



Clinical trial results:

Multicenter, randomized, parallel-group, double-blind, placebo-controlled clinical trial for evaluating the clinical efficacy and safety of intradermal immunotherapy with polymerised Phleum pratense, in patients with allergic rhino-conjunctivitis with or without mild to moderate asthma, sensitised to Phleum pratense pollen.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-000429-18 |
| Trial protocol | ES |
| Global end of trial date | 28 September 2017 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 14 October 2018 |
| First version publication date | 14 October 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | DIA-PhI-01-14 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | DIATER Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A. |
| Sponsor organisation address | Avda. Gregorio Peces Barba 2, Madrid, Spain, 28918 |
| Public contact | Medical department, DIATER Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A., 0034 914966013, departamento.medico@diater.com |
| Scientific contact | Medical department, DIATER Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A., 0034 914966013, departamento.medico@diater.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 24 August 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 September 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Efficacy assessment of Polymerized Phleum pratense immunotherapy administered intradermally

Protection of trial subjects:

After study inclusion, and throughout the study period, the following rescue medication was allowed for the control of the study disease

Eye symptoms:

Topical antihistamines (eye drops): nedocromil

Nasal symptoms:

Antihistamines: loratadine.

Topical nasal corticosteroids: nasal budesonide.

Oral corticosteroids: deflazacort

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 08 October 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 | Spain: 153 |
| Worldwide total number of subjects | 153 |
| EEA total number of subjects | 153 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 15 |
| Adults (18-64 years) | 138 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment period (from the date of the first site ready to recruit to the date for the last patient entered into the study): July 2015 to February 2016. FPFV: 08-OCT-2014; LPLV: 28-SEP-2017

Pre-assignment

Screening details:

Additionally to the 153 enrolled patients , 2 patients signing the Informed consent was screened but did not fulfill the selection criteria

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 155 ^[1] |
| Number of subjects completed | 153 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-----------------------------------|
| Reason: Number of subjects | Not meeting selection criteria: 2 |
|----------------------------|-----------------------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects starting the pre-assignment period is the number of screened subjects signing informed consent The number of subjects reported as enrolled is the number of randomized subjects meeting the selection criteria.

Period 1

| | |
|------------------------------|---|
| Period 1 title | First year |
| 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:

To ensure adequate blinding of the investigational drug and preserve the blinded nature of the clinical trial, all treatments were packaged identically. The randomization and centre numbers were included in the label of each drug package and the labelling was done in such a way that neither the investigator nor the patient could identify the product administered. The blinded envelopes for each subject were safeguarded in the pharmacy service and by the Sponsor

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo- 1st year |

Arm description:

Placebo. First year of follow-up. first cycle of treatment

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intradermal use |

Dosage and administration details:

IMP was administered preseasonally and weekly during 6 weeks (0.1 ml of Placebo in each single volar forearm per visit: 0.2 ml total / treatment visit)

| | |
|------------------|-------------------|
| Arm title | Active 1-1st year |
|------------------|-------------------|

Arm description:

Active IMP at low dose. First year of follow-up. first cycle of treatment

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Polymerized Phleum pratense |
| Investigational medicinal product code | Phl p pol |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intradermal use |

Dosage and administration details:

IMP (0.3 microgram /ml) was administered preseasonally and weekly during 6 weeks (0.1 ml of IMP in one volar forearm and 0.1 ml of matching placebo in the other volar forearm in each single visit)

| | |
|------------------|--------------------|
| Arm title | Active 2- 1st year |
|------------------|--------------------|

Arm description:

Active IMP at high dose. First year of follow-up. first cycle of treatment

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Polymerized Phleum pratense |
| Investigational medicinal product code | Phl p pol |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intradermal use |

Dosage and administration details:

IMP (0.3 microgram /ml) was administered preseasonally and weekly during 6 weeks (0.1 ml of IMP in each volar forearm per visit. 0.2 ml total / treatment visit))

| Number of subjects in period 1 | Placebo- 1st year | Active 1-1st year | Active 2- 1st year |
|---------------------------------------|-------------------|-------------------|--------------------|
| Started | 56 | 44 | 53 |
| Treated | 53 | 42 | 53 |
| Completed | 51 | 38 | 49 |
| Not completed | 5 | 6 | 4 |
| Consent withdrawn by subject | 5 | 4 | - |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | - | 1 | 2 |
| Lost to follow-up | - | 1 | 1 |

Period 2

| | |
|------------------------------|----------------|
| Period 2 title | Second year |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

As defined in the protocol, after the first year of follow-up, blinding was opened for the placebo group to receive during the second year of treatment the active treatment with the best efficacy/safety ratio . According to this, these patients were receiving the high dose of active treatment during the second

period .

the arms initially assigned to Active 1 and Active 2 remained blinded during the second year.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|------------------|
| Arm title | Placebo-Active 2 |
|------------------|------------------|

Arm description:

Active IMP at high doses during second year for patients initially receiving placebo during the first year

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Polymerized Phleum pratense |
| Investigational medicinal product code | Phl p pol |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intradermal use |

Dosage and administration details:

IMP (0.3 microgram /ml) was administered preseasonally and weekly during 6 weeks (0.1 ml of IMP in each volar forearm per visit. 0.2 ml total / treatment visit)

| | |
|------------------|--------------------|
| Arm title | Active 1- 2nd year |
|------------------|--------------------|

Arm description:

active IMP at low dose. Second year of follow-up. Second cycle of treatment

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Polymerized Phleum pratense |
| Investigational medicinal product code | Phl p pol |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intradermal use |

Dosage and administration details:

IMP (0.3 microgram /ml) was administered preseasonally and weekly during 6 weeks (0.1 ml of IMP in one volar forearm and 0.1 ml of matching placebo in the other volar forearm in each single visit)

| | |
|------------------|--------------------|
| Arm title | Active 2- 2nd year |
|------------------|--------------------|

Arm description:

Active IMP at high dose. Second year of follow-up. Second cycle of treatment

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Polymerized Phleum pratense |
| Investigational medicinal product code | Phl p pol |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intradermal use |

Dosage and administration details:

IMP (0.3 microgram /ml) was administered preseasonally and weekly during 6 weeks (0.1 ml of IMP in each volar forearm per visit) (0.2 ml total/ treatment visit)

| Number of subjects in period 2 | Placebo-Active 2 | Active 1- 2nd year | Active 2- 2nd year |
|---------------------------------------|------------------|--------------------|--------------------|
| Started | 51 | 38 | 49 |
| Treated | 51 | 37 | 47 |
| Completed | 49 | 36 | 45 |
| Not completed | 2 | 2 | 4 |
| Consent withdrawn by subject | - | 2 | - |

| | | | |
|--------------------------|---|---|---|
| Adverse event, non-fatal | 1 | - | - |
| Lost to follow-up | 1 | - | 4 |

Baseline characteristics

Reporting groups

| | |
|--|--------------------|
| Reporting group title | Placebo- 1st year |
| Reporting group description: Placebo. First year of follow-up. first cycle of treatment | |
| Reporting group title | Active 1-1st year |
| Reporting group description: Active IMP at low dose. First year of follow-up. first cycle of treatment | |
| Reporting group title | Active 2- 1st year |
| Reporting group description: Active IMP at high dose. First year of follow-up. first cycle of treatment | |

| Reporting group values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year |
|---------------------------|-------------------|-------------------|--------------------|
| Number of subjects | 56 | 44 | 53 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | 5 | 3 | 7 |
| Adults (18-64 years) | 51 | 41 | 46 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 31.7 | 33.5 | 30.6 |
| standard deviation | ± 10.5 | ± 10.8 | ± 11.1 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 32 | 21 | 27 |
| Male | 24 | 23 | 26 |

| Reporting group values | Total | | |
|---------------------------|-------|--|--|
| Number of subjects | 153 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | 15 | | |
| Adults (18-64 years) | 138 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 80 | | |
| Male | 73 | | |

Subject analysis sets

| | |
|----------------------------|---------------|
| Subject analysis set title | PP population |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Subjects completing the first year of follow-up according to protocol, no protocol violation related to the primary endpoint and a valid Symptom and medication questionnaire registered during the first peak pollen season

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | ITT Population |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

all randomized subjects receiving at least one dose of study drug

| Reporting group values | PP population | ITT Population | |
|---------------------------------------|---------------|----------------|--|
| Number of subjects | 109 | 148 | |
| Age categorical Units: Subjects | | | |
| Adolescents (12-17 years) | 12 | 15 | |
| Adults (18-64 years) | 97 | 133 | |
| Age continuous Units: years | | | |
| arithmetic mean | 31.8 | 32.0 | |
| standard deviation | ± 11.1 | ± 10.9 | |
| Gender categorical Units: Subjects | | | |
| Female | 60 | 80 | |
| Male | 49 | 68 | |

End points

End points reporting groups

| | |
|---|-----------------------------|
| Reporting group title | Placebo- 1st year |
| Reporting group description: Placebo. First year of follow-up. first cycle of treatment | |
| Reporting group title | Active 1-1st year |
| Reporting group description: Active IMP at low dose. First year of follow-up. first cycle of treatment | |
| Reporting group title | Active 2- 1st year |
| Reporting group description: Active IMP at high dose. First year of follow-up. first cycle of treatment | |
| Reporting group title | Placebo-Active 2 |
| Reporting group description: Active IMP at high doses during second year for patients initially receiving placebo during the first year | |
| Reporting group title | Active 1- 2nd year |
| Reporting group description: active IMP at low dose. Second year of follow-up. Second cycle of treatment | |
| Reporting group title | Active 2- 2nd year |
| Reporting group description: Active IMP at high dose. Second year of follow-up. Second cycle of treatment | |
| Subject analysis set title | PP population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Subjects completing the first year of follow-up according to protocol, no protocol violation related to the primary endpoint and a valid Symptom and medication questionnaire registered during the first peak pollen season | |
| Subject analysis set title | ITT Population |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: all randomized subjects receiving at least one dose of study drug | |

Primary: Combined symptom and medication score - First year- PP

| | |
|---|--|
| End point title | Combined symptom and medication score - First year- PP |
| End point description: The primary endpoint was calculated by (mean symptom score + mean symptomatic medication score) /2. Scale range: 0-3 Symptom score (ocular/nasal) registered during the pollen season by the patient for each of 7 symptoms evaluated on a 4-point scale: 0 corresponds to "no" symptoms, 1:"mild symptoms"; 2:"moderate" symptoms, 3:"severe" symptoms. Symptomatic medication score calculated individually according to type and doses of rescue medication recorded by the patient and ranging from 0 (no medication) to 24 (ocular and oral antihistamine + nasal and oral corticosteroid, all at maximum doses) and converted into a 0-3 scale range. PP population | |
| End point type | Primary |
| End point timeframe: Registered during the first pollen season (May-June) after the first year of treatment | |

| End point values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year | |
|--------------------------------------|-------------------|-------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 42 | 32 | 35 | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.65 (± 0.31) | 0.69 (± 0.37) | 0.50 (± 0.26) | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | combined score- first year- PP |
| Statistical analysis description: PP population | |
| Comparison groups | Active 2- 1st year v Placebo- 1st year |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.0203 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.29 |
| upper limit | -0.02 |
| Variability estimate | Standard deviation |

Notes:

[1] - The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|--|---------------------------------------|
| Statistical analysis title | combined score- first year- PP |
| Statistical analysis description: PP population | |
| Comparison groups | Active 1-1st year v Placebo- 1st year |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.6407 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.12 |
| upper limit | 0.19 |
| Variability estimate | Standard deviation |

Notes:

[2] - The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|---|--|
| Statistical analysis title | Combined score First year-PP |
| Statistical analysis description: | |
| PP population | |
| Comparison groups | Active 1-1st year v Active 2- 1st year |
| Number of subjects included in analysis | 67 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[3] |
| P-value | = 0.0174 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 0.35 |
| Variability estimate | Standard deviation |

Notes:

[3] - The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
Difference between both active treatments was not prespecified in the protocol but defined and analysed before unblinding.

Secondary: Combined symptom and medication score - First year- ITT

| | |
|--|---|
| End point title | Combined symptom and medication score - First year- ITT |
| End point description: | |
| The primary endpoint was calculated by (mean symptom score + mean symptomatic medication score) /2. Scale range: 0-3 | |
| Symptom score (ocular/nasal) registered during the pollen season by the patient for each of 7 symptoms evaluated on a 4-point scale: 0 corresponds to "no" symptoms, 1:"mild symptoms"; 2:"moderate" symptoms, 3:"severe" symptoms. Symptomatic medication score (4-point scale from 0 to 3) calculated individually according to type and doses of rescue medication recorded by the patient and ranging from 0 (no medication) to 24 (ocular and oral antihistamine + nasal and oral corticosteroid, all at maximum doses) and converted into a 0-3 scale. | |
| ITT population | |
| End point type | Secondary |
| End point timeframe: | |
| Registered during the first pollen season (May-June) after the first year of treatment | |

| End point values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year | |
|--------------------------------------|-------------------|-------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 42 | 32 | 37 | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.65 (± 0.31) | 0.69 (± 0.37) | 0.57 (± 0.42) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Combined score 1st year-ITT |
| Statistical analysis description: | |
| ITT population | |
| Comparison groups | Active 2- 1st year v Placebo- 1st year |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | = 0.3083 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.25 |
| upper limit | 0.08 |
| Variability estimate | Standard deviation |

Notes:

[4] - The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|---|---------------------------------------|
| Statistical analysis title | combined score- 1st year- ITT |
| Comparison groups | Active 1-1st year v Placebo- 1st year |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.6407 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.12 |
| upper limit | 0.19 |
| Variability estimate | Standard deviation |

Notes:

[5] - The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Combined score 1st year-ITT |
| Statistical analysis description: | |
| ITT population | |

| | |
|---|--|
| Comparison groups | Active 1-1st year v Active 2- 1st year |
| Number of subjects included in analysis | 69 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[6] |
| P-value | = 0.2101 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 0.31 |
| Variability estimate | Standard deviation |

Notes:

[6] - Analysis of the difference between active treatments was not predefined in the protocol but defined and analyzed before unblinding.

The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

Secondary: Combined symptom and medication score - 2nd year v 1st year- ITT

| | |
|-----------------|--|
| End point title | Combined symptom and medication score - 2nd year v 1st year- ITT |
|-----------------|--|

End point description:

evolution of the score over time was obtained by means of intragroup comparison. ITT population

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

End point timeframe:

Symptoms and medication score was registered during the first and second pollen season after entering into the study

| End point values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year | Placebo-Active 2 |
|--------------------------------------|-------------------|-------------------|--------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 42 | 32 | 37 | 40 |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.65 (± 0.31) | 0.69 (± 0.37) | 0.57 (± 0.42) | 0.46 (± 0.3) |

| End point values | Active 1- 2nd year | Active 2- 2nd year | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 37 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.54 (± 0.29) | 0.61 (± 0.47) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | combined score- 2nd year vs first year |
| Comparison groups | Placebo-Active 2 v Placebo- 1st year |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | = 0.0003 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | -0.09 |
| Variability estimate | Standard deviation |

Notes:

[7] - Difference in means between first and second period was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|---|--|
| Statistical analysis title | Combined score 2nd years v first year |
| Comparison groups | Active 1- 2nd year v Active 1-1st year |
| Number of subjects included in analysis | 64 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| P-value | = 0.0083 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | -0.04 |
| Variability estimate | Standard deviation |

Notes:

[8] - Difference in means between periods was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|---|---|
| Statistical analysis title | combined score- 2nd year vs first year |
| Statistical analysis description: | |
| ITT population | |
| Comparison groups | Active 2- 2nd year v Active 2- 1st year |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| P-value | = 0.9532 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.13 |
| upper limit | 0.12 |
| Variability estimate | Standard deviation |

Notes:

[9] - Difference in means between periods was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

Secondary: Allergen concentration eliciting a positive Conjunctival challenge test: change from baseline

| | |
|-----------------|---|
| End point title | Allergen concentration eliciting a positive Conjunctival challenge test: change from baseline |
|-----------------|---|

End point description:

The test was performed by applying a single drop of allergen solution directly into the conjunctival sac of the eye followed by observation for allergic symptoms (i.e. redness, itchiness). The allergen was applied at increasing concentrations administered at 10-minute intervals until reaching the maximum concentration or a positive result, whatever happened first.

An increase in the concentration eliciting a positive result indicates a better tolerance to the allergen exposure.

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

End point timeframe:

at baseline and after the first and second pollen season

| End point values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year | Placebo-Active 2 |
|--------------------------------------|-------------------|-------------------|--------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 51 | 37 | 48 | 48 |
| Units: µg/ml | | | | |
| arithmetic mean (standard deviation) | 17.14 (± 56.79) | 152.59 (± 494.59) | 269.91 (± 674.96) | 365.52 (± 770.75) |

| End point values | Active 1- 2nd year | Active 2- 2nd year | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 43 | | |
| Units: µg/ml | | | | |
| arithmetic mean (standard deviation) | 318.84 (± 720.23) | 404.75 (± 758.16) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | conjunctival challenge test- first year |
|----------------------------|---|

Statistical analysis description:

ITT population. Change from baseline after first year of treatment

| | |
|-------------------|---------------------------------------|
| Comparison groups | Active 1-1st year v Placebo- 1st year |
|-------------------|---------------------------------------|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| P-value | = 0.1058 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 135.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.13 |
| upper limit | 301.04 |
| Variability estimate | Standard deviation |

Notes:

[10] - Mean difference between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
an increase in the concentration eliciting a positive test indicates a better tolerance to the allergen exposure

| | |
|-----------------------------------|---|
| Statistical analysis title | conjunctival challenge test- first year |
|-----------------------------------|---|

Statistical analysis description:

ITT population. Change from baseline after first year of treatment.

| | |
|---|--|
| Comparison groups | Active 2- 1st year v Placebo- 1st year |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| P-value | = 0.0128 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 252.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 56.19 |
| upper limit | 449.34 |
| Variability estimate | Standard deviation |

Notes:

[11] - Mean difference between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
an increase in the concentration eliciting a positive test indicates a better tolerance to the allergen exposure

| | |
|-----------------------------------|---|
| Statistical analysis title | conjunctival challenge test- first year |
|-----------------------------------|---|

Statistical analysis description:

ITT population. Change from baseline after the first year of treatment

| | |
|---|--|
| Comparison groups | Active 1-1st year v Active 2- 1st year |
| Number of subjects included in analysis | 85 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[12] |
| P-value | = 0.3767 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | -117.31 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -379.86 |
| upper limit | 145.24 |
| Variability estimate | Standard deviation |

Notes:

[12] - Mean difference between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

Difference between both active treatment was not pre-especified in the protocol but it was analysed before unblinding.

An increase in the concentration eliciting a positive test indicates a better tolerance to the allergen exposure

| | |
|-----------------------------------|--|
| Statistical analysis title | conjunctival challenge test- second year |
|-----------------------------------|--|

Statistical analysis description:

ITT population. Change from baseline after second year of treatment

| | |
|---|---|
| Comparison groups | Active 1- 2nd year v Active 2- 2nd year |
| Number of subjects included in analysis | 78 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[13] |
| P-value | = 0.6123 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | -85.9 |

Confidence interval

| | |
|----------------------|--------------------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -422.08 |
| upper limit | 250.27 |
| Variability estimate | Standard deviation |

Notes:

[13] - Mean difference between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

Difference between both active treatment was not pre-especified in the protocol but defined and analysed before unblinding

an increase in the concentration eliciting a positive test indicates a better tolerance to the allergen exposure

| | |
|-----------------------------------|--|
| Statistical analysis title | conjunctival challenge test- second year |
|-----------------------------------|--|

Statistical analysis description:

ITT population. Change from baseline after second year of treatment.

Placebo group was receiving active treatment during the 2nd year. This is an intragroup comparison. Change from baseline after first (placebo period) and second year(Active treatment) of follow-up was compared.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo-Active 2 v Placebo- 1st year |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[14] |
| P-value | = 0.0019 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 365.52 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 141.72 |
| upper limit | 589.32 |
| Variability estimate | Standard deviation |

Notes:

[14] - Difference in means between 2 periods of the placebo group was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference an increase in the concentration eliciting a positive test indicates a better tolerance to the allergen exposure

Secondary: Rhinoconjunctivitis symptoms score- PP

| | |
|-----------------|--|
| End point title | Rhinoconjunctivitis symptoms score- PP |
|-----------------|--|

End point description:

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

End point timeframe:

measured during the first and second pollen season (May-June) after starting IT with the IMP.

| End point values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year | Placebo-Active 2 |
|--------------------------------------|-------------------|-------------------|--------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 42 | 32 | 35 | 37 |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.85 (± 0.43) | 0.90 (± 0.49) | 0.75 (± 0.43) | 0.63 (± 0.40) |

| End point values | Active 1- 2nd year | Active 2- 2nd year | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 30 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.82 (± 0.45) | 0.81 (± 0.53) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Symptoms score- intergroup-first year-PP |
|----------------------------|--|

Statistical analysis description:

PP population

| | |
|-------------------|---------------------------------------|
| Comparison groups | Active 1-1st year v Placebo- 1st year |
|-------------------|---------------------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| P-value | = 0.6772 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.17 |
| upper limit | 0.26 |
| Variability estimate | Standard deviation |

Notes:

[15] - The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|---|---|
| Statistical analysis title | Symptoms score- intergroup- first year PP |
| Statistical analysis description: | |
| PP population | |
| Comparison groups | Active 2- 1st year v Placebo- 1st year |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[16] |
| P-value | = 0.2867 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.09 |
| Variability estimate | Standard deviation |

Notes:

[16] - The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|---|--|
| Statistical analysis title | Symptoms score- intergroup-first year-PP |
| Statistical analysis description: | |
| PP population | |
| Comparison groups | Active 2- 1st year v Active 1-1st year |
| Number of subjects included in analysis | 67 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[17] |
| P-value | = 0.1876 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.15 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 0.38 |
| Variability estimate | Standard deviation |

Notes:

[17] - The difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference. Difference between active treatments was not pre-specified in the protocol but was defined and analysed before unblinding

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Symptoms score- intragroup-PP |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Follow-up PP population: Second year v First year

| | |
|---|--|
| Comparison groups | Active 1- 2nd year v Active 1-1st year |
| Number of subjects included in analysis | 60 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[18] |
| P-value | = 0.1404 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.1 |

Confidence interval

| | |
|----------------------|--------------------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | 0.03 |
| Variability estimate | Standard deviation |

Notes:

[18] - Difference in means between two periods was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference.

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Symptoms score- intragroup-PP |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Follow-up PP population: Second year v First year

| | |
|---|---|
| Comparison groups | Active 2- 2nd year v Active 2- 1st year |
| Number of subjects included in analysis | 65 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[19] |
| P-value | = 0.6265 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.05 |

Confidence interval

| | |
|----------------------|--------------------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 0.24 |
| Variability estimate | Standard deviation |

Notes:

[19] - Difference in means between two periods was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference.

| | |
|---|--------------------------------------|
| Statistical analysis title | Symptoms score- intragroup-PP |
| Statistical analysis description: | |
| Follow-up PP population: Second year v First year | |
| Comparison groups | Placebo-Active 2 v Placebo- 1st year |
| Number of subjects included in analysis | 79 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[20] |
| P-value | = 0.0016 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.36 |
| upper limit | -0.09 |
| Variability estimate | Standard deviation |

Notes:

[20] - Difference in means between periods was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference.

Secondary: Medication consumption score-PP

| | |
|---|---------------------------------|
| End point title | Medication consumption score-PP |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| measured during the first and second pollen season (May-June) after starting IT with the IMP. | |

| End point values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year | Placebo-Active 2 |
|--------------------------------------|-------------------|-------------------|--------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 42 | 32 | 35 | 37 |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.45 (± 0.34) | 0.48 (± 0.41) | 0.24 (± 0.21) | 0.28 (± 0.25) |

| End point values | Active 1- 2nd year | Active 2- 2nd year | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 30 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.26 (± 0.25) | 0.24 (± 0.24) | | |

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Medication score- Intergroup-PP |
| Statistical analysis description: PP population first year | |
| Comparison groups | Active 1-1st year v Placebo- 1st year |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| P-value | = 0.7411 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 0.2 |
| Variability estimate | Standard deviation |

Notes:

[21] - Difference in mean between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference.

| | |
|---|--|
| Statistical analysis title | Medication score- Intergroup-PP |
| Statistical analysis description: PP population first year | |
| Comparison groups | Active 2- 1st year v Placebo- 1st year |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[22] |
| P-value | = 0.0018 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | -0.08 |
| Variability estimate | Standard deviation |

Notes:

[22] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference.

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Medication score- Intergroup-PP |
|-----------------------------------|---------------------------------|

| | |
|---|--|
| Statistical analysis description: | |
| PP populatin first year | |
| Comparison groups | Active 2- 1st year v Active 1-1st year |
| Number of subjects included in analysis | 67 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[23] |
| P-value | = 0.0058 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.07 |
| upper limit | 0.4 |
| Variability estimate | Standard deviation |

Notes:

[23] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference. Difference between active treatments was no pre-specified in the protocol but defined and analysed unblinding

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Medication score- Intragroup-PP |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Follow-up PP population: second year v First year

| | |
|---|--|
| Comparison groups | Active 1- 2nd year v Active 1-1st year |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[24] |
| P-value | = 0.0009 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | -0.08 |
| Variability estimate | Standard deviation |

Notes:

[24] - Difference in means between two periods was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference.

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Medication score- Intragroup-PP |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Follow-up PP population: second year v First year

| | |
|-------------------|---|
| Comparison groups | Active 2- 2nd year v Active 2- 1st year |
|-------------------|---|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| P-value | = 0.8967 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.11 |
| upper limit | 0.1 |
| Variability estimate | Standard deviation |

Notes:

[25] - Difference in means between two periods was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference.

| | |
|---|--------------------------------------|
| Statistical analysis title | Medication score- Intragroup-PP |
| Statistical analysis description: | |
| Follow-up PP population: second year v First year | |
| Comparison groups | Placebo-Active 2 v Placebo- 1st year |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[26] |
| P-value | = 0.0111 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | -0.03 |
| Variability estimate | Standard deviation |

Notes:

[26] - Difference in means between two periods was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference.

Secondary: Serum Specific IgE antibodies- Phleum Pratense- Change from baseline

| | |
|-----------------|--|
| End point title | Serum Specific IgE antibodies- Phleum Pratense- Change from baseline |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline, preseasonally after first year of IMP administration and preseasonally after second year of IMP administration

| End point values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year | Placebo-Active 2 |
|--------------------------------------|-------------------|-------------------|--------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 38 | 48 | 47 |
| Units: kU/L | | | | |
| arithmetic mean (standard deviation) | 2.38 (± 12.72) | 2.37 (± 10.46) | 2.01 (± 10.43) | -1.78 (± 15.89) |

| End point values | Active 1- 2nd year | Active 2- 2nd year | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 46 | | |
| Units: kU/L | | | | |
| arithmetic mean (standard deviation) | -2.29 (± 6.96) | -2.89 (± 8.98) | | |

Statistical analyses

| Statistical analysis title | sIgE-Phleum pratense- first year |
|--|---------------------------------------|
| Statistical analysis description: ITT population. Change from baseline after first year of treatment. | |
| Comparison groups | Active 1-1st year v Placebo- 1st year |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[27] |
| P-value | = 0.9948 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.08 |
| upper limit | 5.05 |
| Variability estimate | Standard deviation |

Notes:

[27] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| Statistical analysis title | sIgE-Phleum pratense- first year- |
|--|--|
| Statistical analysis description: ITT population. Change from baseline after first year of treatment. | |
| Comparison groups | Active 2- 1st year v Placebo- 1st year |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[28] |
| P-value | = 0.8752 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.07 |
| upper limit | 4.32 |
| Variability estimate | Standard deviation |

Notes:

[28] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|--|--|
| Statistical analysis title | sIgE-Phleum pratense- first year |
| Statistical analysis description: ITT population. Change from baseline after first year of treatment. | |
| Comparison groups | Active 1-1st year v Active 2- 1st year |
| Number of subjects included in analysis | 86 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[29] |
| P-value | = 0.36 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.15 |
| upper limit | 4.87 |
| Variability estimate | Standard deviation |

Notes:

[29] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
Difference between both active treatments was not pre-especified in the protocol but it was analysed before unblinding.

| | |
|--|--------------------------------------|
| Statistical analysis title | sIgE-Phleum pratense- 2nd year |
| Statistical analysis description: ITT population. Change from baseline after second year of treatment. Placebo group was receiving active treatment during the 2nd year. Placebo group was receiving active treatment during the 2nd year. This is an intragroup comparison. Change from baseline after first (placebo period) and second year(Active treatment) of follow-up was compared. | |
| Comparison groups | Placebo-Active 2 v Placebo- 1st year |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[30] |
| P-value | = 0.4476 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.44 |
| upper limit | 2.89 |
| Variability estimate | Standard deviation |

Notes:

[30] - Difference in means between 2 periods of the placebo group was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|---|---|
| Statistical analysis title | sIgE-Phleum pratense- 2nd year |
| Statistical analysis description: ITT population. Change from baseline after second year of treatment. | |
| Comparison groups | Active 1- 2nd year v Active 2- 2nd year |
| Number of subjects included in analysis | 82 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[31] |
| P-value | = 0.7448 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.02 |
| upper limit | 4.21 |
| Variability estimate | Standard deviation |

Notes:

[31] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
Difference between both active treatments was not pre-especified in the protocol but it was defined and analysed before unblinding.

Secondary: Serum specific IgG4-Phleum pratense- change from baseline

| | |
|--|---|
| End point title | Serum specific IgG4-Phleum pratense- change from baseline |
| End point description: ITT population | |
| End point type | Secondary |
| End point timeframe: Baseline, preseasonally after first year of IMP administration and preseasonally after second year of IMP administration | |

| End point values | Placebo- 1st year | Active 1-1st year | Active 2- 1st year | Placebo-Active 2 |
|--------------------------------------|-------------------|-------------------|--------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 38 | 48 | 47 |
| Units: µg/ml | | | | |
| arithmetic mean (standard deviation) | 0.03 (± 0.11) | 0.01 (± 0.09) | -0.00 (± 0.11) | 0.01 (± 0.25) |

| End point values | Active 1- 2nd year | Active 2- 2nd year | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 46 | | |
| Units: µg/ml | | | | |
| arithmetic mean (standard deviation) | -0.02 (± 0.17) | -0.05 (± 0.19) | | |

Statistical analyses

| Statistical analysis title | sIgG4-Phleum pratense- first year |
|--|---------------------------------------|
| Statistical analysis description: ITT population. Change from baseline after first year of treatment. | |
| Comparison groups | Placebo- 1st year v Active 1-1st year |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[32] |
| P-value | = 0.448 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.06 |
| upper limit | 0.03 |
| Variability estimate | Standard deviation |

Notes:

[32] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| Statistical analysis title | sIgG4-Phleum pratense- first year |
|--|--|
| Statistical analysis description: ITT population. Change from baseline after first year of treatment. | |
| Comparison groups | Active 2- 1st year v Placebo- 1st year |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[33] |
| P-value | = 0.1566 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 0.01 |
| Variability estimate | Standard deviation |

Notes:

[33] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|--|--|
| Statistical analysis title | sIgG4-Phleum pratense- first year |
| Statistical analysis description: ITT population. Change from baseline after first year of treatment. | |
| Comparison groups | Active 2- 1st year v Active 1-1st year |
| Number of subjects included in analysis | 86 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[34] |
| P-value | = 0.5068 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.06 |
| Variability estimate | Standard deviation |

Notes:

[34] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
Difference between both active treatments was not pre-especified in the protocol but it was analysed before unblinding.

| | |
|--|--------------------------------------|
| Statistical analysis title | sIgG4-Phleum pratense- 2nd year |
| Statistical analysis description: ITT population. Change from baseline after second year of treatment. Placebo group was receiving active treatment during the 2nd year. Change from baseline after first (placebo period) and second year(Active treatment) of follow-up was compared. | |
| Comparison groups | Placebo-Active 2 v Placebo- 1st year |
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[35] |
| P-value | = 0.8443 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.01 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 0.08 |
| Variability estimate | Standard deviation |

Notes:

[35] - Difference in means between both periods of the placebo group was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | sIgG4-Phleum pratense- 2nd year |
|-----------------------------------|---------------------------------|

Statistical analysis description:

ITT population. Change from baseline after second year of treatment.

| | |
|---|---|
| Comparison groups | Active 1- 2nd year v Active 2- 2nd year |
| Number of subjects included in analysis | 82 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[36] |
| P-value | = 0.4724 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.11 |
| Variability estimate | Standard deviation |

Notes:

[36] - Difference in means between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
Difference between both active treatments was not pre-especified in the protocol but it was analysed before unblinding.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Although IMP was administered preseasonally for 6 weeks in each period (total IMP exposure 12 weeks during the study), adverse events were reported during the whole study period until last assessment visit (around 20 months from the first treatment visit)

Adverse event reporting additional description:

The occurrence of adverse events was to be sought by non-directive questioning of the patient at each visit during the clinical trial. Adverse events also could have been detected when they were volunteered by the patient during or between visits or through physical examination or other assessments.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Active 1- Year 1 |
|-----------------------|------------------|

Reporting group description:

Low dose of Active IMP during the first period of assessment

| | |
|-----------------------|------------------|
| Reporting group title | Active 2- year 1 |
|-----------------------|------------------|

Reporting group description:

High dose of Active IMP during the first period of assessment

| | |
|-----------------------|------------------|
| Reporting group title | Placebo - year 1 |
|-----------------------|------------------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | Active 1- Year 2 |
|-----------------------|------------------|

Reporting group description:

low dose of active IMP during the second year of assessment

| | |
|-----------------------|------------------|
| Reporting group title | Active 2- year 2 |
|-----------------------|------------------|

Reporting group description:

High dose of active IMP during the second year of assessment

| | |
|-----------------------|--------------------------|
| Reporting group title | Placebo-Active 2- year 2 |
|-----------------------|--------------------------|

Reporting group description:

Group initially assigned to placebo arm for the first year but switching to Active 2 (high dose of active IMP) for the second year

| Serious adverse events | Active 1- Year 1 | Active 2- year 1 | Placebo - year 1 |
|---|---|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 53 (0.00%) | 0 / 53 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | Additional description: mild urticaria resolved spontaneously in less than 2 days. this SAE was not related to the study drug | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 53 (0.00%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Active 1- Year 2 | Active 2- year 2 | Placebo-Active 2- year 2 |
|---|---|------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 47 (0.00%) | 0 / 51 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | Additional description: mild urticaria resolved spontaneously in less than 2 days. this SAE was not related to the study drug | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 47 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Active 1- Year 1 | Active 2- year 1 | Placebo - year 1 |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 42 (30.95%) | 19 / 53 (35.85%) | 15 / 53 (28.30%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 53 (1.89%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Administration site pruritus | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 6 / 53 (11.32%) | 0 / 53 (0.00%) |
| occurrences (all) | 3 | 7 | 0 |
| Administration site erythema | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 53 (5.66%) | 0 / 53 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Local reaction | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 53 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Eye pruritus | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 53 (0.00%) | 2 / 53 (3.77%) |
| occurrences (all) | 0 | 0 | 2 |
| Conjunctivitis allergic | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 1 / 53 (1.89%) 1 | 0 / 53 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 53 (1.89%) | 5 / 53 (9.43%) |
| occurrences (all) | 0 | 1 | 5 |
| Nasal pruritus | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 53 (0.00%) | 2 / 53 (3.77%) |
| occurrences (all) | 0 | 0 | 2 |
| Catarrh | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 53 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 1 | 0 | 1 |
| Sneezing | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 53 (1.89%) | 2 / 53 (3.77%) |
| occurrences (all) | 0 | 1 | 2 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 53 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 53 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 4 / 53 (7.55%) | 2 / 53 (3.77%) |
| occurrences (all) | 1 | 5 | 2 |

| Non-serious adverse events | Active 1- Year 2 | Active 2- year 2 | Placebo-Active 2- year 2 |
|---|------------------|------------------|-----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 37 (35.14%) | 20 / 47 (42.55%) | 24 / 51 (47.06%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 1 / 47 (2.13%) | 4 / 51 (7.84%) |
| occurrences (all) | 3 | 2 | 6 |
| General disorders and administration site conditions | | | |

| | | | |
|--|---------------------|-----------------------|-----------------------|
| Administration site pruritus subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 6 | 7 / 47 (14.89%) 12 | 6 / 51 (11.76%) 16 |
| Administration site erythema subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 5 | 2 / 47 (4.26%) 2 | 1 / 51 (1.96%) 1 |
| Local reaction subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 2 / 47 (4.26%) 2 | 1 / 51 (1.96%) 1 |
| Eye disorders | | | |
| Eye pruritus subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 47 (0.00%) 0 | 5 / 51 (9.80%) 5 |
| Conjunctivitis allergic subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 1 / 47 (2.13%) 1 | 3 / 51 (5.88%) 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 47 (0.00%) 0 | 1 / 51 (1.96%) 1 |
| Nasal pruritus subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 47 (0.00%) 0 | 3 / 51 (5.88%) 3 |
| Catarrh subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 3 / 47 (6.38%) 3 | 5 / 51 (9.80%) 5 |
| Sneezing subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 47 (0.00%) 0 | 4 / 51 (7.84%) 4 |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 47 (0.00%) 0 | 3 / 51 (5.88%) 3 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 1 / 47 (2.13%) 1 | 4 / 51 (7.84%) 5 |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 47 (0.00%) 0 | 1 / 51 (1.96%) 1 |
|--|-------------------------|-------------------------|-------------------------|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 23 June 2015 | Increase in the number of participant sites |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported