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 Units: Subjects			
Adults (18-64 years)	32	24	31
Age continuous Units: years			
arithmetic mean	28.3	25.4	27.5
standard deviation	± 7.5	± 5	± 7.3
Gender categorical Units: Subjects			
Female	21	12	14
Male	11	12	17
Race 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 Units: Subjects			
Adults (18-64 years)	28	31	146
Age continuous Units: years			
arithmetic mean	27.9	28	
standard deviation	± 6.7	± 7	-
Gender categorical Units: Subjects			
Female	12	11	70
Male	16	20	76

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

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 occurrences (all)	0 / 28 (0.00%) 0	2 / 31 (6.45%) 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. 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: