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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	DIA-Phl-01-14

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

Efficacy assessment of Polymerized Phleum pratense inmunotherapy administed intradermally

Protection of trial subjects:

After study inclusion, and throughout the study period, the following rescue medication was allowed for the control of the study disease
Eye symptoms:
Topical antihistamines (eye drops): nedocromil
Nasal symptoms:
Antihistamines: loratadine.
Topical nasal corticosteroids: nasal budesonide.
Oral corticosteroids: deflazacort

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 153
Worldwide total number of subjects	153
EEA total number of subjects	153

Notes:

Subjects enrolled per age group

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

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Pre-assignment period milestones

Number of subjects started	155[1]
Number of subjects completed	153

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not meeting selection criteria: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects starting the pre-assignment period is the number of screened subjects signing informed consent The number of subjects reported as enrolled is the number of randomized subjects meeting the selection criteria.

Period 1

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

Blinding implementation details:

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

Arm title	Active 1-1st year

Arm description:	
Active IMP at low dose. First year of follow-up. first cycle of treatment	
Arm type	Experimental
Investigational medicinal product name	Polymerized Phleum pratense
Investigational medicinal product code	Phl p pol
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intradermal use
Dosage and administration details:	
IMP (0.3 microgram /ml) was administered preseasonally and weekly during 6 weeks (0.1 ml of IMP in one volar forearm and 0.1 ml of matching placebo in the other volar forearm in each single visit)	
Arm title	Active 2- 1st year
Arm description:	
Active IMP at high dose. First year of follow-up. first cycle of treatment	
Arm type	Experimental
Investigational medicinal product name	Polymerized Phleum pratense
Investigational medicinal product code	Phl p pol
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intradermal use
Dosage and administration details:	
IMP (0.3 microgram /ml) was administered preseasonally and weekly during 6 weeks (0.1 ml of IMP in each volar forearm per visit. 0.2 ml total / treatment visit))	

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

Period 2

Period 2 title	Second year
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Blinding implementation details:	
As defined in the protocol, after the first year of follow-up, blinding was opened for the placebo group to receive during the second year of treatment the active treatment with the best efficacy/safety ratio . According to this, these patients were receiving the high dose of active treatment during the second	

period .
the arms initally asigned to Active 1 and Active 2 remained blinded during the second year.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo-Active 2

Arm description:

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

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

Dosage and administration details:

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

Arm title	Active 1- 2nd year

Arm description:

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

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

Dosage and administration details:

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

Arm title	Active 2- 2nd year

Arm description:

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

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

Dosage and administration details:

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

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

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

Baseline characteristics

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

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

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

Subject analysis sets	
Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

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

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

Subject analysis set description:

all randomized subjects receiving at least one dose of study drug

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

Notes:

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

Secondary: Combined symptom and medication score - First year- ITT	
End point title	Combined symptom and medication score - First year- ITT

End point description:

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

End point type	Secondary

End point timeframe:

Registered during the first pollen season (May-June) after the first year of treatment

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

End point title	Allergen concentration eliciting a positive Conjuntival challenge test: change from baseline

End point description:

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

End point type	Secondary

End point timeframe:

at baseline and after the first and second pollen seasson

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

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

Statistical analyses

Statistical analysis title	conjuctival challenge test- first year

Statistical analysis description:

ITT population. Change from baseline after first year of treatment

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

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

Notes:

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

Statistical analysis title	conjuctival challenge test- first year

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	conjuctival challenge test- first year

Statistical analysis description:

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

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

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

Notes:

[12] - Mean difference between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
Difference between both active treatment was not pre-especified in the protocol but it was analysed before unblinding.
An increase in the concentration eliciting a positive test indicates a better tolerance to the allergen exposure

Statistical analysis title	conjuctival challenge test- second year

Statistical analysis description:

ITT population. Change from baseline after second year of treatment

Comparison groups	Active 1- 2nd year v Active 2- 2nd year
Number of subjects included in analysis	78
Analysis specification	Post-hoc
Analysis type	other[13]
P-value	= 0.6123
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-85.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-422.08
upper limit	250.27
Variability estimate	Standard deviation

Notes:

[13] - Mean difference between 2 groups was tested using a two-sided unpaired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference
Difference between both active treatment was not pre-especified in the protocol but defined and analysed before unblinding
an increase in the concentration eliciting a positive test indicates a better tolerance to the allergen exposure

Statistical analysis title	conjuctival challenge test- second year

Statistical analysis description:

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

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

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

Notes:

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

Secondary: Rhinoconjuctivitis symptoms score- PP

End point title	Rhinoconjuctivitis symptoms score- PP

End point description:

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

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

Statistical analysis description:

PP population

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

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

Notes:

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

Statistical analysis title	Symptoms score- intergroup- first year PP

Statistical analysis description:

PP population

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

Notes:

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

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

Statistical analysis description:

PP population

Comparison groups	Active 2- 1st year v Active 1-1st year
Number of subjects included in analysis	67
Analysis specification	Post-hoc
Analysis type	other[17]
P-value	= 0.1876
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.15

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

Notes:

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

Statistical analysis title	Symptoms score- intragroup-PP

Statistical analysis description:

Follow-up PP population: Second year v First year

Comparison groups	Active 1- 2nd year v Active 1-1st year
Number of subjects included in analysis	60
Analysis specification	Post-hoc
Analysis type	other[18]
P-value	= 0.1404
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.03
Variability estimate	Standard deviation

Notes:

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

Statistical analysis title	Symptoms score- intragroup-PP

Statistical analysis description:

Follow-up PP population: Second year v First year

Comparison groups	Active 2- 2nd year v Active 2- 1st year
Number of subjects included in analysis	65
Analysis specification	Post-hoc
Analysis type	other[19]
P-value	= 0.6265
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.24
Variability estimate	Standard deviation

Notes:

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

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

Notes:

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

Secondary: Medication consumption score-PP

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

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

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

Statistical analyses

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

Notes:

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

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

Notes:

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

Statistical analysis title	Medication score- Intergroup-PP

Statistical analysis description:

PP populatin first year

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

Notes:

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

Statistical analysis title	Medication score- Intragroup-PP

Statistical analysis description:

Follow-up PP population: second year v First year

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

Notes:

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

Statistical analysis title	Medication score- Intragroup-PP

Statistical analysis description:

Follow-up PP population: second year v First year

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

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

Notes:

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

Statistical analysis title	Medication score- Intragroup-PP

Statistical analysis description:

Follow-up PP population: second year v First year

Comparison groups	Placebo-Active 2 v Placebo- 1st year
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.0111
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	-0.03
Variability estimate	Standard deviation

Notes:

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

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

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

End point description:

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

Statistical analysis title	sIgE-Phleum pratense- first year

Statistical analysis description:

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

Comparison groups	Active 1-1st year v Placebo- 1st year
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.9948
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.08
upper limit	5.05
Variability estimate	Standard deviation

Notes:

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

Statistical analysis title	sIgE-Phleum pratense- first year-

Statistical analysis description:

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

Comparison groups	Active 2- 1st year v Placebo- 1st year

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

Notes:

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

Statistical analysis title	sIgE-Phleum pratense- first year

Statistical analysis description:

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

Comparison groups	Active 1-1st year v Active 2- 1st year
Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	other[29]
P-value	= 0.36
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.15
upper limit	4.87
Variability estimate	Standard deviation

Notes:

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

Statistical analysis title	sIgE-Phleum pratense- 2nd year

Statistical analysis description:

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

Comparison groups	Placebo-Active 2 v Placebo- 1st year

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

Notes:

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

Statistical analysis title	sIgE-Phleum pratense- 2nd year

Statistical analysis description:

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

Comparison groups	Active 1- 2nd year v Active 2- 2nd year
Number of subjects included in analysis	82
Analysis specification	Post-hoc
Analysis type	other[31]
P-value	= 0.7448
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.02
upper limit	4.21
Variability estimate	Standard deviation

Notes:

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

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

End point title	Serum specific IgG4-Phleum pratense- change from baseline

End point description:

ITT population

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

Statistical analysis title	sIgG4-Phleum pratense- first year

Statistical analysis description:

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

Comparison groups	Placebo- 1st year v Active 1-1st year
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.448
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.03
Variability estimate	Standard deviation

Notes:

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

Statistical analysis title	sIgG4-Phleum pratense- first year

Statistical analysis description:

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

Comparison groups	Active 2- 1st year v Placebo- 1st year

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

Notes:

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

Statistical analysis title	sIgG4-Phleum pratense- first year

Statistical analysis description:

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

Comparison groups	Active 2- 1st year v Active 1-1st year
Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	other[34]
P-value	= 0.5068
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.06
Variability estimate	Standard deviation

Notes:

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

Statistical analysis title	sIgG4-Phleum pratense- 2nd year

Statistical analysis description:

ITT population. Change from baseline after second year of treatment. Placebo group was receiving active treatment during the 2nd year. Change from baseline after first (placebo period) and second year(Active treatment) of follow-up was compaired.

Comparison groups	Placebo-Active 2 v Placebo- 1st year
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.8443
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.01

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

Notes:

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

Statistical analysis title	sIgG4-Phleum pratense- 2nd year

Statistical analysis description:

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

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

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Active 1- Year 1

Reporting group description:

Low dose of Active IMP during the first period of assessment

Reporting group title	Active 2- year 1

Reporting group description:

High dose of Active IMP during the first period of assessment

Reporting group title	Placebo - year 1

Reporting group description: -

Reporting group title	Active 1- Year 2

Reporting group description:

low dose of active IMP during the second year of assessment

Reporting group title	Active 2- year 2

Reporting group description:

High dose of active IMP during the second year of asssessment

Reporting group title	Placebo-Active 2- year 2

Reporting group description:

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported