided

Notes:

[19] - p-value from 2-sided two-sample t-test

Secondary: 4d_Specific compared with unspecific treatment effect: ALLERGOVIT® birch vs ALLERGOVIT® grasses

End point title	4d_Specific compared with unspecific treatment effect: ALLERGOVIT® birch vs ALLERGOVIT® grasses
End point description:	
Specific compared with unspecific treatment effect: ALLERGOVIT® birch vs ALLERGOVIT® grasses	
Specific treatment effect of ALLERGOVIT® birch: ECCpost birch – ECCpre birch, given ALLERGOVIT® birch; unspecific treatment effect of ALLERGOVIT® grasses: ECCpost birch – ECCpre birch, given ALLERGOVIT® grasses.	

End point type	Secondary
End point timeframe:	
Baseline (pre treatment) to end of treatment (at approximately 9 months).	

End point values	Unspecific treatment effect of ALLERGOVIT® grasses	Specific treatment effect of ALLERGOVIT® birch		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41 ^[20]	43 ^[21]		
Units: score				
arithmetic mean (standard deviation)	-3.32 (± 11.42)	-9.81 (± 14.01)		

Notes:

[20] - Full analysis set

[21] - Full analysis set

Statistical analyses

Statistical analysis title	Specific (birch) vs Unspecific (grasses) effect
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Statistical analysis description:

The specific treatment effect of ALLERGOVIT® birch (mean difference in adjusted AUC TNSS -9.81 [±14.01]) was significantly ($p = 0.0221$) larger than the unspecific treatment effect of ALLERGOVIT® grasses (mean difference in adjusted AUC TNSS -3.32 [±11.42]). Thus, superiority of the specific treatment effects of ALLERGOVIT® grasses or birch over the unspecific treatment effects of ALLERGOVIT® birch or grasses, respectively, could be shown.

Comparison groups	Unspecific treatment effect of ALLERGOVIT® grasses v Specific treatment effect of ALLERGOVIT® birch
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0221 ^[22]
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)

Notes:

[22] - p-value from 2-sided two-sample t-test

Secondary: 5a_Grass pollen specific IgG4: ALLERGOVIT® grasses-treated subjects

End point title	5a_Grass pollen specific IgG4: ALLERGOVIT® grasses-treated subjects
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End point description:

Data summarizes the changes from baseline in grass pollen specific IgG4 (serum) in patients treated with ALLERGOVIT® grasses. Within the treatment group analysis.

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® grasses (pre grass)	ALLERGOVIT® grasses (post grass)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 ^[23]	45 ^[24]		
Units: mg/L				
arithmetic mean (standard deviation)	0.5 (± 1.31)	3.02 (± 4.67)		

Notes:

[23] - Full analysis set

[24] - Full analysis set

Statistical analyses

Statistical analysis title	Grass pollen specific IgG4 change from baseline
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Statistical analysis description:

Grass pollen specific IgG4 change from baseline in subjects treated with ALLERGOVIT® grasses

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 45.

Comparison groups	ALLERGOVIT® grasses (pre grass) v ALLERGOVIT® grasses (post grass)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[25]
Method	Wilcoxon signed rank test
Parameter estimate	Mean difference (net)
Point estimate	2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	3.58

Notes:

[25] - p-value from 2-sided Wilcoxon signed rank test to test differences between baseline and final visit.

Secondary: 5b_Birch pollen specific IgG4: ALLERGOVIT® grasses-treated subjects

End point title	5b_Birch pollen specific IgG4: ALLERGOVIT® grasses-treated subjects
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End point description:

Data summarizes the changes from baseline in birch pollen specific IgG4 (serum) in patients treated with ALLERGOVIT® grasses. Within the treatment group analysis.

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® grasses (pre grass)	ALLERGOVIT® grasses (post grass)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 ^[26]	45 ^[27]		
Units: mg/L				
arithmetic mean (standard deviation)	0.94 (± 2.14)	0.87 (± 1.97)		

Notes:

[26] - Full analysis set

[27] - Full analysis set

Statistical analyses

Statistical analysis title	Birch pollen specific IgG4 change from baseline
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Statistical analysis description:

Birch pollen specific IgG4 change from baseline in subjects treated with ALLERGOVIT® grasses.

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 45.

Comparison groups	ALLERGOVIT® grasses (pre grass) v ALLERGOVIT® grasses (post grass)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3414 ^[28]
Method	Wilcoxon signed rank test
Parameter estimate	Mean difference (net)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.03

Notes:

[28] - p-value from 2-sided Wilcoxon signed rank test to test differences between baseline and final visit.

Secondary: 5c_Grass pollen specific IgG4: ALLERGOVIT® birch-treated subjects

End point title	5c_Grass pollen specific IgG4: ALLERGOVIT® birch-treated subjects
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End point description:

Data summarizes the changes from baseline in grass pollen specific IgG4 (serum) in patients treated with ALLERGOVIT® birch. Within the treatment group analysis.

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® birch (pre birch)	ALLERGOVIT® birch (post birch)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48 ^[29]	48 ^[30]		
Units: mg/L				
arithmetic mean (standard deviation)	0.53 (± 1.32)	0.49 (± 0.78)		

Notes:

[29] - Full analysis set

[30] - Full analysis set

Statistical analyses

Statistical analysis title	Grass pollen specific IgG4 change from baseline
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Statistical analysis description:

Grass pollen specific IgG4 change from baseline in subjects treated with ALLERGOVIT® birch.

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 48.

Comparison groups	ALLERGOVIT® birch (pre birch) v ALLERGOVIT® birch (post birch)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.584 ^[31]
Method	Wilcoxon signed rank test
Parameter estimate	Mean difference (net)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.17

Notes:

[31] - p-value from 2-sided Wilcoxon signed rank test to test differences between baseline and final visit.

Secondary: 5d_Birch pollen specific IgG4: ALLERGOVIT® birch-treated subjects

End point title	5d_Birch pollen specific IgG4: ALLERGOVIT® birch-treated subjects
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End point description:

Data summarizes the changes from baseline in birch pollen specific IgG4 (serum) in patients treated with ALLERGOVIT® birch. Within the treatment group analysis.

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® birch (pre birch)	ALLERGOVIT® birch (post birch)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48 ^[32]	48 ^[33]		
Units: mg/L				
arithmetic mean (standard deviation)	0.68 (± 0.77)	2.89 (± 2.73)		

Notes:

[32] - Full analysis set

[33] - Full analysis set

Statistical analyses

Statistical analysis title	Birch pollen specific IgG4 change from baseline
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Statistical analysis description:

Birch pollen specific IgG4 change from baseline in patients treated with ALLERGOVIT® birch.

The value for 'Subjects in this analysis' shown below is not correct and is due to a validation error of the EudraCT database system. The correct value for 'Subjects in this analysis' is 48.

Comparison groups	ALLERGOVIT® birch (pre birch) v ALLERGOVIT® birch (post birch)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[34]
Method	Wilcoxon signed rank test
Parameter estimate	Mean difference (net)
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.61
upper limit	2.81

Notes:

[34] - p-value from 2-sided Wilcoxon signed rank test to test differences between baseline and final visit.

Secondary: 6a_Clinical chemistry: Blood transaminases; Transferase

End point title	6a_Clinical chemistry: Blood transaminases; Transferase
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End point description:

Clinical chemistry: blood transaminases, transferase

Alanine aminotransferase; Aspartate aminotransferase; Gamma glutamyl transferase.

Change to baseline: Final Visit - Baseline

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[35]	47 ^[36]		
Units: U/mL				
arithmetic mean (confidence interval 95%)				
Alanine aminotransferase	11.6 (-7 to 30.3)	5.3 (-2.6 to 13.2)		
Aspartate aminotransferase	7.2 (-0.6 to 14.9)	5.1 (1.4 to 8.9)		
Gamma glutamyl transferase	4.6 (-1.9 to 11.1)	1.1 (-4.1 to 6.2)		

Notes:

[35] - Safety set

[36] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: 6b_Clinical chemistry: Blood Bilirubin; Creatinine; Glucose

End point title	6b_Clinical chemistry: Blood Bilirubin; Creatinine; Glucose
End point description:	
Clinical chemistry: Blood Bilirubin, Creatinine, Glucose	
Change to baseline: Final Visit - Baseline	
End point type	Secondary
End point timeframe:	
Baseline (pre treatment) to end of treatment (at approximately 9 months).	

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[37]	47 ^[38]		
Units: mg/dL				
arithmetic mean (confidence interval 95%)				
Bilirubin	0.036 (-0.051 to 0.123)	-0.005 (-0.078 to 0.067)		
Creatinine	0.075 (0.043 to 0.107)	0.056 (0.025 to 0.087)		
Glucose	1.1 (-4.9 to 7.1)	-0.6 (-5.7 to 4.5)		

Notes:

[37] - Safety set

[38] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: 7a_Haematology: Haemoglobin

End point title	7a_Haematology: Haemoglobin
End point description: Haematology: Haemoglobin	
Change to baseline: Final Visit - Baseline	
End point type	Secondary
End point timeframe: Baseline (pre treatment) to end of treatment (at approximately 9 months).	

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 ^[39]	47 ^[40]		
Units: g/dL				
arithmetic mean (confidence interval 95%)				
Haemoglobin	-0.33 (-0.57 to -0.08)	-0.31 (-0.56 to -0.07)		

Notes:

[39] - Safety set

[40] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: 7b_Haematology: Leukocytes; Platelets

End point title	7b_Haematology: Leukocytes; Platelets
End point description: Haematology: Leukocytes, Platelets	
Change to baseline: Final Visit - Baseline	
End point type	Secondary
End point timeframe: Baseline (pre treatment) to end of treatment (at approximately 9 months).	

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43 ^[41]	47 ^[42]		
Units: 10 ⁹ /L				
arithmetic mean (confidence interval 95%)				
Leukocytes	-0.37 (-0.86 to 0.11)	0.14 (-0.27 to 0.56)		
Platelets	7.1 (-1.9 to 16.2)	13.8 (4.7 to 22.9)		

Notes:

[41] - Safety set

[42] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: 8a_Vital signs: Systolic blood pressure; Diastolic blood pressure

End point title	8a_Vital signs: Systolic blood pressure; Diastolic blood pressure
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End point description:

Vital signs: Systolic blood pressure; Diastolic blood pressure

Change to baseline: Final Visit - Baseline

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[43]	48 ^[44]		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
Systolic blood pressure	0.9 (-2 to 3.8)	2.2 (-0.8 to 5.2)		
Diastolic blood pressure	-0.5 (-3 to 2)	1.8 (-0.7 to 4.3)		

Notes:

[43] - Safety set

[44] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: 8b_Vital signs: Heart rate

End point title	8b_Vital signs: Heart rate
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End point description:

Vital signs: Heart rate

Change to baseline: Final Visit - Baseline

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[45]	48 ^[46]		
Units: bpm				
arithmetic mean (confidence interval 95%)				
Heart rate	1.5 (-1.6 to 4.6)	1.6 (-1.7 to 5)		

Notes:

[45] - Safety set

[46] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: 8c_Vital signs: Respiratory rate

End point title	8c_Vital signs: Respiratory rate
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End point description:

Vital signs: Respiratory rate

Change to baseline: Final Visit - Baseline

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[47]	48 ^[48]		
Units: breaths/min				
arithmetic mean (confidence interval 95%)				
Respiratory rate	-0.4 (-1 to 0.1)	-0.3 (-1.1 to 0.4)		

Notes:

[47] - Safety set

[48] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: 9_Tolerability assessment: Investigator; Patient

End point title	9_Tolerability assessment: Investigator; Patient
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End point description:

Tolerability assessment: Investigator; Patient

Performed by the patient and the investigator, using a 5-point score (Likert scale);
score 1=very bad; score 5=very good

Evaluated as continuous variable.

End point type	Secondary
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End point timeframe:

Baseline (pre treatment) to end of treatment (at approximately 9 months).

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45 ^[49]	48 ^[50]		
Units: score				
arithmetic mean (confidence interval 95%)				
Investigator	4.2 (4 to 4.5)	4.4 (4.2 to 4.6)		
Patient	4 (3.8 to 4.3)	4.3 (4.1 to 4.5)		

Notes:

[49] - Safety set

Investigator

N=45 (available for analysis)

Patient

N=44 (available for analysis)

[50] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: 10_Severity of allergic symptoms during the pollen seasons

End point title	10_Severity of allergic symptoms during the pollen seasons
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End point description:

Severity of allergic symptoms during the grass pollen season and the birch pollen season, measured by a VRS in patients treated with ALLERGOVIT® grasses or ALLERGOVIT® birch.

Patients rated at home their symptoms during the birch and grass pollen season, respectively. The rating of symptoms during the birch pollen season was performed in calendar week 19. The symptoms experienced during the grass pollen season were rated in calendar week 26.

The score scale was from 1 (very good) to 10 (very poor).

VRS=Visual rating scale

End point type	Secondary
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End point timeframe:

Calendar week 19 and calendar week 26.

End point values	ALLERGOVIT® grasses	ALLERGOVIT® birch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44 ^[51]	46 ^[52]		
Units: score				
arithmetic mean (confidence interval 95%)				
Grass pollen season	4.18 (3.42 to 4.94)	4.89 (4.29 to 5.5)		
Birch pollen season	4.52 (3.83 to 5.22)	4.24 (3.66 to 4.81)		

Notes:

[51] - Full analysis set

[52] - Full analysis set

Statistical analyses

Statistical analysis title	Diff. btw treat groups: grass pollen season
Statistical analysis description:	
Grass pollen season	
Difference between the treatment groups within one pollen season.	
Comparison groups	ALLERGOVIT® grasses v ALLERGOVIT® birch
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0588 ^[53]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	4.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.07
upper limit	5.02

Notes:

[53] - p-value from two-sided Mann-Whitney U-test comparing the results from the different treatments within a season

Statistical analysis title	Diff. btw treat groups: birch pollen season
Statistical analysis description:	
Birch pollen season	
Difference between the treatment groups within one pollen season.	
Comparison groups	ALLERGOVIT® grasses v ALLERGOVIT® birch
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7132
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	4.38

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.94
upper limit	4.82

Secondary: 11_Quality of life (SF-12 Questionnaire)

End point title	11_Quality of life (SF-12 Questionnaire)
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End point description:

QoL completed during the grass pollen season and the birch pollen season, measured by the SF-12 Questionnaire

The questionnaire was completed by the patients treated with ALLERGOVIT® grasses or ALLERGOVIT® birch during the grass pollen season and the birch pollen season. Additionally, three scores gained from the data of the SF-12 were analyzed and compared between the treatment groups. These were the physical component summary score, the mental health score, and the utility index score.

Data for one item of the questionnaire of the SF-12 is available directly in the EudraCT database entry. Results of the complete questionnaire and of the analysis of the three scores gained from the data are provided in the attached files.

QoL=Quality of life

End point type	Secondary
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End point timeframe:

Calendar week 19 and calendar week 26.

End point values	Birch pollen season: ALLERGOVIT® grasses	Grass pollen season: ALLERGOVIT® grasses	Birch pollen season: ALLERGOVIT® birch	Grass pollen season: ALLERGOVIT® birch
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46 ^[54]	46 ^[55]	48 ^[56]	48 ^[57]
Units: subject				
Excellent	6	4	8	6
Very good	21	22	15	15
Good	11	15	17	21
Fair	7	3	4	4
Poor	0	0	2	0
Missing	0	0	0	0

Notes:

[54] - Full analysis set

[55] - Full analysis set

[56] - Full analysis set

[57] - Full analysis set

Attachments (see zip file)	Study AL 1303AV__ QoL SF-12/QoL-SF12_AL1303AV (AL05)- QoL-SF12__AL1303AV (AL05)_scores gained--EudraCT.pdf
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Statistical analyses

Statistical analysis title	Birch pollen season: overall QoL
Statistical analysis description: Birch pollen season: overall QoL - data from from patients treated with ALLERGOVIT® grasses or ALLERGOVIT® birch.	
Comparison groups	Birch pollen season: ALLERGOVIT® grasses v Birch pollen season: ALLERGOVIT® birch
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7102 ^[58]
Method	Wilcoxon (Mann-Whitney)

Notes:

[58] - p-value from two-sided Mann-Whitney U-test comparing the results from the different treatments within a season

Statistical analysis title	Grass pollen season: overall QoL
Statistical analysis description: Grass pollen season: overall QoL - data from from patients treated with ALLERGOVIT® grasses or ALLERGOVIT® birch.	
Comparison groups	Grass pollen season: ALLERGOVIT® grasses v Grass pollen season: ALLERGOVIT® birch
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.395 ^[59]
Method	Wilcoxon (Mann-Whitney)

Notes:

[59] - p-value from two-sided Mann-Whitney U-test comparing the results from the different treatments within a season

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the period from the first screening including trial-related procedures until 30 days after the last IMP application or trial-related procedure were recorded.

Adverse event reporting additional description:

In total, 7 serious treatment-emergent SAEs were reported in 3 patients (3.2%), which were not related to IMP or trial procedures.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	ALLERGOVIT® grasses
Reporting group description: -	
Reporting group title	ALLERGOVIT® birch
Reporting group description: -	

Serious adverse events	ALLERGOVIT® grasses	ALLERGOVIT® birch	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)	2 / 48 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Ventricular extrasystoles			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin erosion			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ALLERGOVIT® grasses	ALLERGOVIT® birch	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 47 (76.60%)	31 / 48 (64.58%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 47 (8.51%)	4 / 48 (8.33%)	
occurrences (all)	4	8	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	8 / 47 (17.02%)	8 / 48 (16.67%)	
occurrences (all)	22	13	
Injection site pruritus			
subjects affected / exposed	8 / 47 (17.02%)	6 / 48 (12.50%)	
occurrences (all)	11	14	

Injection site swelling subjects affected / exposed occurrences (all)	11 / 47 (23.40%) 19	5 / 48 (10.42%) 7	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	12 / 47 (25.53%) 13	16 / 48 (33.33%) 26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2014	The original trial protocol, dated 13 Dec 2013, was amended once on 28 Feb 2014 to final Trial Protocol 2.0 prior to enrollment of any patient (first patient, first screening was on 03 Apr 2014).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported