Clinical trial results:
Randomised double blind placebo controlled pivotal study to evaluate efficacy and safety of rPhleum in adult and adolescent patients suffering from rhinoconjunctivitis +/- controlled asthma

Summary

EudraCT number	2009-011504-36
Trial protocol	DE GB PL FR ES
Global end of trial date	09 August 2013

Results information

Result version number	v1 (current)
This version publication date	03 November 2017
First version publication date	03 November 2017

Trial information

Trial identification

Sponsor protocol code	AL0906rP

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	Department of Clinical Trials, ALLERGOPHARMA GMBH & CO. KG., 0049 40427650,
Scientific contact	Department of Clinical Trials, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the hypothesis that the recombinant allergen preparation rPhleum is suitable for an efficacious SCIT in grass pollen allergic patients and that the trial product is sufficient to suppress allergic symptoms caused by natural grass pollen exposure. The trial medication was tested versus placebo.

The trial population consisted of patients (with or without controlled asthma) who had rhinoconjunctivitis caused by grass pollen. At the onset of the grass pollen season in the baseline year of the trial, the patients started their documentation of allergic symptoms and use of rescue medication in a patient’s diary (nature and severity of symptoms, at the same time each day). This procedure was repeated during the following 2 seasons of the double-blind treatment period. Standardised diaries in local language were used, asking for details relevant for the statistical evaluation.

SCIT =Subcutaneous immunotherapy

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.

Aluminium levels in plasma and urine were measured before treatment, after up-dosing, after 1 year of treatment, at the final visit, and the follow-up visit (6 months after individual subject's last dose administration).
The cumulative amount of injected aluminium was calculated for each treatment year by summing up the aluminium dose [mg]. Aluminium values in blood plasma that were above 7.5 µg/L (International System of Units (SI): 0.278 µmol/L) were considered abnormal in this trial, based on the reference values from the study’s central laboratory. The median aluminium values plasma at baseline were: 5.85 µg/L active treatment group; 6.10 µg/L placebo group.
During the up-titration a steady increase in plasma level for aluminium was seen, a steady-state was reached during the maintenance period; 6 months after discontinuation of the treatment, the aluminium levels returned to nearly the values observed at baseline. The aluminium analysis in urine did not yield any further clinically relevant data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 95
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Germany: 76
Worldwide total number of subjects	195
EEA total number of subjects	195

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)	13
Adults (18-64 years)	182
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in study centers in several countries in Europe.
Overall, 806 subjects were screened for eligibility; of these, 195 subjects were randomised to treatment according to the exclusion and inclusion criteria.

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active treatment (rPhleum)

Arm description: -

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

Dosage and administration details:

Strength 1 (0.78 µg/mL); Strength 2 (6.25 µg/mL); Strength 3 (50 µg/mL); Strength 4 (200 µg/mL).

The investigational product (rPhleum), manufactured and supplied by Allergopharma, was a mixture of recombinant major allergens of Timothy Grass Pollen (Phleum pratense) adsorbed onto aluminium-hydroxide.

During the clinical trial, vials with four different concentrations were used:
At the beginning of the treatment, injections had to be administered in intervals of 7 (+ 7 days). The dose was increased progressively by one step at a time only, provided that the previous dose has been well tolerated. After the maximum individually tolerated dose (= maintenance dose) had been reached, the injection intervals were prolonged to 2, and finally 4 weeks (+ 2 weeks). During the grass pollen season the maintenance dose had to be reduced to 50% of the maximum individually tolerated dose. After the end of grass pollen season the dosage had to be re-adjusted again to 100%.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo in sterile suspension containing histamine dihydrochloride in 2 different strengths for subcutaneous injection in the upper arm. The placebo-preparation used was the verum-solution without

any allergen active substance.

Number of subjects in period 1	Active treatment (rPhleum)	Placebo
Started	92	103
Completed	78	95
Not completed	14	8
Consent withdrawn by subject	4	2
Adverse event, non-fatal	8	-
Lost to follow-up	2	1
In/exclusion criteria;	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Active treatment (rPhleum)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Active treatment (rPhleum)	Placebo	Total
Number of subjects	92	103	195
Age categorical Units: Subjects			
Adolescents (12-17 years)	6	7	13
Adults (18-64 years)	86	96	182
Age continuous Units: years			
arithmetic mean	29.87	31.41	
standard deviation	± 11.02	± 10.09	-
Gender categorical Units: Subjects			
Female	32	51	83
Male	60	52	112
Race Units: Subjects			
African	1	1	2
Asian	1	0	1
Caucasian	89	100	189
Other	1	2	3

End points

End points reporting groups

Reporting group title	Active treatment (rPhleum)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: 1_Change of the AUC of the ma-RC-SS; Change from baseline

End point title	1_Change of the AUC of the ma-RC-SS; Change from baseline

End point description:

Change of the AUC: ma-RC-SS from baseline season to season after 1 and 2 treatment years.

AUC for each patient was calculated for the 42 day evaluation period (i.e. -10 days before peak pollen count until 31 days after peak pollen count). The peak pollen count for each centre was defined (BDRM), based on the actual pollen counts for the respective year.

Symptoms:
• Eyes (itching, tear flow, redness)
• Nose (sneezing, itching, running, blockage)
• Lungs (cough, wheezing, dyspnoea)

Score intensity:
0 = absent symptoms (no sign/symptom evident)
1 = mild symptoms, minimal inconvenience
2 = moderate, bothersome but tolerable symptoms
3 = severe symptoms that interfered with daily living activities

Daily medication scores: assigned as in AMS Scoring Conventions for Allergopharma clinical studies

AMS=Advanced Medical Services GmbH (CRO)
AUC=Area under the curve
BDRM=Blind Data Review Meeting
ma-RC-SS=Medication-adjusted rhinoconjunctivitis symptom score

End point type	Primary

End point timeframe:

Baseline to 1 and 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[1]	95[2]		
Units: score				
median (full range (min-max))				
1st year	-188 (-660 to 402)	-129 (-569 to 295)		
2nd year	-232 (-724 to 181)	-187.5 (-656 to 273)		

Notes:

[1] - Full analysis set; Change from baseline
1st year N=77
2nd year N=77

[2] - Full analysis set; Change from baseline
1st year N=92
2nd year N=94

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)

Statistical analysis description:

The difference between treatment groups in the median change of the AUC.
The primary endpoint was tested in a confirmatory sense for the FAS using the 2-sided Wilcoxon Mann-Whitney U-Test at a significance level of alpha = 0.05.

FAS=Full analysis set

The number of subjects in this analysis is N=169; the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Placebo v Active treatment (rPhleum)
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2918
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline (after 2 years of treatment)

Statistical analysis description:

The difference between treatment groups in the median change of the AUC
The primary endpoint was tested in a confirmatory sense for the FAS using the 2-sided Wilcoxon Mann-Whitney U-Test at a significance level of alpha = 0.05.

The number of subjects in this analysis is N=171; the number N=173 below is due to an innate error of the EudraCT database system.

FAS=Full analysis set

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1124
Method	Wilcoxon (Mann-Whitney)

Secondary: 2_Change of the AUC of the ma-RC-SS: sensitivity analysis ('worst case'); Change from baseline

End point title	2_Change of the AUC of the ma-RC-SS: sensitivity analysis ('worst case'); Change from baseline

End point description:

Change of the AUC: ma-RC-SS from baseline season to season after 1 and 2 treatment years: sensitivity analysis ('worst case ma-RC-SS').

For sensitivity analyses ('worst case'), the missing score values were replaced by the patient’s highest

value of the defined time period (if not more than 25% of the values were missing).

The actual number of patients contributing data for this evaluation is shown under the results table.

AUC=Area under the curve
ma-RC-SS=Medication-adjusted rhinoconjunctivitis symptom score

End point type	Secondary

End point timeframe:

Baseline to 1 and 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[3]	95[4]		
Units: score				
median (full range (min-max))				
1st year	-188 (-660 to 402)	-131 (-559 to 295)		
2nd year	-230 (-724 to 181)	-163 (-656 to 273)		

Notes:

[3] - Full analysis set; Change from baseline
1st year N=77
2nd year N=77

[4] - Full analysis set; Change from baseline
1st year N=92
2nd year N=94

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)

Statistical analysis description:

The difference between treatment groups in the median change of the AUC.

The number of subjects in this analysis is N=169;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3378
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline (after 2 years of treatment)

Statistical analysis description:

The difference between treatment groups in the median change of the AUC.

The number of subjects in this analysis is N=171;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1392
Method	Wilcoxon (Mann-Whitney)

Secondary: 3_Change of the AUC of the RC-SMS; Change from baseline

End point title	3_Change of the AUC of the RC-SMS; Change from baseline

End point description:

Change of the AUC: RC-SMS from baseline season to season after 1 and 2 treatment years.

The actual number of patients contributing data for this evaluation is shown under the results table.

AUC=Area under the curve
RC=Rhinoconjunctivitis
SMS=Symptom and medication score

End point type	Secondary

End point timeframe:

Baseline to 1 and 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[5]	95[6]		
Units: score				
median (full range (min-max))				
1st year	-159 (-800 to 380)	-129.5 (-717 to 325)		
2nd year	-271 (-838 to 556)	-215.5 (-844 to 398)		

Notes:

[5] - Full analysis set; Change from baseline
1st year N=77
2nd year N=77
[6] - Full analysis set; Change from baseline
1st year N=92
2nd year N=94

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)

Statistical analysis description:

The difference between treatment groups in the median change of the AUC.

The number of subjects in this analysis is N=169;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Placebo v Active treatment (rPhleum)

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1805
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Wilcoxon-Mann-Whitney-U-Test, Active vs. Placebo

Statistical analysis title	Change from baseline (after 2 years of treatment)

Statistical analysis description:

The difference between treatment groups in the median change of the AUC.

The number of subjects in this analysis is N=171;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0723
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Wilcoxon-Mann-Whitney-U-Test, Active vs. Placebo

Secondary: 4a_AUC of RC-symptom score; Change from baseline

End point title	4a_AUC of RC-symptom score; Change from baseline

End point description:

Change of the AUC:RC-symptom score from baseline season to season after 1 and 2 treatment years.

The actual number of patients contributing data for this evaluation is shown under the results table.

AUC=Area under the curve
RC=Rhinoconjunctivitis

End point type	Secondary

End point timeframe:

Baseline to 1 and 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[9]	95[10]		
Units: score				
median (full range (min-max))				
1st year	-131 (-499 to 231)	-102.5 (-439 to 255)		
2nd year	-175.5 (-534 to 429)	-133.5 (-527 to 176)		

Notes:

[9] - Full analysis set; Change from baseline
1st year N=77
2nd year N=77

[10] - Full analysis set; Change from baseline
1st year N=92
2nd year N=94

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)
Statistical analysis description:	
The number of subjects in this analysis is N=169; the number N=173 below is due to an innate error of the EudraCT database system.	
Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2085
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline (after 2 years of treatment)
Statistical analysis description:	
The number of subjects in this analysis is N=171; the number N=173 below is due to an innate error of the EudraCT database system.	
Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0683
Method	Wilcoxon (Mann-Whitney)

Secondary: 4b_AUC of RC-medication score; Change from baseline

End point title	4b_AUC of RC-medication score; Change from baseline
End point description:	
Change of the AUC:RC-medication score from baseline season to season after 1 and 2 treatment years. The actual number of patients contributing data for this evaluation is shown under the results table. AUC=Area under the curve RC=Rhinoconjunctivitis	
End point type	Secondary
End point timeframe:	
Baseline to 1 and 2 years after treatment.	

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[11]	95[12]		
Units: score				
median (full range (min-max))				
1st year	-57 (-404 to 153)	-57.3 (-291 to 230)		
2nd year	-96.5 (-371 to 127)	-88.5 (-384 to 300)		

Notes:

[11] - Full analysis set; Change from baseline
1st year N=77
2nd year N=77
[12] - Full analysis set; Change from baseline
1st year N=92
2nd year N=94

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=169;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3539
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline (after 2 years of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=171;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0922
Method	Wilcoxon (Mann-Whitney)

Secondary: 5a_AUC of SMS; Change from baseline

End point title	5a_AUC of SMS; Change from baseline

End point description:

Change of the AUC: SMS change from baseline season to season after 1 and 2 treatment years.

The actual number of patients contributing data for this evaluation is shown under the results table.

AUC=Area under the curve

SMS=Symptom and medication score

End point type	Secondary

End point timeframe:

Baseline to 1 and 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[13]	95[14]		
Units: score				
median (full range (min-max))				
1st year	-165 (-832 to 381)	-125.8 (-931 to 325)		
2nd year	-274 (-904 to 649)	-229 (-956 to 458)		

Notes:

[13] - Full analysis set; Change from baseline
1st year N=77
2nd year N=77

[14] - Full analysis set; Change from baseline
1st year N=92
2nd year N=94

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=169;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2107
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline (after 2 years of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=171;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1421
Method	Wilcoxon (Mann-Whitney)

Secondary: 5b_AUC of symptom score; Change from baseline

End point title	5b_AUC of symptom score; Change from baseline

End point description:

Change of the AUC: symptom score (SS) from baseline season to season after 1 and 2 treatment years.

The actual number of patients contributing data for this evaluation is shown under the results table.

AUC=Area under the curve
SS=Symptom score

End point type	Secondary

End point timeframe:

Baseline to 1 and 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[15]	95[16]		
Units: score				
median (full range (min-max))				
1st year	-141 (-566 to 260)	-122 (-612 to 361)		
2nd year	-176.5 (-572 to 522)	-136.5 (-636 to 285)		

Notes:

[15] - Full analysis set; Change from baseline
1st year N=77
2nd year N=77

[16] - Full analysis set; Change from baseline
1st year N=92
2nd year N=94

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=169;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2401
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline (after 2 years of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=171;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1148
Method	Wilcoxon (Mann-Whitney)

Secondary: 5c_AUC of medication score; Change from baseline

End point title	5c_AUC of medication score; Change from baseline

End point description:

Change of the AUC: medication score from baseline season to season after 1 and 2 treatment years.

The actual number of patients contributing data for this evaluation is shown under the results table.

AUC=Area under the curve

End point type	Secondary

End point timeframe:

Baseline to 1 and 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[17]	95[18]		
Units: score				
median (full range (min-max))				
1st year	-56.5 (-404 to 205)	-53.3 (-319 to 230)		
2nd year	-99.5 (-371 to 210)	-88.5 (-384 to 304)		

Notes:

[17] - Full analysis set; Change from baseline
1st year N=77
2nd year N=77

[18] - Full analysis set; Change from baseline
1st year N=92
2nd year N=94

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=169;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4854
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline (after 2 years of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=171;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156
Method	Wilcoxon (Mann-Whitney)

Secondary: 6_Immunological profile: IgG (specific total) and IgG4 to Phleum pratense; Change from baseline

End point title	6_Immunological profile: IgG (specific total) and IgG4 to Phleum pratense; Change from baseline

End point description:

At screening visit as well as at final visit of the double blind phase, the following immunological assessments were performed: specific total IgG to Phleum pratense and specific IgG4 to Phleum pratense.

The actual number of patients contributing data for this evaluation is shown under the results table.

End point type	Secondary

End point timeframe:

Baseline to 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[19]	95[20]		
Units: mg/L				
median (full range (min-max))				
IgG	38.1 (-2 to 171)	-0.4 (-8 to 6)		

IgG4	29.4 (0 to 30)	0 (-3 to 2)		

Notes:

[19] - Full analysis set; Change from baseline
IgG (total specific) N=71
IgG4 N=71

[20] - Full analysis set; Change from baseline
IgG (total specific) N=82
IgG4 N=82

Statistical analyses

Statistical analysis title	Change from baseline (2 years of treatment) IgG

Statistical analysis description:

Change from baseline (after 2 years of treatment) IgG (specific, total).

The number of subjects in this analysis is N=152;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline (2 years of treatment); IgG4

Statistical analysis description:

Change from baseline (after 2 year of treatment) IgG4

The number of subjects in this analysis is N=153;
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: 7_Number of RC well days overall; Change from baseline

End point title	7_Number of RC well days overall; Change from baseline

End point description:

The number of RC 'well days' within the 42 day evaluation period, defined as the number of days with RC symptom score ≤ 2 and RC medication score = 0 (as summarized for the endpoint 1).
Change from baseline.

The actual number of patients contributing data for this evaluation is shown under the results table.

RC=Rhinoconjunctivitis

End point type	Secondary

End point timeframe:

Baseline to 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[21]	85[22]		
Units: day				
median (full range (min-max))	4 (-7 to 42)	5 (-23 to 39)		

Notes:

[21] - Full analysis set; Change from baseline

[22] - Full analysis set; Change from baseline

Statistical analyses

Statistical analysis title	Change from baseline (after 2 years of treatment)
Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2831
Method	Wilcoxon (Mann-Whitney)

Secondary: 8_Responder analysis overall

End point title	8_Responder analysis overall

End point description:

Patient’s response to the trial medication was defined as an at least 40% decrease of the AUC of ma-RC-SS from baseline to end of each treatment year.

Shown are patients who were responders by treatment year.
The number of subjects 'Missing' for a particular evaluation time point are shown under the results table.

ma-RC-SS=Medication-adjusted rhinoconjunctivitis symptom score

End point type	Secondary

End point timeframe:

Baseline to 1 and 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[23]	95[24]		
Units: subject				
Responders after 1st year	33	40		
Responders after 2nd year	43	46		

Notes:

[23] - Missing
N=1
N=1

Non responders
N=44
N=34

[24] - Missing
N=3
N=1

Non responders
N=52
N=48

Statistical analyses

Statistical analysis title	Change from baseline (after 1 year of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=73 (responders with at least 40% decrease of AUC of ma-RC-SS from baseline);
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Statistical analysis title	Change from baseline (after 2 years of treatment)

Statistical analysis description:

The number of subjects in this analysis is N=89 (responders with at least 40% decrease of AUC of ma-RC-SS from baseline);
the number N=173 below is due to an innate error of the EudraCT database system.

Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.442
Method	Fisher exact

Secondary: 9_Conjunctival provocation test

End point title	9_Conjunctival provocation test

End point description:

Conjunctival provocation test

CPT reproduces the events occurring by instilling an allergen on the ocular surface.

A lyophilised 6 grass pollen allergen cocktail with a standardised activity to be reconstituted and diluted for the provocation test was supplied by Allergopharma. At the performance of the first test the initial concentration was 5 SBU/ml. After having applied the initial concentration a titration with increasing

concentrations was done until a positive test result was achieved. The highest possible concentration was 5000 SBU/ml.

CPT=Conjunctival provocation test

End point type	Secondary

End point timeframe:

Baseline to 2 years after treatment.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[25]	95[26]		
Units: subject				
Missing	8	6		
Unchanged	14	37		
Partly improved	9	12		
Improved	47	40		

Notes:

[25] - Full analysis set; Change from baseline

[26] - Full analysis set; Change from baseline

Statistical analyses

Statistical analysis title	Change from baseline (after 2 years of treatment)
Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0025 [27]
Method	Mantel-Haenszel

Notes:

[27] - The difference in improvement in conjunctival provocation test results between the active treatment group and placebo group was statistically significant.

Secondary: 10_European Quality of Life Questionnaire (EQ-5D) score; Change from baseline

End point title	10_European Quality of Life Questionnaire (EQ-5D) score; Change from baseline

End point description:

European Quality of Life Questionnaire (EQ-5D) score; Change from baseline .

The scores from the EQ-5D were used with the patient’s time from first treatment to end of trial as a measure of disease burden. The EQ-5D score was derived from the answers to the five questions using the utility (value set) of the UK population.

Questions for EQ-5D were: Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/Depression
The score scale was from 1 to 3 (For full health i.e. health state 11111, the EQ-5D score was 1).

The actual number of patients contributing data for this evaluation is shown within the results table.

End point type	Secondary

End point timeframe:

Start of treatment (Baseline) to the end of the trial.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[28]	85[29]		
Units: score				
median (full range (min-max))	0.00 (-0.3 to 0.2)	0.00 (-0.3 to 0.3)		

Notes:

[28] - Full analysis set

[29] - Full analysis set

Statistical analyses

Statistical analysis title	Change from baseline to end of treatment
Comparison groups	Placebo v Active treatment (rPhleum)
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.507 [30]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - The median overall EQ-5D scores did not change from baseline to final visit and at each time point the median score value was 1, reflecting full health in both treatment groups.

Secondary: 11_European Quality of Life Questionnaire (EQ-5D) score/QALY; Change from baseline

End point title	11_European Quality of Life Questionnaire (EQ-5D) score/QALY; Change from baseline

End point description:

European Quality of Life Questionnaire (EQ-5D) score/QALY; Change from baseline.

The scores from the EQ-5D were used with the patient's time from first treatment to end of trial in years to calculate QALYs as a measure of disease burden.

QALY was derived by multiplying the EQ-5D score with the patient's time from first treatment to end of trial in years: QALY = EQ-5D Score * (Date of last patient's visit – Date of patient's first treatment + 1)/365.

The actual number of patients contributing data for this evaluation is shown within the results table.

EQ-5D=European Quality of Life Questionnaire
QALY=Quality Adjusted Life Year

End point type	Secondary

End point timeframe:

Start of treatment (Baseline) to the end of trial.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[31]	86[32]		
Units: score				
median (full range (min-max))	1.65 (0.4 to 1.7)	1.65 (0.3 to 1.7)		

Notes:

[31] - Full analysis set

[32] - Full analysis set

Statistical analyses

Statistical analysis title	Change from baseline to end of treatment
Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8791 [33]
Method	Wilcoxon (Mann-Whitney)

Notes:

[33] - The median value for quality adjusted life years (QALYs) was 1.65 in both treatment groups indicating no difference between groups in disease burden.

Secondary: 12_European Quality of Life Questionnaire (EQ-5D): General Health; Visual Analogue Scale (VAS); Change from baseline

End point title	12_European Quality of Life Questionnaire (EQ-5D): General Health; Visual Analogue Scale (VAS); Change from baseline

End point description:

European Quality of Life Questionnaire (EQ-5D): General Health; Visual Analogue Scale (VAS); Change from baseline.

Patients were asked to assess their general health status by marking on a VAS from 0 (worst) to 100 (best) to rate their general health at baseline and at final visit.

The actual number of patients contributing data for this evaluation is shown within the results table.

EQ-5D=European Quality of Life Questionnaire
VAS=Visual Analogue Scale

End point type	Secondary

End point timeframe:

Start of treatment (Baseline) to the end of the trial.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[34]	84[35]		
Units: score				
median (full range (min-max))	0 (-35 to 25)	0 (-30 to 45)		

Notes:

[34] - Full analysis set

[35] - Full analysis set

Statistical analyses

Statistical analysis title	Change from baseline to end of treatment
Comparison groups	Active treatment (rPhleum) v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3924 [36]
Method	Wilcoxon (Mann-Whitney)

Notes:

[36] - The median score was 90 in both treatment groups and at both time points indicating an assessment of good health in both groups and at both time points.

Secondary: 13a_Vital signs: Systolic blood pressure

End point title	13a_Vital signs: Systolic blood pressure

End point description:

Vital signs: Systolic blood pressure

Change from baseline visit to the last visit of double-blind phase and end of entire trial were evaluated to obtain further data for the safety evaluation.

The actual number of patients contributing data for this evaluation is shown under the results table.

End point type	Secondary

End point timeframe:

Baseline to the end of 2nd year of treatment (end of the double-blind treatment phase) and to the end of the follow-up phase.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[37]	102[38]		
Units: mmHg				
median (full range (min-max))				
End of 2nd year of treatment	0 (-20 to 30)	0 (-40 to 45)		
End of 6 month (follow-up)	0 (-30 to 28)	0 (-42 to 30)		

Notes:

[37] - Safety set

End of 2nd year of treatment N=69
Follow-up N=57

[38] - Safety set

End of 2nd year of treatment N=80
Follow-up N=64

Statistical analyses

No statistical analyses for this end point

Secondary: 13b_Vital signs: Diastolic blood pressure

End point title	13b_Vital signs: Diastolic blood pressure

End point description:

Vital signs: Diastolic blood pressure

Change from baseline visit to the last visit of double-blind phase and end of entire trial were evaluated to obtain further data for the safety evaluation.

The actual number of patients contributing data for this evaluation is shown under the results table.

End point type	Secondary

End point timeframe:

Baseline to the end of 2nd year of treatment (end of the double-blind treatment phase) and to the end of the follow-up phase.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[39]	102[40]		
Units: mmHg				
median (full range (min-max))				
End of 2nd year of treatment	0 (-18 to 18)	0 (-20 to 30)		
End of 6 month (follow-up	0 (-19 to 20)	0 (-30 to 20)		

Notes:

[39] - Safety set

End of 2nd year of treatment N=69
Follow-up N=57

[40] - Safety set

End of 2nd year of treatment N=80
Follow-up N=64

Statistical analyses

No statistical analyses for this end point

Secondary: 13c_Vital signs: Heart rate

End point title	13c_Vital signs: Heart rate

End point description:

Vital signs: Heart rate

Change from baseline visit to the last visit of double-blind phase and end of entire trial were evaluated to obtain further data for the safety evaluation.

The actual number of patients contributing data for this evaluation is shown under the results table.

bmp=Beats per min

End point type	Secondary

End point timeframe:

Baseline to the end of 2nd year of treatment (end of the double-blind treatment phase) and to the end of the follow-up phase.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[41]	102[42]		
Units: bmp				
median (full range (min-max))				
End of 2nd year of treatment	1 (-23 to 25)	2 (-38 to 34)		
End of 6 month (follow-up)	0 (-29 to 45)	0 (-38 to 22)		

Notes:

[41] - Safety set

End of 2nd year of treatment N=69
Follow-up N=57

[42] - Safety set

End of 2nd year of treatment N=80
Follow-up N=64

Statistical analyses

No statistical analyses for this end point

Secondary: 13d_Vital signs: Respiratory rate

End point title	13d_Vital signs: Respiratory rate

End point description:

Changes in vital signs: Respiratory rate

Change from baseline visit to the last visit of double-blind phase and end of entire trial were evaluated to obtain further data for the safety evaluation.

The actual number of patients contributing data for this evaluation is shown under the results table.

End point type	Secondary

End point timeframe:

Baseline to the end of 2nd year of treatment (end of the double-blind treatment phase) and to the end of the follow-up phase.

End point values	Active treatment (rPhleum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[43]	102[44]		
Units: breaths per min				
median (full range (min-max))				
End of 2nd year of treatment	0 (-12 to 4)	0 (-8 to 8)		
End of 6 month (follow-up	0 (-12 to 6)	0 (-6 to 7)		

Notes:

[43] - Safety set

End of 2nd year of treatment N=68
Follow-up N=56

[44] - Safety set

End of 2nd year of treatment N=78
Follow-up N=62

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 3 years from the start of the study.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1
Reporting groups	
Reporting group title	Active treatment (rPhleum)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Active treatment (rPhleum)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 90 (10.00%)	6 / 102 (5.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Endoscopy upper gastrointestinal tract			
subjects affected / exposed	0 / 90 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon neoplasm			
subjects affected / exposed	0 / 90 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Electric shock			
subjects affected / exposed	0 / 90 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 90 (1.11%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 90 (2.22%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 90 (1.11%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 90 (1.11%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 90 (2.22%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	2 / 90 (2.22%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	0 / 90 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	1 / 90 (1.11%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	0 / 90 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 90 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active treatment (rPhleum)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 90 (75.56%)	75 / 102 (73.53%)	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 90 (8.89%)	10 / 102 (9.80%)	
occurrences (all)	10	18	
General disorders and administration site conditions			
Injection site erythema			

subjects affected / exposed	8 / 90 (8.89%)	5 / 102 (4.90%)	
occurrences (all)	25	28	
Injection site oedema			
subjects affected / exposed	10 / 90 (11.11%)	5 / 102 (4.90%)	
occurrences (all)	22	8	
Injection site pain			
subjects affected / exposed	5 / 90 (5.56%)	13 / 102 (12.75%)	
occurrences (all)	7	23	
Injection site pruritus			
subjects affected / exposed	10 / 90 (11.11%)	4 / 102 (3.92%)	
occurrences (all)	18	4	
Injection site swelling			
subjects affected / exposed	17 / 90 (18.89%)	13 / 102 (12.75%)	
occurrences (all)	49	20	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 90 (4.44%)	6 / 102 (5.88%)	
occurrences (all)	5	7	
Cough			
subjects affected / exposed	6 / 90 (6.67%)	2 / 102 (1.96%)	
occurrences (all)	7	2	
Dyspnoea			
subjects affected / exposed	8 / 90 (8.89%)	1 / 102 (0.98%)	
occurrences (all)	9	1	
Oropharyngeal pain			
subjects affected / exposed	3 / 90 (3.33%)	9 / 102 (8.82%)	
occurrences (all)	5	14	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	9 / 90 (10.00%)	1 / 102 (0.98%)	
occurrences (all)	10	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 90 (3.33%)	6 / 102 (5.88%)	
occurrences (all)	4	7	
Infections and infestations			

Bronchitis			
subjects affected / exposed	5 / 90 (5.56%)	11 / 102 (10.78%)	
occurrences (all)	7	11	
Nasopharyngitis			
subjects affected / exposed	23 / 90 (25.56%)	36 / 102 (35.29%)	
occurrences (all)	36	62	
Pharyngitis			
subjects affected / exposed	2 / 90 (2.22%)	8 / 102 (7.84%)	
occurrences (all)	2	9	
Sinusitis			
subjects affected / exposed	0 / 90 (0.00%)	6 / 102 (5.88%)	
occurrences (all)	0	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2012	• Altered the primary endpoint to change of the area under the curve (AUC) of the medication-adjusted Rhinoconjunctivitis Symptom Score (ma-RC-SS) from the baseline season to the season after 2 years of treatment. The former primary endpoint (change of AUC of the Rhinoconjunctivitis Symptom-Medication-Score [RC-SMS] after 2 years) became an additional secondary endpoint. • Added additional safety laboratory assessments for aluminium, at the final visit of the treatment phase as well as 6 months after the last individual application of trial medication. • Specified parameters: IgE and IgG. • Added as secondary endpoints: changes of rhinoconjunctivitis symptom score, rhinoconjunctivitis medication score, symptom score and medication score after 1, 2, and 3 years. • Added as a secondary endpoint: change of AUC of the medication-adjusted Rhinoconjunctivitis Symptom Score (ma-RC-SS) after 1 and 3 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported