# Clinical trial results:
# A multicentre randomised placebo-controlled double-blind clinical trial for evaluation of the optimal dose for safety and efficacy of specific immunotherapy with an aluminium hydroxide-adsorbed Allergoid preparation of house dust mite (Dermatophagoides pteronyssinus) in patients with controlled allergic bronchial asthma and rhinitis/rhinoconjunctivitis

## Summary

| | |
|---|---|
| EudraCT number | 2011-002248-29 |
| Trial protocol | PL ES |
| Global end of trial date | 02 April 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 November 2017 |
| First version publication date | 29 November 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | AL1009ac |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | ALLERGOPHARMA GMBH & CO. KG. |
| Sponsor organisation address | Hermann-Körner-Straße 52, Reinbek, Germany, 21465 |
| Public contact | Clinical Trials Information, Allergopharma GmbH & Co. KG, 0049 40427650, |
| Scientific contact | Clinical Trials Information, Allergopharma GmbH & Co. KG, 0049 40427650, |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 26 November 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 02 April 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Evaluate the optimal dose for efficacy and tolerability of specific immunotherapy with an aluminium hydroxide-adsorbed allergoid preparation of major allergens of D. pteronyssinus in patients with controlled allergic asthma (acc. to GINA 2006) and allergic rhinoconjunctivitis, caused by house dust mite.

This trial consisted of 2 parts:
i) intracutaneous test (ICT), which is briefly summarized
ii) dose range finding (DRF), which is presented in detail

In the ICT part, patients (N=21 randomised, N=16 FAS) received an injection of 5000, 2500, and 500 SBE/mL of allergen extracts from D. pteronyssinus; each concentration was assessed after 2, 4, 6, and 8h to determine the appropriate wheal size swelling area and the read-off time for efficacy evaluation during the DRF part. For further investigations, the chosen concentration was 5000 SBE/mL, assessed after 6 h.

ICT=Intracutaneous test
DRF=Dose range finding
FAS=Full analysis set
SBE=Standardized biological unit

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki (October 2000 and following amendments), Good Clinical Practices guidelines, and local legal requirements. Other than routine care, no specific measures were implemented for the protection of trial subjects.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 May 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 151 |
| Country: Number of subjects enrolled | Spain: 16 |
| Worldwide total number of subjects | 167 |
| EEA total number of subjects | 167 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 167 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Overall, 413 subjects were screened for eligibility. Of these, 167 subjects were randomised to treatment according to the exclusion and inclusion criteria: 21 patients were recruited into the ICT part and further 146 patients were recruited into the dose DRF part of the study; those participating in the ICT were not eligible for the DRF part.

### Pre-assignment

Screening details:

Subjects were screened and randomised to treatment according to the exclusion and inclusion criteria.

### Period 1

| | |
|---|---|
| Period 1 title | Dose range finding (DRF) (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 |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description: -

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo: solution containing aluminium hydroxide (Al(OH)3) in normal saline (9 g/L sodium chloride) was applied.

Injection volume (0.1 mL at minimum 1.0 mL at maximum for matching Strength A placebo and 0.6 - 1.0 mL strength B placebo) was matching the volume of the corresponding active preparation.

The injections were administered slowly, strictly subcutaneously, under sterile precautionary measures, on the extensor side of the upper arm, a hand’s breadth above the elbow, using a short-ground cannula. After each administration at the trial center, the patient was kept under close supervision for at least 30 minutes.

| | |
|---|---|
| **Arm title** | 600 PNU |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | D. pteronyssinus allergoid preparation 600 PNU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

D. pteronyssinus allergoid preparation 600 PNU

For the injection volume and administration details of the active treatment, please see the description above for Placebo.

PNU=Protein nitrogen unit

| **Arm title** | 1800 PNU |
|---|---|
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | D. pteronyssinus allergoid preparation 1800 PNU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

D. pteronyssinus allergoid preparation 1800 PNU

For the injection volume and administration details of the active treatment, please see the description above for Placebo.

PNU=Protein nitrogen unit

| **Arm title** | 3000 PNU |
|---|---|
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | D. pteronyssinus allergoid preparation 3000 PNU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

D. pteronyssinus allergoid preparation 3000 PNU

For the injection volume and administration details of the active treatment, please see the description above for Placebo.

PNU=Protein nitrogen unit

| **Arm title** | 5400 PNU |
|---|---|
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | D. pteronyssinus allergoid preparation 5400 PNU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

D. pteronyssinus allergoid preparation 5400 PNU

For the injection volume and administration details of the active treatment, please see the description above for Placebo.

PNU=Protein nitrogen unit

| **Number of subjects in period 1[1]** | Placebo | 600 PNU | 1800 PNU |
|---|---|---|---|
| Started | 32 | 24 | 31 |
| Completed | 29 | 24 | 29 |
| Not completed | 3 | 0 | 2 |
| Consent withdrawn by subject | 1 | - | 2 |
| Adverse event, non-fatal | 1 | - | - |
| Pregnancy | - | - | - |
| Lost to follow-up | 1 | - | - |

| **Number of subjects in period 1[1]** | 3000 PNU | 5400 PNU |
|---|---|---|
| Started | 28 | 31 |
| Completed | 25 | 26 |
| Not completed | 3 | 5 |
| Consent withdrawn by subject | 3 | 1 |
| Adverse event, non-fatal | - | - |
| Pregnancy | - | 3 |
| Lost to follow-up | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: This study was performed as 2 independent parts i.e. ICT and DRF. The number of randomised subjects was 21 in the ICT part and 146 in the DRF part. Subjects could participate either in the ICT or in the DRF part, but not both.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | 600 PNU |
| Reporting group description: - | |
| Reporting group title | 1800 PNU |
| Reporting group description: - | |
| Reporting group title | 3000 PNU |
| Reporting group description: - | |
| Reporting group title | 5400 PNU |
| Reporting group description: - | |

| Reporting group values | Placebo | 600 PNU | 1800 PNU |
|---|---|---|---|
| Number of subjects | 32 | 24 | 31 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 32 | 24 | 31 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 28.3 | 25.4 | 27.5 |
| standard deviation | ± 7.5 | ± 5 | ± 7.3 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 21 | 12 | 14 |
| Male | 11 | 12 | 17 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 1 |
| White | 32 | 24 | 30 |

| Reporting group values | 3000 PNU | 5400 PNU | Total |
|---|---|---|---|
| Number of subjects | 28 | 31 | 146 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 28 | 31 | 146 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 27.9 | 28 | |
| standard deviation | ± 6.7 | ± 7 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 12 | 11 | 70 |
| Male | 16 | 20 | 76 |

| Race<br>Units: Subjects | | | |
|---|---|---|---|
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 0 | 0 | 1 |
| White | 28 | 30 | 144 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | 600 PNU |
| Reporting group description: - | |
| Reporting group title | 1800 PNU |
| Reporting group description: - | |
| Reporting group title | 3000 PNU |
| Reporting group description: - | |
| Reporting group title | 5400 PNU |
| Reporting group description: - | |

### Primary: 1_Absolute change of the swelling area at 6h -- Late phase reaction (LPR)

| | |
|---|---|
| End point title | 1_Absolute change of the swelling area at 6h -- Late phase reaction (LPR) |

End point description:

Change to baseline: Final Visit - Baseline
Swelling area (cm²) of the LPR (6h) including change of swelling area (cm²) of the LPR (6h) after ICT.

Measurement of the absolute change of the swelling area (in cm2) of the LPR, 6 h after ICT with a solution of of placebo or the mite allergoid preparation of the major allergens of D. pteronyssinus, from baseline (Visit S4) to the measurement after 1 year of treatment (Visit T17).

Data collected were recorded in an electronic case report form completed by the study sites staff. ICT data of Visit S4 and of Visit T17 (area and volume of the immediate reaction after 20 minutes and the LPR after 6 hours) were captured by using the optical device Primos 3D. For the quantitative evaluation of this data, a specific analytical software was used; the results of these evaluations were transferred to the clinical database.

ICT=Intracutaneous testing
LPR=Late phase reaction

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Baseline (S4), after 1 year of treatment (T17).

S1 = Day 0
S4 = 32 weeks after S1
T1 (randomization) = 52 weeks (1 year) after S1
T17 =36 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 27[1] | 23 | 27 | 24 |
| Units: cm2 | | | | |
| least squares mean (confidence interval 95%) | -6.41 (-10.96 to -1.87) | 7.98 (3.17 to 12.8) | 6.3 (1.83 to 10.78) | 10.83 (6.04 to 15.61) |

Notes:

[1] - Full analysis set, for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: cm2 | | | | |
| least squares mean (confidence interval 95%) | 8.64 (4.11 to 13.17) | | | |

## Statistical analyses

| **Statistical analysis title** | 1_Placebo vs 600 PNU |
|---|---|

Statistical analysis description:

To assess treatment differences, an analysis of covariance (ANCOVA) model was used with the change of the swelling area (visit S4 baseline – visit T17 end of treatment) as the dependent variable, treatment and center as fixed effect, and the size of the baseline swelling area (visit S4) as covariable.

| Comparison groups | Placebo v 600 PNU |
|---|---|
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | < 0.0001 [3] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -14.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.92 |
| upper limit | -7.86 |

Notes:

[2] - ANCOVA for change of the swelling area [cm2] of late phase reaction (after 6h), including variable center.
LS Mean: least square mean estimated from analysis of covariance including the baseline value as covariate and treatment group as fixed effect.
[3] - F-test

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|

Statistical analysis description:

Please see description above for the statistical analysis item 1_Placebo vs 600 PNU.

| Comparison groups | Placebo v 1800 PNU |
|---|---|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.0001 [5] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -12.72 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19 |
| upper limit | -6.43 |

Notes:

[4] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[5] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|

Statistical analysis description:

Please see description above for the statistical analysis item 1_Placebo vs 600 PNU.

| | |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[6] |
| P-value | < 0.0001 [7] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -17.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.69 |
| upper limit | -10.8 |

Notes:

[6] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[7] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|

Statistical analysis description:

Please see description above for the statistical analysis item 1_Placebo vs 600 PNU.

| | |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[8] |
| P-value | < 0.0001 [9] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -15.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.37 |
| upper limit | -8.74 |

Notes:

[8] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[9] - F-test

| **Statistical analysis title** | 5_600 PNU vs 5400 PNU |
|---|---|

Statistical analysis description:

Please see description above for the statistical analysis item 1_Placebo vs 600 PNU.

| | |
|---|---|
| Comparison groups | 600 PNU v 5400 PNU |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[10] |
| P-value | = 0.8421 [11] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.21 |
| upper limit | 5.89 |

Notes:

[10] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[11] - F-test

| **Statistical analysis title** | 6_600 PNU vs 3000 PNU |
|---|---|

Statistical analysis description:

600 PNU vs 3000 PNU

To assess differences between treatment groups, an analysis of covariance (ANCOVA) model was used with the change of the swelling area (visit S4 baseline – visit T17 end of treatment), as the dependent variable, treatment and center as fixed effect, and the size of the baseline swelling area (visit S4) as covariable.

| | |
|---|---|
| Comparison groups | 600 PNU v 3000 PNU |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.4031 [13] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -2.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.57 |
| upper limit | 3.87 |

Notes:

[12] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[13] - F-test

| **Statistical analysis title** | 7_600 PNU vs 1800 PNU |
|---|---|

Statistical analysis description:

600 PNU vs 1800 PNU

Please see description above for the statistical analysis item 6_600 PNU vs 3000 PNU.

| | |
|---|---|
| Comparison groups | 600 PNU v 1800 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[14] |
| P-value | = 0.6098 [15] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -1.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.81 |
| upper limit | 8.16 |

Notes:

[14] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[15] - F-test

| **Statistical analysis title** | 8_1800 PNU vs 5400 PNU |
|---|---|

Statistical analysis description:

1800 PNU vs 5400 PNU

Please see description above for the statistical analysis item 6_600 PNU vs 3000 PNU.

| | |
|---|---|
| Comparison groups | 1800 PNU v 5400 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[16] |
| P-value | = 0.4648 [17] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -2.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.65 |
| upper limit | 3.97 |

Notes:

[16] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[17] - F-test

| **Statistical analysis title** | 9_1800 PNU vs 3000 PNU |
|---|---|

Statistical analysis description:

1800 PNU vs 3000 PNU

Please see description above for the statistical analysis item 6_600 PNU vs 3000 PNU.

| | |
|---|---|
| Comparison groups | 1800 PNU v 3000 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[18] |
| P-value | = 0.1673 [19] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -4.52 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.97 |
| upper limit | 1.92 |

Notes:

[18] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[19] - F-test

| **Statistical analysis title** | 10_3000 PNU vs 5400 PNU |
|---|---|

Statistical analysis description:

3000 PNU vs 5400 PNU

Please see description above for the statistical analysis item 6_600 PNU vs 3000 PNU.

| | |
|---|---|
| Comparison groups | 3000 PNU v 5400 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[20] |
| P-value | = 0.5124 [21] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | 2.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.41 |
| upper limit | 8.78 |

Notes:

[20] - For the statistical analysis, please see description above item 1_Placebo vs 600 PNU.

[21] - F-test

## Primary: 2_Responder analysis for the primary endpoint

| End point title | 2_Responder analysis for the primary endpoint |
|---|---|

End point description:

Change to baseline: Final Visit - Baseline

Two criteria for responder analysis were evaluated:
- Patients were defined as responders if the LPR (area in cm2) at 6 h for ICT was reduced by at least 50% between baseline and after treatment.
- Patients were defined as responders if the LPR (area in cm2) at 6 h for ICT was reduced by at least 30% between baseline and after treatment.

Statistical analysis is shown below for the comparison of placebo vs active dose treatment group. For the comparisons between active dose treatment groups, no statistically significant results were observed (data are not shown).

LPR=Late phase reaction

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (S4), after 1 year of treatment (T17).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T17=36 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 27[22] | 23 | 27 | 24 |
| Units: subject | | | | |
| Improvement at least 50% | 2 | 10 | 7 | 11 |
| Improvement at least 30% | 4 | 13 | 15 | 16 |

Notes:

[22] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: subject | | | | |
| Improvement at least 50% | 10 | | | |
| Improvement at least 30% | 17 | | | |

**Statistical analyses**

| Statistical analysis title | 1_Placebo vs 600 PNU - reduction of 50 % |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0029 |
| Method | Chi-squared |

| Statistical analysis title | 2_Placebo vs 1800 PNU - reduction of 50 % |
|---|---|
| Comparison groups | Placebo v 1800 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0679 |
| Method | Chi-squared |

| Statistical analysis title | 3_Placebo vs 3000 PNU - reduction of 50 % |
|---|---|
| Comparison groups | Placebo v 3000 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0017 |
| Method | Chi-squared |

| **Statistical analysis title** | 4_Placebo vs 5400 PNU - reduction of 50 % |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0088 |
| Method | Chi-squared |

| **Statistical analysis title** | 5_Placebo vs 600 PNU - reduction of 30 % |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0019 |
| Method | Chi-squared |

| **Statistical analysis title** | 6_Placebo vs 1800 PNU - reduction of 30 % |
|---|---|
| Comparison groups | Placebo v 1800 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0017 |
| Method | Chi-squared |

| **Statistical analysis title** | 7_Placebo vs 3000 PNU - reduction of 30 % |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 |
| Method | Chi-squared |

| Statistical analysis title | 8_Placebo vs 5400 PNU - reduction of 30 % |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 |
| Method | Chi-squared |

## Secondary: 3_Absolute change of the swelling volume at 6h -- Late phase reaction (LPR)

| End point title | 3_Absolute change of the swelling volume at 6h -- Late phase reaction (LPR) |
|---|---|

End point description:

Volume (mL) of the LPR (6 h after ICT), including change of volume (mL) of the LPR (6 h after ICT).
LS Mean: least square mean estimated from analysis of covariance including the baseline value as covariate and center and treatment group as fixed effects.

Data recording and measuring are described in the endpoint 1 above.

Statistical analysis is shown below for the comparison of placebo vs active dose treatment group.
For the comparisons between active dose treatment groups, no statistically significant results were observed (data are not shown).

LPR=Late phase reaction

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

End point timeframe:

Baseline (S4), after 1 year of treatment (T17).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T17=36 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 27[23] | 23 | 27 | 24 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | -0.98 (-1.79 to -0.17) | 1.63 (0.76 to 2.5) | 1.72 (0.92 to 2.53) | 2.13 (1.28 to 2.98) |

Notes:

[23] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 2.03 (1.22 to 2.84) | | | |

## Statistical analyses

| **Statistical analysis title** | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[24] |
| P-value | < 0.0001 [25] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -2.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.8 |
| upper limit | -1.41 |

Notes:

[24] - ANCOVA for change of the swelling volume [mL] of late phase reaction (after 6h), including variable center.
LS Mean: least square mean estimated from analysis of covariance including the baseline value as covariate and treatment group as fixed effect.
[25] - F-test

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | 1800 PNU v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[26] |
| P-value | < 0.0001 [27] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.84 |
| upper limit | -1.56 |

Notes:

[26] - ANCOVA for change of the swelling volume [mL] of late phase reaction (after 6h), including variable center.
LS Mean: least square mean estimated from analysis of covariance including the baseline value as covariate and treatment group as fixed effect.
[27] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[28] |
| P-value | < 0.0001 [29] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -3.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.28 |
| upper limit | -1.94 |

Notes:

[28] - ANCOVA for change of the swelling volume [mL] of late phase reaction (after 6h), including variable center.
LS Mean: least square mean estimated from analysis of covariance including the baseline value as covariate and treatment group as fixed effect.
[29] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[30] |
| P-value | < 0.0001 [31] |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -3.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.16 |
| upper limit | -1.86 |

Notes:

[30] - ANCOVA for change of the swelling volume [mL] of late phase reaction (after 6h), including variable center.
LS Mean: least square mean estimated from analysis of covariance including the baseline value as covariate and treatment group as fixed effect.
[31] - F-test

## Secondary: 4_Absolute change of the swelling area at 20min -- Early phase reaction (EPR)

| End point title | 4_Absolute change of the swelling area at 20min -- Early phase reaction (EPR) |
|---|---|

End point description:

Change to baseline: Final Visit - Baseline
Swelling area (cm²) of the early phase (20 min) reaction including change of swelling area (cm²) of the EPR (20 min after ICT).

LS Mean: least square mean estimated from analysis of covariance including the baseline value as covariate and center and treatment group as fixed effects.

Data recording and measuring are described in the endpoint 1 above.

Statistical analysis is shown below for the comparison of placebo vs active dose treatment group.
For the comparisons between active dose treatment groups, no statistically significant results were observed (data are not shown).

EPR=Early phase reaction

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

End point timeframe:

Baseline (S4), after 1 year of treatment (T17).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T17=36 weeks after T1

| **End point values** | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 27[32] | 24 | 28 | 24 |
| Units: cm2 | | | | |
| least squares mean (confidence interval 95%) | 0.79 (-0.29 to 1.87) | 1.15 (0 to 2.3) | 1.99 (0.92 to 3.05) | 3.01 (1.86 to 4.16) |

Notes:

[32] - Full analysis set for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: cm2 | | | | |
| least squares mean (confidence interval 95%) | 0.91 (-0.18 to 1.99) | | | |

## Statistical analyses

| **Statistical analysis title** | 1_Placebo vs 600 PNU |
|---|---|

Statistical analysis description:

ANCOVA for change of the swelling area [cm2] of EPR

EPR=early phase reaction

| Comparison groups | Placebo v 600 PNU |
|---|---|
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6522 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.94 |
| upper limit | 1.22 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8 |

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|

Statistical analysis description:
ANCOVA for change of the swelling area [cm2] of EPR

EPR=early phase reaction

| | |
|---|---|
| Comparison groups | 1800 PNU v Placebo |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1213 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.72 |
| upper limit | 0.32 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.77 |

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|

Statistical analysis description:
ANCOVA for change of the swelling area [cm2] of EPR

EPR=early phase reaction

| | |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0063 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -2.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.79 |
| upper limit | -0.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8 |

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|

Statistical analysis description:

ANCOVA for change of the swelling area [cm2] of EPR

EPR=early phase reaction

| | |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8788 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.65 |
| upper limit | 1.41 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.77 |

## Secondary: 5_Absolute change of the swelling volume at 20min -- Early phase reaction (EPR)

| | |
|---|---|
| End point title | 5_Absolute change of the swelling volume at 20min -- Early phase reaction (EPR) |

End point description:

Volume (mL) of the EPR (20 min after ICT) including change of volume (mL) of the EPR (20 min after ICT).

LS Mean: least square mean estimated from analysis of covariance including the baseline value as covariate and center and treatment group as fixed effects.

Data recording and measuring are described in the endpoint 1 above.

Statistical analysis is shown below for the comparison of placebo vs active dose treatment group. For the comparisons between active dose treatment groups, no statistically significant results were observed (data are not shown).

EPR=Early phase reaction

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

End point timeframe:

Baseline (S4), after 1 year of treatment (T17).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T17=36 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 27[33] | 24 | 28 | 24 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 0.13 (-0.02 to 0.29) | 0.19 (0.03 to 0.35) | 0.36 (0.21 to 0.51) | 0.48 (0.31 to 0.64) |

Notes:

[33] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 0.21 (0.05 to 0.36) | | | |

**Statistical analyses**

| Statistical analysis title | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6065 [34] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.17 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.11 |

Notes:

[34] - F-test

| Statistical analysis title | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | 1800 PNU v Placebo |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.041 [35] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -0.23 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | -0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.11 |

Notes:
[35] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0028 [36] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.57 |
| upper limit | -0.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.11 |

Notes:
[36] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4876 [37] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.11 |

Notes:
[37] - F-test

| **Secondary: 6_Changes in specific IgE to D. pteronyssinus (IU/mL)** | |
|---|---|
| End point title | 6_Changes in specific IgE to D. pteronyssinus (IU/mL) |

End point description:

Determination of specific IgE to D. pteronyssinus - a of major allergen of house dust mites.

The amino acid sequences of D. pteronyssinus and D. farinae allergens can have about 80% sequence identity; therefore both cross reactivity and species specificity would be expected.

LS Mean: least square mean was estimated from the analysis of covariance, including the baseline value as covariate and treatment group as fixed effect.

Statistical analysis is shown below for the comparison of placebo group vs active dose treatment group. For the comparisons between active dose treatment groups, no statistically significant results were observed (data are not shown).

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

End point timeframe:

Baseline (visit S1), after 1 year of treatment (visit T16).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T16=35 weeks after T1

| **End point values** | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28[38] | 23 | 30 | 25 |
| Units: IU/mL | | | | |
| least squares mean (confidence interval 95%) | 2.43 (-1.43 to 6.29) | -2.32 (-6.54 to 1.91) | -3.93 (-7.64 to -0.22) | -4.41 (-8.46 to -0.35) |

Notes:

[38] - Full analysis set for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: IU/mL | | | | |
| least squares mean (confidence interval 95%) | -1.31 (-5.17 to 2.55) | | | |

## Statistical analyses

| **Statistical analysis title** | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1021 [39] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 4.75 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.96 |
| upper limit | 10.45 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.88 |

Notes:
[39] - (F-test)

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | Placebo v 1800 PNU |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0208 [40] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 6.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 11.74 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.72 |

Notes:
[40] - (F-test)

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0167 [41] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 6.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.26 |
| upper limit | 12.42 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.82 |

Notes:
[41] - (F-test)

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1804 [42] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 3.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.76 |
| upper limit | 9.25 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.78 |

Notes:

[42] - (F-test)

## Secondary: 7_Changes in specific IgE to D. farinae (IU/mL)

| | |
|---|---|
| End point title | 7_Changes in specific IgE to D. farinae (IU/mL) |

End point description:

Determination of specific IgE to D. farinae - a major allergen of house dust mites.

Please refer to the description shown in endpoint 6.

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

End point timeframe:

Baseline (visit S1), after 1 year of treatment (visit T16).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T16=35 weeks after T1

| **End point values** | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28[43] | 23 | 30 | 25 |
| Units: IU/mL | | | | |
| least squares mean (confidence interval 95%) | 6.05 (3.17 to 8.93) | 3.62 (0.47 to 6.78) | 1.29 (-1.49 to 4.06) | 2.85 (-0.19 to 5.9) |

Notes:

[43] - Full analysis set for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: IU/mL | | | | |
| least squares mean (confidence interval 95%) | 3.18 (0.28 to 6.07) | | | |

**Statistical analyses**

| **Statistical analysis title** | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2616 [44] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 2.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.83 |
| upper limit | 6.69 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.15 |

Notes:
[44] - F-test

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | 1800 PNU v Placebo |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0209 [45] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 4.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 8.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.04 |

Notes:
[45] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1307 [46] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.96 |
| upper limit | 7.36 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.1 |

Notes:
[46] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1704 [47] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 2.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.25 |
| upper limit | 7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.09 |

Notes:
[47] - F-test

## Secondary: 8_Changes in specific IgG D. pteronyssinus (mg/L)

| End point title | 8_Changes in specific IgG D. pteronyssinus (mg/L) |
|---|---|

End point description:

Determination of specific IgG D. pteronyssinus - a major allergen of house dust mites.

Please refer to the description shown in endpoint 6.

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

End point timeframe:

Baseline (visit S1), after 1 year of treatment (visit T16).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T16=35 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28[48] | 24 | 30 | 25 |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | -0.54 (-2.73 to 1.65) | -4.02 (-6.38 to -1.66) | -6.47 (-8.58 to -4.36) | -7.56 (-9.88 to -5.24) |

Notes:

[48] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | -9.38 (-11.57 to -7.2) | | | |

**Statistical analyses**

| Statistical analysis title | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0346 [49] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 3.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.26 |
| upper limit | 6.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.63 |

Notes:

[49] - F-test

| Statistical analysis title | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | Placebo v 1800 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 [50] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 5.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.89 |
| upper limit | 8.97 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.53 |

Notes:

[50] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [51] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 7.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.81 |
| upper limit | 10.22 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.62 |

Notes:

[51] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [52] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 8.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.75 |
| upper limit | 11.93 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.56 |

Notes:

[52] - F-test

## Secondary: 9_Changes in specific IgG D. farinae (mg/L)

| | |
|---|---|
| End point title | 9_Changes in specific IgG D. farinae (mg/L) |

End point description:

Determination of specific IgG D. farinae - a major allergen of house dust mites.

Please refer to the description shown in endpoint 6.

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

End point timeframe:

Baseline (visit S1), after 1 year of treatment (visit T16).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T16=35 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28[53] | 24 | 30 | 25 |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | -0.96 (-3.18 to 1.25) | -4.85 (-7.24 to -2.45) | -6.92 (-9.06 to -4.78) | -7.6 (-9.95 to -5.25) |

Notes:

[53] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | -7.45 (-9.67 to -5.24) | | | |

### Statistical analyses

| Statistical analysis title | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0202 [54] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 3.88 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 7.15 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.65 |

Notes:
[54] - F-test

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | Placebo v 1800 PNU |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 [55] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 5.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.88 |
| upper limit | 9.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.56 |

Notes:
[55] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [56] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 6.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.39 |
| upper limit | 9.87 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.64 |

Notes:
[56] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [57] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 6.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.35 |
| upper limit | 9.62 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.58 |

Notes:

[57] - F-test

## Secondary: 10_Changes in specific IgG4 D. pteronyssinus (mg/L)

| | |
|---|---|
| End point title | 10_Changes in specific IgG4 D. pteronyssinus (mg/L) |

End point description:

Determination of specific IgG4 D. pteronyssinus - a major allergen of house dust mites.

Please refer to the description shown in endpoint 6.

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

End point timeframe:

Baseline (visit S1), after 1 year of treatment (visit T16).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T16=35 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28[58] | 24 | 30 | 25 |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | -0.03 (-0.68 to 0.62) | -1.07 (-1.78 to -0.37) | -2.44 (-3.07 to -1.82) | -2.16 (-2.85 to -1.47) |

Notes:

[58] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | -3.04 (-3.7 to -2.38) | | | |

## Statistical analyses

| **Statistical analysis title** | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.033 [59] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.09 |
| upper limit | 2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.48 |

Notes:
[59] - F-test

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | Placebo v 1800 PNU |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [60] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 2.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.51 |
| upper limit | 3.32 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.46 |

Notes:
[60] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [61] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 2.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.18 |
| upper limit | 3.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.48 |

Notes:
[61] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [62] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 3.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.08 |
| upper limit | 3.94 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.47 |

Notes:
[62] - F-test

## Secondary: 11_Changes in specific IgG4 D. farinae (mg/L)

| End point title | 11_Changes in specific IgG4 D. farinae (mg/L) |
|---|---|

End point description:

Determination of specific IgG4 D. farinae - a major allergen of house dust mites.

Please refer to the description shown in endpoint 6.

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

End point timeframe:

Baseline (visit S1), after 1 year of treatment (visit T16).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T16=35 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28[63] | 24 | 30 | 25 |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | 0.11 (-0.46 to 0.68) | -0.68 (-1.3 to -0.06) | -1.81 (-2.37 to -1.26) | -1.37 (-1.98 to -0.77) |

Notes:

[63] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | -1.95 (-2.53 to -1.37) | | | |

**Statistical analyses**

| Statistical analysis title | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0654 [64] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 1.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.43 |

Notes:

[64] - F-test

| Statistical analysis title | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | Placebo v 1800 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [65] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 1.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.13 |
| upper limit | 2.72 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4 |

Notes:

[65] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 [66] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 2.32 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.42 |

Notes:

[66] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [67] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 2.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.25 |
| upper limit | 2.87 |

| Variability estimate | Standard error of the mean |
|---|---|
| Dispersion value | 0.41 |

Notes:

[67] - F-test

## Secondary: 12_Change of minimal asthma control dose

| End point title | 12_Change of minimal asthma control dose |
|---|---|

End point description:

The change of minimal asthma control dose as assessed by the Asthma Control Test (ACT). This endpoint was analyzed for the subset of patients who had asthma control only under Fluticasone treatment of either 500 µg/day or 200 µg/day; patients with controlled asthma without Fluticasone were excluded from this analysis. Asthma control was defined by a sum score of at least 20 points in the ACT.

Asthma Control Test and Score
Each of the 5 questions regarding asthma symptoms or medication use, had a score 1 (worst score) to 5 (best score). Refr. Kosinski M, Bayliss MS, Turner-Bowker DM, Fortin EW. Asthma Control Test™: A User's Guide. Lincoln (RI): QualityMetric Incorporated, 2004.

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

End point timeframe:

Baseline, post treatment (T18 and/or T19).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T17=36 weeks after T1
T18=42 weeks after T1
T19=50 weeks after T1

| **End point values** | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15[68] | 12 | 13 | 8 |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -100 (± 352.5) | -175 (± 283.2) | -246.2 (± 166.4) | -187.5 (± 258.8) |

Notes:

[68] - Full analysis set for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -376.9 (± 200.6) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: 13_Changes in asthma control test score between baseline and post-

| treatment | |
|---|---|
| End point title | 13_Changes in asthma control test score between baseline and post-treatment |

End point description:

Please refer to the description for endpoint 12.

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

End point timeframe:

Baseline, post treatment (T18 and/or T19).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T17=36 weeks after T1
T18=42 weeks after T1
T19=50 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13[69] | 7 | 9 | 6 |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | -1.77 (-3.97 to 0.42) | -4.33 (-6.87 to 1.8) | -4.83 (-7.31 to -2.36) | -3.63 (-6.37 to -0.88) |

Notes:

[69] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | -4.00 (-6.18 to -1.83) | | | |

## Statistical analyses

| Statistical analysis title | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0963 [70] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 2.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.48 |
| upper limit | 5.6 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.49 |

Notes:
[70] - F-test

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | Placebo v 1800 PNU |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0432 [71] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 3.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 6.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.45 |

Notes:
[71] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2662 [72] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 1.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.48 |
| upper limit | 5.18 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.64 |

Notes:
[72] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0816 [73] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 2.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 4.75 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.24 |

Notes:

[73] - F-test

## Secondary: 14_Changes in morning PEF (L/min)

| | |
|---|---|
| End point title | 14_Changes in morning PEF (L/min) |

End point description:

Only morning PEF after treatment, that had been measured at the same corticoid dose as the before treatment PEF were used for comparison.

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

End point timeframe:

Baseline, post treatment (T18 and/or T19).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T17=36 weeks after T1
T18=42 weeks after T1
T19=50 weeks after T1

| End point values | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13[74] | 7 | 9 | 6 |
| Units: L/min | | | | |
| least squares mean (confidence interval 95%) | 4.1 (-38.14 to 46.34) | -52.09 (-108.98 to 4.79) | -41.99 (-92.04 to 8.06) | -87.56 (-150.2 to -24.92) |

Notes:

[74] - Full analysis set for all treatment groups

| End point values | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: L/min | | | | |
| least squares mean (confidence interval 95%) | -22.49 (-68.41 to 23.44) | | | |

## Statistical analyses

| **Statistical analysis title** | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1208 [75] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 56.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.46 |
| upper limit | 127.85 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 35.45 |

Notes:
[75] - F-test

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | Placebo v 1800 PNU |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1666 [76] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 46.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.03 |
| upper limit | 112.21 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 32.72 |

Notes:
[76] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |

| | |
|---|---|
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0165 [77] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 91.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17.68 |
| upper limit | 165.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 36.6 |

Notes:

[77] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | Placebo v 5400 PNU |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.403 [78] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 26.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.97 |
| upper limit | 90.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 31.45 |

Notes:

[78] - F-test

## Secondary: 15_Changes in morning PEF in relation to predicted value (%)

| End point title | 15_Changes in morning PEF in relation to predicted value (%) |
|---|---|

End point description:

The change of the morning PEF before and after treatment was analyzed in the same way as the change in the ACT score. Only morning PEF after treatment, that had been measured at the same corticoid dose as the before treatment PEF were used for comparison.

Lung function tests were assessed as PEF relative to the expected normal value. Percentages were analyzed as smallest values post injection and post ICT and as highest decrease of PEF between pre and post injection and between pre and post ICT at each visit.

Mean values of minimal values at each visit did not change substantially over time. No relevant differences between the treatment groups were observed, especially not at doses 3000 or 5400 PNU vs with placebo group. All 5 treatment groups were similar in their mean highest decrease of PEF in (% ) between pre and 30 min post injection over all visits. Pre and post ICT measurements did not show any substantial changes on average wrt. to PEF values.

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

End point timeframe:

Baseline, post treatment (T18 and/or T19).

S1=Day 0
S4 (baseline)=32 weeks after S1.
T1 (randomisation)=52 weeks (1 year) after S1
T17=36 weeks after T1
T18=42 weeks after T1
T19=50 weeks after T1

| **End point values** | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13[79] | 7 | 9 | 6 |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -3.51 (-10.01 to 2.99) | -8.91 (-17.76 to -0.06) | -7.82 (-15.63 to -0.01) | -12.71 (-22.79 to -2.63) |

Notes:

[79] - Full analysis set for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -4.29 (-11.4 to 2.83) | | | |

**Statistical analyses**

| **Statistical analysis title** | 1_Placebo vs 600 PNU |
|---|---|
| Comparison groups | Placebo v 600 PNU |
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3264 [80] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 5.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.58 |
| upper limit | 16.37 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.43 |

Notes:

[80] - F-test

| **Statistical analysis title** | 2_Placebo vs 1800 PNU |
|---|---|
| Comparison groups | 1800 PNU v Placebo |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3957 [81] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 4.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.84 |
| upper limit | 14.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.02 |

Notes:
[81] - F-test

| **Statistical analysis title** | 3_Placebo vs 3000 PNU |
|---|---|
| Comparison groups | Placebo v 3000 PNU |
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.132 [82] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 9.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.89 |
| upper limit | 21.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.98 |

Notes:
[82] - F-test

| **Statistical analysis title** | 4_Placebo vs 5400 PNU |
|---|---|
| Comparison groups | 5400 PNU v Placebo |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8709 [83] |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 0.78 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.83 |
| upper limit | 10.38 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.75 |

Notes:

[83] - F-test

## Secondary: 16_Vital signs: Systolic blood pressure (SBP); Diastolic blood pressure (DBP)

| | |
|---|---|
| End point title | 16_Vital signs: Systolic blood pressure (SBP); Diastolic blood pressure (DBP) |

End point description:

Vital signs: systolic blood pressure, diastolic blood pressure, pulse rate, and respiratory rate were measured for all patients. The mean changes in all treatment groups were marginal and similar over time. Mean changes within the screening period from screening visit S1 to Visit T1 and from T1 to the final Visit T19 were very similar, indicating no effect of the treatment with study medication on these mean values.

Prior to each injections, vital sign measurements were performed as well. From Visit T9 onward vital signs were assessed post injection: at visits T9 to T12 at 10 minutes, 20, 30 , 60 , 180, and 360 min after the injection and at visits T13 to T16 at 30 minutes after the injection in order capture any possible systemic reaction. Individual smallest values post-injection at each visit and the highest decreases from pre- to post injection at each visit in each single parameter were analyzed. The 4 active treatment groups showed no stat significant difference vs placebo.

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

End point timeframe:

Screening (S1), during treatment (T1-T16), final visit (T19).

Results for SBP and DBP are shown only for the difference between screening visit (S1), prior to the first injection of study medication on Visit T1, and at the final Visit (T19).

| **End point values** | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 30[84] | 24 | 29 | 25 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic blood pressure | -1.7 (± 9.69) | -0.46 (± 11.31) | 2.21 (± 10.88) | 1.28 (± 8.06) |
| Diastolic blood pressure | -4.53 (± 7.95) | 1.67 (± 8.61) | -0.83 (± 11.73) | 0.36 (± 8.93) |

Notes:

[84] - Safety set for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|---|---|---|---|
| Systolic blood pressure | -1.17 (± 11.91) | | | |
| Diastolic blood pressure | -1.14 (± 9.04) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 17_Vital signs: Respiratory rate

| End point title | 17_Vital signs: Respiratory rate |
|---|---|

End point description:

Please refer to the description shown for endpoint 16.

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

End point timeframe:

Screening (S1), during treatment (T1-T16), final visit (T19).

Results for respiratory rate are shown only for the difference between screening visit (S1), prior to the first injection of study medication on Visit T1, and at the final Visit (T19).

| **End point values** | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 30[85] | 24 | 29 | 25 |
| Units: breaths/min | | | | |
| arithmetic mean (standard deviation) | -0.6 (± 2.79) | 0.04 (± 1.63) | -0.97 (± 2.85) | 0.44 (± 1.66) |

Notes:

[85] - Safety set for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: breaths/min | | | | |
| arithmetic mean (standard deviation) | -0.41 (± 1.8) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 18_Vital signs: Heart rate

| End point title | 18_Vital signs: Heart rate |
|---|---|

End point description:

Please refer to the description shown for endpoint 16.

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

End point timeframe:

Screening (S1), during treatment (T1-T16), final visit (T19).

Results for the heart rate are shown only for the difference between screening visit (S1), prior to the first injection of study medication on Visit T1, and at the final Visit (T19).

| **End point values** | Placebo | 600 PNU | 1800 PNU | 3000 PNU |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 30[86] | 24 | 29 | 25 |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 0.8 (± 10.36) | 1.38 (± 10.68) | 3 (± 9.59) | -1 (± 9.04) |

Notes:

[86] - Safety set for all treatment groups

| **End point values** | 5400 PNU | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | 1.03 (± 7.98) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the start of the study (signing of the informed consent) until the end of the study (last study visit i.e. 144.6 weeks after study start).

Adverse event reporting additional description:

Data shown represent the 'Safety analysis set'.
AEs and SAEs shown below are from the DRF part of the study.

During the ICT part of the study, 3 non serious AEs were reported (cough, decrease value of PEF, itching edema 20 cm diameter after ICT).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | 600 PNU |
| Reporting group description: - | |
| Reporting group title | 1800 PNU |
| Reporting group description: - | |
| Reporting group title | 3000 PNU |
| Reporting group description: - | |
| Reporting group title | 5400 PNU |
| Reporting group description: - | |

| Serious adverse events | Placebo | 600 PNU | 1800 PNU |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 1 / 24 (4.17%) | 1 / 31 (3.23%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Scar hernia-post operative | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 24 (0.00%) | 0 / 31 (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 |
| Vascular disorders | | | |
| Varices of lower legs | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Immune system disorders | | | |
| Anaphylactic reaction grade II | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 24 (0.00%) | 0 / 31 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma exacerbation | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Viral meningitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 24 (0.00%) | 0 / 31 (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 |
| Acute appendicitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 1 / 31 (3.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | 3000 PNU | 5400 PNU | |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 3 / 31 (9.68%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Scar hernia-post operative | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Varices of lower legs | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction grade II | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma exacerbation | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Viral meningitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute appendicitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | 600 PNU | 1800 PNU |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 32 (46.88%) | 13 / 24 (54.17%) | 13 / 31 (41.94%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Allergy test | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peak expiratory flow rate decreased | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Nasal polypectomy | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 3 / 31 (9.68%) |
| occurrences (all) | 0 | 1 | 6 |
| Injection site oedema | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Injection site papule | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injection site pruritus | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 1 | 2 |
| Injection site swelling | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 2 / 24 (8.33%) | 2 / 31 (6.45%) |
| occurrences (all) | 0 | 2 | 3 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 24 (0.00%) | 2 / 31 (6.45%) |
| occurrences (all) | 2 | 0 | 2 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | 1 / 24 (4.17%) | 3 / 31 (9.68%) |
| occurrences (all) | 4 | 2 | 3 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis atopic | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 2 / 24 (8.33%) | 2 / 31 (6.45%) |
| occurrences (all) | 1 | 2 | 2 |
| Influenza | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 4 / 24 (16.67%) | 3 / 31 (9.68%) |
| occurrences (all) | 2 | 4 | 3 |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 24 (4.17%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 2 / 24 (8.33%) | 1 / 31 (3.23%) |
| occurrences (all) | 3 | 2 | 1 |

| | | | |
|---|---|---|---|
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 24 (0.00%) | 2 / 31 (6.45%) |
| occurrences (all) | 0 | 0 | 2 |

| **Non-serious adverse events** | 3000 PNU | 5400 PNU | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 28 (39.29%) | 19 / 31 (61.29%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Allergy test | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 31 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peak expiratory flow rate decreased | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 31 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 31 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 31 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Surgical and medical procedures<br>Nasal polypectomy<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 28 (3.57%)<br>1 | <br><br>0 / 31 (0.00%)<br>0 | |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 28 (3.57%)<br>1 | <br><br>0 / 31 (0.00%)<br>0 | |
| General disorders and administration site conditions<br>Injection site erythema<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site oedema<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site papule<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site swelling<br>subjects affected / exposed<br>occurrences (all) | <br><br>4 / 28 (14.29%)<br>13<br><br><br>1 / 28 (3.57%)<br>2<br><br><br>0 / 28 (0.00%)<br>0<br><br><br>0 / 28 (0.00%)<br>0<br><br><br>1 / 28 (3.57%)<br>3 | <br><br>4 / 31 (12.90%)<br>9<br><br><br>3 / 31 (9.68%)<br>5<br><br><br>0 / 31 (0.00%)<br>0<br><br><br>2 / 31 (6.45%)<br>2<br><br><br>5 / 31 (16.13%)<br>10 | |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 28 (0.00%)<br>0 | <br><br>1 / 31 (3.23%)<br>1 | |
| Gastrointestinal disorders<br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 28 (0.00%)<br>0 | <br><br>1 / 31 (3.23%)<br>1 | |
| Respiratory, thoracic and mediastinal disorders<br>Asthma<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea | <br><br>4 / 28 (14.29%)<br>4<br><br> | <br><br>1 / 31 (3.23%)<br>1<br><br> | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 28 (0.00%) | 2 / 31 (6.45%) | |
| occurrences (all) | 0 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | 7 / 31 (22.58%) | |
| occurrences (all) | 3 | 9 | |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 2 / 31 (6.45%) | |
| occurrences (all) | 0 | 2 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 31 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 31 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0 | 2 / 31 (6.45%)<br>2 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 13 February 2012 | Changes of the trial schedule, implementation of the lung function test before and after ICT, change in the point of times to be investigated in the ICT trial part, implementation of an optical device for the assessment of the ICT reaction (wheal or swelling). |
| 05 June 2012 | Changes of the trial schedule, of exclusion criteria and clarification for the use of asthma medication. |
| 20 September 2012 | This amendment concerned the prolongation of the trial to implement a second screening period and change of 1 exclusion criterion. |
| 11 January 2013 | Spain only: This amendment concerned the clarification of 1 exclusion criterion, the submission of additional sites in Poland and Spain. Further the amendment concerned changes of the administrative structure and assessment of additional allergens for Spanish patients.<br><br>Poland only: Implementation of a possible second check of inclusion and exclusion criteria for patients, which dropped out in the first screening phase according to the 2 changed exclusion criteria. |
| 11 September 2013 | Spain only: prolongation of the screening period. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Rudert, M; Tribanek, M; Karjalainen, M; Haefner, D; Narkus, A; New objective method to measure skin test results within clinical trials; Allergy; 2013; 68 (Suppl. 97), 1104.

Notes: