# 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)<br>AL1303AV_Lay Summary_final German (AL1303AV_Lay Summary_final German 2016-10-11 (AL05).pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | AL1303AV |

**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 (uptitration), 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 |
|---|---|

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 (uptitration), 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 |
|---|---|

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 |
|---|---|

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<br>Units: Subjects | | | |
| Adults (18-64 years) | 47 | 46 | 93 |
| From 65-84 years | 0 | 2 | 2 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 34.2 | 33 | |
| standard deviation | ± 9.8 | ± 11.2 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 25 | 28 | 53 |
| Male | 22 | 20 | 42 |
| Race<br>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 |
|---|---|

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 |
|---|---|

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) |
|---|---|
| Subject analysis set type | Full analysis |

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) |
|---|---|
| Subject analysis set type | Full analysis |

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) |
|---|---|
| Subject analysis set type | Safety analysis |

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) |
|---|---|
| Subject analysis set type | Full analysis |

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 |

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 |

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 |
|---|---|

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 |

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 |

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

[5] - 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |

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 |

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

End point description:
Vital signs: Systolic blood pressure; Diastolic blood pressure

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[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 |
|---|---|

End point description:
Vital signs: Heart rate

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[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 |
|---|---|

End point description:

Vital signs: Respiratory rate

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[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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 | Diffr. 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 | Diffr. 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) |
|---|---|

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 |
|---|---|

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 |

### 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 |

### 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<br>subjects affected / exposed<br>occurrences (all) | 11 / 47 (23.40%)<br>19 | 5 / 48 (10.42%)<br>7 | |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 12 / 47 (25.53%)<br>13 | 16 / 48 (33.33%)<br>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