Clinical trial results:
Multicentre, double-blind, randomized, placebo-controlled, parallel-group, clinical trial to evaluates the clinical efficacy and safety of immunotherapy with purified major allergen Alt a 1 in patients with allergic rhinoconjunctivitis with or without mild to moderate asthma, sensitized the fungus Alternaria alternata

Summary

EudraCT number	2010-024440-15
Trial protocol	ES
Global end of trial date	19 July 2016
Results information	
Result version number	v2 (current)
This version publication date	23 November 2018
First version publication date	04 January 2018
Version creation reason	• New data added to full data set • Correction of full data set Corrections in P values , analysis type and comparison groups. Addition of intragroup comparions vs baseline in secondary endpoints

Trial information

Trial identification	
Sponsor protocol code	DIA-ALT-0111
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	DIATER Laboratorio de Diagnostico y Aplicaciones Terapéuticas S.A.
Sponsor organisation address	Avda. Gregorio Peces Barba, 2 , Leganés, Madrid , Spain, 28918
Public contact	Silvia Fernández Anaya, DIATER Laboratorio de Diagnostico y Aplicaciones Terapéuticas S.A., +34 91 496 60 13, departamento.medico@diater.com
Scientific contact	Silvia Fernández Anaya, DIATER Laboratorio de Diagnostico y Aplicaciones Terapéuticas S.A., +34 91 496 60 13, 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	16 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2016
Global end of trial reached?	Yes
Global end of trial date	19 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of specific immunotherapy with purified major allergen Alt a 1 of the fungus Alternaria alternata administered subcutaneously

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): levocabastine, at usual doses.

Nasal symptoms:
Antihistamines: loratadine.
Topical nasal corticosteroids: nasal budesonide.
Oral corticosteroids: deflazacort

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	29 September 2011
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: 113
Worldwide total number of subjects	113
EEA total number of subjects	113

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	48
Adults (18-64 years)	65
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Wash-out period for the following symptomatic medications:
Loratadine: 7 days, Ketotifen: 7 days, other anti-histamininc medications: 7 days
Short-acting beta-2 adrenergics: 4 hours, long-acting beta-2 adrenergics: 12 hours, antileukotrienes: 24 hours, inhaled corticosteroids: 12 hours, chromones: 24 hours

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	Active-1, Year-1

Arm description:

Concentration 0.25 µg/ml

Arm type	Experimental
Investigational medicinal product name	Alt a 1 Active-1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cluster dose schedule: 5 visits with escalation dose to the optimal dose for 5 weeks.
Optimal dose schedule: 1 monthly optimal dose of 0.8 mL for 11 months.

Arm title	Active-2, Year-1

Arm description:

Concentration 0.46 µg/ml

Arm type	Experimental
Investigational medicinal product name	Alt a 1 Active-2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cluster dose schedule: 5 visits with escalation dose to the optimal dose for 5 weeks.
Optimal dose schedule: 1 monthly optimal dose of 0.8 mL for 11 months.

Arm title	Placebo, Year-1

Arm description:

Patients allocated to this arm received a matching Placebo and were switched to Active-2 in the second year of the study

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	Subcutaneous use

Dosage and administration details:

Cluster dose schedule: 5 visits with escalation dose to the optimal dose for 5 weeks.
Optimal dose schedule: 1 monthly optimal dose of 0.8 mL for 11 months.

Number of subjects in period 1	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1
Started	37	46	30
Completed	32	40	22
Not completed	5	6	8
Physician decision	-	1	-
Adverse event, non-fatal	1	-	-
Lost to follow-up	4	4	7
Development of exclusion criteria	-	1	-
Protocol deviation	-	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active 1, Year-2

Arm description:

Concentration 0.25 µg/ml

Arm type	Experimental
Investigational medicinal product name	Alt a 1 Active-1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 monthly dose of 0.8 mL for 12 months.

Arm title	Active-2, Year-2
Arm description:	
Concentration 0.46 µg/ml	
Arm type	Experimental
Investigational medicinal product name	Alt a 1 Active-2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 monthly dose of 0.8 mL for 12 months.

Arm title	Placebo in Year-1, Active-2 in Year-2
Arm description:	
Patients allocated to this arm received a matching Placebo in the first year of treatment and were switched to Active-2 (concentration 0.46 µg/ml) in the second year of the study	
Arm type	Placebo
Investigational medicinal product name	Placebo in Year-1, Active-2 in Year-2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cluster dose schedule: 5 visits with escalation dose of Active-2 to the optimal dose for 5 weeks.
Optimal dose schedule: 1 monthly optimal dose of 0.8 mL for 11 months.

Number of subjects in period 2	Active 1, Year-2	Active-2, Year-2	Placebo in Year-1, Active-2 in Year-2
Started	32	40	22
Completed	30	37	21
Not completed	2	3	1
Lost to follow-up	1	3	1
Concomitant disease / required other treatment	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Active-1, Year-1
Reporting group description:	
Concentration 0.25 µg/ml	
Reporting group title	Active-2, Year-1
Reporting group description:	
Concentration 0.46 µg/ml	
Reporting group title	Placebo, Year-1
Reporting group description:	
Patients allocated to this arm received a matching Placebo and were switched to Active-2 in the second year of the study	

Reporting group values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1
Number of subjects	37	46	30
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	14	20	14
Adults (18-64 years)	23	26	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	22.2	20.2	21.0
standard deviation	± 8.8	± 7.0	± 8.4
Gender categorical			
Units: Subjects			
Female	18	20	9
Male	19	26	21

Reporting group values	Total		
Number of subjects	113		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	48		

Adults (18-64 years)	65		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	47		
Male	66		

End points

End points reporting groups

Reporting group title	Active-1, Year-1
Reporting group description: Concentration 0.25 µg/ml	
Reporting group title	Active-2, Year-1
Reporting group description: Concentration 0.46 µg/ml	
Reporting group title	Placebo, Year-1
Reporting group description: Patients allocated to this arm received a matching Placebo and were switched to Active-2 in the second year of the study	
Reporting group title	Active 1, Year-2
Reporting group description: Concentration 0.25 µg/ml	
Reporting group title	Active-2, Year-2
Reporting group description: Concentration 0.46 µg/ml	
Reporting group title	Placebo in Year-1, Active-2 in Year-2
Reporting group description: Patients allocated to this arm received a matching Placebo in the first year of treatment and were switched to Active-2 (concentration 0.46 µg/ml) in the second year of the study	
Subject analysis set title	Active 1 (baseline)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Active 1 baseline values in the ITT - Population	
Subject analysis set title	Active 2 (baseline)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Active 2 baseline values in the ITT - Population	
Subject analysis set title	Placebo (Baseline)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo baseline values in the ITT - Population	

Primary: Combined symptom and medication score at 12 months - PP

End point title	Combined symptom and medication score at 12 months - PP
End point description: The primary endpoint was calculated by (mean symptom score + mean symptomatic medication score)/2 Symptom score: registered by the patient for each of 8 symptoms evaluated on a 4-point Likert scale: 0 corresponds to "no" symptoms, 1: "mild symptoms"; 2: "moderate" symptoms, 3 "severe" symptoms. Symptomatic medication score (4-point Likert scale from 0 to 3): calculated individually according to type of rescue medication recorded by the patient. 0 corresponds to "No" medication, 1: local antihistamine; 2: local corticosteroid, 3: oral corticosteroid. The means and SD were calculated for each study group at the evaluable monitoring visit. The means obtained were compared two-by – two between groups using the bilateral T-test with 95% confidence intervals. Statistical significance was set at <0.05. Per Protocol Population	
End point type	Primary
End point timeframe: Assessed after 12 months at Visit 16 (V16)	

End point values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	29	15	
Units: Score				
arithmetic mean (standard deviation)	0.46 (± 0.65)	0.23 (± 0.27)	0.62 (± 0.67)	

Statistical analyses

Statistical analysis title	Active-2 v Placebo
Statistical analysis description:	
Combination of mean symptom score and mean symptomatic medication score	
Comparison groups	Active-2, Year-1 v Placebo, Year-1
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	= 0.0449
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Statistical analysis title	Active 1 v Placebo
Statistical analysis description:	
Combination of mean symptom score and mean symptomatic medication score	
Comparison groups	Active-1, Year-1 v Placebo, Year-1
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	other[2]
P-value	= 0.4885
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[2] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically

significant difference in baseline values amongs groups, mean scores at V16 was compared.

Statistical analysis title	Active 1 v Active 2
Statistical analysis description:	
Combination of mean symptom score and mean symptomatic medication score	
Comparison groups	Active-1, Year-1 v Active-2, Year-1
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	other[3]
P-value	= 0.1391
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[3] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Secondary: Prick test with Alternaria alternata extract at 12 months

End point title	Prick test with Alternaria alternata extract at 12 months
End point description:	
Area of the wheal. ITT population	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	40	22	
Units: mm2				
arithmetic mean (standard deviation)	25.5 (± 19.6)	22.1 (± 16.4)	49.9 (± 44.9)	

Statistical analyses

Statistical analysis title	Active-2 v Placebo
Comparison groups	Active-2, Year-1 v Placebo, Year-1

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
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	Active 1 v Placebo
Comparison groups	Active-1, Year-1 v Placebo, Year-1
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
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	Active 1 v Active 2
Comparison groups	Active-1, Year-1 v Active-2, Year-1
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[6] - 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: IgG4 levels at 12 months

End point title	IgG4 levels at 12 months

End point description:

Serum levels of purified Alt a1 allergen specific IgG4 antibodies.
ITT population

End point type	Secondary

End point timeframe:

12 months

End point values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	39	22	
Units: µg/L				
arithmetic mean (standard deviation)	1099.0 (± 1768.0)	1578.0 (± 2198.0)	45.0 (± 49.6)	

Statistical analyses

Statistical analysis title	Active-2 v Placebo

Statistical analysis description:

The population evaluable by ITT was used: randomized patients who received at least one dose of the drug.

Comparison groups	Active-2, Year-1 v Placebo, Year-1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[7] - 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	Active 1 v Placebo
Comparison groups	Active-1, Year-1 v Placebo, Year-1
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[8] - 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	Active 1 v Active 2
Comparison groups	Active-1, Year-1 v Active-2, Year-1
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[9] - 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 at 12 months - ITT

End point title	Combined symptom and medication score at 12 months - ITT

End point description:

This endpoint was calculated by (mean symptom score + mean symptomatic medication score)/2
Symptom score: registered by the patient for each of 8 symptoms evaluated on a 4-point Likert scale: 0 corresponds to "no" symptoms, 1: "mild symptoms"; 2: "moderate" symptoms, 3 "severe" symptoms.
Symptomatic medication score (4-point Likert scale from 0 to 3): calculated individually according to type of rescue medication recorded by the patient. 0 corresponds to "No" medication, 1: local antihistamine; 2: local corticosteroid, 3: oral corticosteroid.
The means and SD were calculated for each study group at the evaluable monitoring visit. The means obtained were compared two-by – two between groups using the bilateral T-test with 95% confidence intervals. Statistical significance was set at <0.05.
ITT population

End point type	Secondary

End point timeframe:

12 months (Visit 16)

End point values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	31	20	
Units: Score				
arithmetic mean (standard deviation)	0.44 (± 0.64)	0.29 (± 0.37)	0.47 (± 0.64)	

Statistical analyses

Statistical analysis title	Active-2 v Placebo
Comparison groups	Active-2, Year-1 v Placebo, Year-1

Number of subjects included in analysis	51
Analysis specification	Post-hoc
Analysis type	other[10]
P-value	= 0.2719
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[10] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Statistical analysis title	Active 1 v Placebo
Comparison groups	Active-1, Year-1 v Placebo, Year-1
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	other[11]
P-value	= 0.8802
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[11] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active-1, Year-1 v Active-2, Year-1
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	other[12]
P-value	= 0.3549
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[12] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Secondary: Prick test with purified allergen Alt a1 at 12 months

End point title	Prick test with purified allergen Alt a1 at 12 months
End point description: Area of the wheal. ITT population	

End point type	Secondary
End point timeframe: 12 months (Visit 16)	

End point values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	40	22	
Units: mm2				
arithmetic mean (standard deviation)	22.7 (± 14.9)	18.7 (± 10.7)	50.3 (± 50.8)	

Statistical analyses

Statistical analysis title	Active-2 v Placebo
Statistical analysis description: ITT population	
Comparison groups	Active-2, Year-1 v Placebo, Year-1
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[13] - 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	Active 1 v Placebo
Comparison groups	Active-1, Year-1 v Placebo, Year-1
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[14] - 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	Active 1 v Active 2
Comparison groups	Active-1, Year-1 v Active-2, Year-1
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
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

Secondary: Symptom score at 12 months

End point title	Symptom score at 12 months

End point description:

Symptom score: registered by the patient for each of 8 symptoms evaluated on a 4-point Likert scale: 0 corresponds to "no" symptoms, 1: "mild symptoms"; 2: "moderate" symptoms, 3 "severe" symptoms.
Symptomatic medication score (4-point Likert scale from 0 to 3): calculated individually according to type of rescue medication recorded by the patient. 0 corresponds to "No" medication, 1: local antihistamine; 2: local corticosteroid, 3: oral corticosteroid
The population evaluable by ITT was used: randomized patients who received at least one dose of the drug.

End point type	Secondary

End point timeframe:

12 months

End point values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	31	20	
Units: score				
arithmetic mean (standard deviation)	0.40 (± 0.46)	0.43 (± 0.43)	0.44 (± 0.50)	

Statistical analyses

Statistical analysis title	Active-2 v Placebo
Statistical analysis description:	
ITT population	
Comparison groups	Active-2, Year-1 v Placebo, Year-1
Number of subjects included in analysis	51
Analysis specification	Post-hoc
Analysis type	other[16]
P-value	= 0.9112
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[16] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Statistical analysis title	Active 1 v Placebo
Comparison groups	Active-1, Year-1 v Placebo, Year-1
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	other[17]
P-value	= 0.8069
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[17] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active-1, Year-1 v Active-2, Year-1
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	other[18]
P-value	= 0.8608
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[18] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Secondary: IgE levels at 12 months

End point title	IgE levels at 12 months

End point description:

Serum levels of purified Alt a 1 allergen specific IgE antibodies.
ITT population

End point type	Secondary

End point timeframe:

12 months

End point values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	39	22	
Units: kU/l				
arithmetic mean (standard deviation)	18.9 (± 22.7)	17.5 (± 17.9)	10.8 (± 10.8)	

Statistical analyses

Statistical analysis title	Active-2 v Placebo

Statistical analysis description:

ITT population

Comparison groups	Active-2, Year-1 v Placebo, Year-1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

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

Statistical analysis title	Active 1 v Placebo
Comparison groups	Active-1, Year-1 v Placebo, Year-1

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

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

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active-1, Year-1 v Active-2, Year-1
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

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

Secondary: Medication score at 12 months

End point title	Medication score at 12 months

End point description:

Symptomatic medication score (4-point Likert scale from 0 to 3): calculated individually according to type of rescue medication recorded by the patient. 0 corresponds to "No" medication, 1: local antihistamine; 2: local corticosteroid, 3: oral corticosteroid
ITT population

End point type	Secondary

End point timeframe:

12 months

End point values	Active-1, Year-1	Active-2, Year-1	Placebo, Year-1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	33	20	
Units: Score				
arithmetic mean (standard deviation)	0.45 (± 0.96)	0.24 (± 0.56)	0.50 (± 1.00)	

Statistical analyses

Statistical analysis title	Active-2 v Placebo

Statistical analysis description:

ITT population

Comparison groups	Active-2, Year-1 v Placebo, Year-1
Number of subjects included in analysis	53
Analysis specification	Post-hoc
Analysis type	other[22]
P-value	= 0.3007
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[22] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Statistical analysis title	Active 1 v Placebo
Comparison groups	Active-1, Year-1 v Placebo, Year-1
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	other[23]
P-value	= 0.8815
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[23] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active-1, Year-1 v Active-2, Year-1
Number of subjects included in analysis	55
Analysis specification	Post-hoc
Analysis type	other[24]
P-value	= 0.3579
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[24] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 12 months (V16). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V16 was compared.

Secondary: Combined symptom and medication score at 24 months - ITT

End point title	Combined symptom and medication score at 24 months - ITT

End point description:

This endpoint was calculated by (mean symptom score + mean symptomatic medication score)/2
Symptom score: registered by the patient for each of 8 symptoms evaluated on a 4-point Likert scale: 0 corresponds to "no" symptoms, 1: "mild symptoms"; 2: "moderate" symptoms, 3 "severe" symptoms.
Symptomatic medication score (4-point Likert scale from 0 to 3): calculated individually according to type of rescue medication recorded by the patient. 0 corresponds to "No" medication, 1: local antihistamine; 2: local corticosteroid, 3: oral corticosteroid.
the means and SD were calculated for each study group at the evaluable monitoring visit. The means obtained were compared two-by – two between groups using the bilateral T-test with 95% confidence intervals. Statistical significance was set at <0.05.
ITT population

End point type	Secondary

End point timeframe:

24 months (Visit 29)

End point values	Active 1, Year-2	Active-2, Year-2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: Score				
arithmetic mean (standard deviation)	0.50 (± 0.65)	0.28 (± 0.34)		

Statistical analyses

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active 1, Year-2 v Active-2, Year-2
Number of subjects included in analysis	31
Analysis specification	Post-hoc
Analysis type	other[25]
P-value	= 0.2859
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[25] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 24 months (V29). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V29 was compared.

Secondary: Prick test with Alternaria alternata extract at 24 months	
End point title	Prick test with Alternaria alternata extract at 24 months
End point description: Area of the wheal. ITT population	
End point type	Secondary
End point timeframe: 24 months	

End point values	Active 1, Year-2	Active-2, Year-2	Placebo in Year-1, Active-2 in Year-2	Active 1 (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	30	36	21	37
Units: mm2				
arithmetic mean (standard deviation)	20 (± 16.3)	19 (± 15.9)	21.6 (± 20.2)	55.7 (± 35.6)

End point values	Active 2 (baseline)	Placebo (Baseline)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	29		
Units: mm2				
arithmetic mean (standard deviation)	41.5 (± 23.5)	42.9 (± 22.9)		

Statistical analyses

Statistical analysis title	Active 1 at 24 months vs baseline
Comparison groups	Active 1, Year-2 v Active 1 (baseline)
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Notes:

[26] - The difference in means between 2 groups 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. This is an intragroup analysis so the number of patients in the analysis is 30.

Statistical analysis title	Active 2 at 24 months vs baseline
Comparison groups	Active-2, Year-2 v Active 2 (baseline)

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[27] - The difference in means between 2 groups 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. This is an intragroup analysis so the number of subjects in the analysis is 36.

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active 1, Year-2 v Active-2, Year-2
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[28] - 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: IgG4 levels at 24 months

End point title	IgG4 levels at 24 months

End point description:

Serum level of purified Alt a1 allergen specific IgG4 antibodies.
ITT Population

End point type	Secondary

End point timeframe:

24 months

End point values	Active 1, Year-2	Active-2, Year-2	Placebo in Year-1, Active-2 in Year-2	Active 1 (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	30	36	21	36
Units: µg/ml				
arithmetic mean (standard deviation)	1917.0 (± 3422.0)	2088.0 (± 1978.0)	1230.0 (± 984.6)	64.7 (± 80.1)

End point values	Active 2 (baseline)	Placebo (Baseline)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	29		
Units: µg/ml				
arithmetic mean (standard deviation)	58.8 (± 83.0)	45.2 (± 67.0)		

Statistical analyses

Statistical analysis title	Active 1 at 24 months vs baseline
Comparison groups	Active 1, Year-2 v Active 1 (baseline)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[29] - The difference in means between 2 groups 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. This is an intragroup analysis so the number of subjects in the analysis is 30.

Statistical analysis title	Active 2 at 24 months vs baseline
Comparison groups	Active-2, Year-2 v Active 2 (baseline)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[30] - The difference in means between 2 groups 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. This is an intragroup analysis so the number of subjects in the analysis is 36.

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active 1, Year-2 v Active-2, Year-2

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[31] - 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: Prick test with purified allergen Alt a1 at 24 months

End point title	Prick test with purified allergen Alt a1 at 24 months
End point description:	
Area of the wheal. ITT population	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Active 1, Year-2	Active-2, Year-2	Placebo in Year-1, Active-2 in Year-2	Active 1 (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	30	36	21	37
Units: mm2				
arithmetic mean (standard deviation)	16.8 (± 11.9)	13.2 (± 12.3)	18.1 (± 14.2)	52.1 (± 28.7)

End point values	Active 2 (baseline)			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: mm2				
arithmetic mean (standard deviation)	42.5 (± 25.8)			

Statistical analyses

Statistical analysis title	Active 1 at 24 months vs baseline
Comparison groups	Active 1, Year-2 v Active 1 (baseline)

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[32] - The difference in means between 2 groups 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. This is an intragroup analysis so the number of subjects in the analysis is 30.

Statistical analysis title	Active 2 at 24 months vs baseline
Comparison groups	Active-2, Year-2 v Active 2 (baseline)
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[33] - The difference in means between 2 groups 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. This is an intragroup analysis so the number of subjects in the analysis is 36.

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active 1, Year-2 v Active-2, Year-2
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[34] - 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: Symptom score at 24 months

End point title	Symptom score at 24 months

End point description:

Symptom score: registered by the patient for each of 8 symptoms evaluated on a 4-point Likert scale: 0 corresponds to “no” symptoms, 1: “mild symptoms”; 2: “moderate” symptoms, 3 “severe” symptoms. Symptomatic medication score (4-point Likert scale from 0 to 3): calculated individually according to

type of rescue medication recorded by the patient. 0 corresponds to "No" medication, 1: local antihistamine; 2: local corticosteroid, 3: oral corticosteroid
The population evaluable by ITT was used: randomized patients who received at least one dose of the drug.

End point type	Secondary

End point timeframe:

24 months

End point values	Active 1, Year-2	Active-2, Year-2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: Score				
arithmetic mean (standard deviation)	0.62 (± 0.61)	0.46 (± 0.56)		

Statistical analyses

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active 1, Year-2 v Active-2, Year-2
Number of subjects included in analysis	31
Analysis specification	Post-hoc
Analysis type	other[35]
P-value	= 0.4519
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[35] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 24 months (V29). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V29 was compared.

Secondary: IgE levels at 24 months

End point title	IgE levels at 24 months

End point description:

Serum levels of purified Alt a1 allergen specific IgE antibodies
ITT population

End point type	Secondary

End point timeframe:

24 months

End point values	Active 1, Year-2	Active-2, Year-2	Placebo in Year-1, Active-2 in Year-2	Active 1 (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	30	36	21	30
Units: kU/l				
arithmetic mean (standard deviation)	17.3 (± 24.8)	23.9 (± 11.8)	15.6 (± 16.0)	17.3 (± 24.8)

End point values	Active 2 (baseline)			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: kU/l				
arithmetic mean (standard deviation)	12.9 (± 11.8)			

Statistical analyses

Statistical analysis title	Active 1 at 24 months vs baseline
Comparison groups	Active 1, Year-2 v Active 1 (baseline)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[36] - The difference in means between 2 groups 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. This is an intragroup comparison. the number of subjects included in the analysis is 30

Statistical analysis title	Active 2 at 24 months vs baseline
Comparison groups	Active-2, Year-2 v Active 2 (baseline)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[37] - The difference in means between 2 groups 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. This is an intragroup comparison. the number of subjects included in the analysis is 36

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active 1, Year-2 v Active-2, Year-2
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[38] - 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: Medication score at 24 months

End point title	Medication score at 24 months

End point description:

Symptomatic medication score (4-point Likert scale from 0 to 3): calculated individually according to type of rescue medication recorded by the patient. 0 corresponds to "No" medication, 1: local antihistamine; 2: local corticosteroid, 3: oral corticosteroid.
ITT population

End point type	Secondary

End point timeframe:

24 months

End point values	Active 1, Year-2	Active-2, Year-2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	19		
Units: Score				
arithmetic mean (standard deviation)	0.36 (± 0.93)	0.16 (± 0.50)		

Statistical analyses

Statistical analysis title	Active 1 v Active 2
Comparison groups	Active 1, Year-2 v Active-2, Year-2

Number of subjects included in analysis	33
Analysis specification	Post-hoc
Analysis type	other[39]
P-value	= 0.4755
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[39] - Two-sided unpaired t-test . Null-hypothesis of no difference. The differences between groups were to be established by calculating the mean difference in the final-baseline score obtained individually for each treatment group at 24 months (V29). However, many patients started with zero in the combined score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values amongs groups, mean scores at V29 was compared.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Two years of treatment	
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	19.1

Reporting groups	
Reporting group title	Active-1, Year-1
Reporting group description:	
Alt a1 - Active 1, adverse events reported during the first year of treatment	
Reporting group title	Active-2, Year-1
Reporting group description:	
Alt a 1 - Active 2; adverse events reported during the first year of treatment	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment, adverse events reported during the first year of treatment	
Reporting group title	Active-1, Year-2
Reporting group description:	
Adverse events reported during the second year of treatment with Active-1	
Reporting group title	Active-2, Year-2
Reporting group description:	
Adverse events reported during the second year of treatment with Active-2	
Reporting group title	Placebo in Year-1, Active-2 in Year-2
Reporting group description:	
Adverse events reported during 1 year of treatment with Active-2 in patients who were treated with placebo in the first year of the study.	

Serious adverse events	Active-1, Year-1	Active-2, Year-1	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 37 (2.70%)	0 / 45 (0.00%)	0 / 29 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 45 (0.00%)	0 / 29 (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

Delivery			
subjects affected / exposed	0 / 37 (0.00%)	0 / 45 (0.00%)	0 / 29 (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
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 45 (0.00%)	0 / 29 (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
Musculoskeletal and connective tissue disorders			
Meniscus injury			
subjects affected / exposed	0 / 37 (0.00%)	0 / 45 (0.00%)	0 / 29 (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
Infections and infestations			
Meningitis virica			
subjects affected / exposed	1 / 37 (2.70%)	0 / 45 (0.00%)	0 / 29 (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 in Year-1, Active-2 in Year-2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	0 / 40 (0.00%)	2 / 22 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 32 (0.00%)	0 / 40 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delivery			
subjects affected / exposed	0 / 32 (0.00%)	0 / 40 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 40 (0.00%)	0 / 22 (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
Musculoskeletal and connective tissue disorders			
Meniscus injury			
subjects affected / exposed	0 / 32 (0.00%)	0 / 40 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Meningitis virica			
subjects affected / exposed	0 / 32 (0.00%)	0 / 40 (0.00%)	0 / 22 (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
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 37 (78.38%)	39 / 45 (86.67%)	20 / 29 (68.97%)
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 37 (32.43%)	17 / 45 (37.78%)	9 / 29 (31.03%)
occurrences (all)	39	85	15
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	3 / 37 (8.11%)	3 / 45 (6.67%)	4 / 29 (13.79%)
occurrences (all)	10	4	9
Injection site pruritus			
subjects affected / exposed	6 / 37 (16.22%)	10 / 45 (22.22%)	2 / 29 (6.90%)
occurrences (all)	14	26	4
Injection site oedema			
subjects affected / exposed	1 / 37 (2.70%)	3 / 45 (6.67%)	1 / 29 (3.45%)
occurrences (all)	1	7	2

Injection site reaction			
subjects affected / exposed	6 / 37 (16.22%)	9 / 45 (20.00%)	4 / 29 (13.79%)
occurrences (all)	12	11	5
Asthenia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 45 (0.00%)	2 / 29 (6.90%)
occurrences (all)	1	0	2
Injection site inflammation			
subjects affected / exposed	0 / 37 (0.00%)	2 / 45 (4.44%)	2 / 29 (6.90%)
occurrences (all)	0	6	4
Injection site pain			
subjects affected / exposed	5 / 37 (13.51%)	0 / 45 (0.00%)	4 / 29 (13.79%)
occurrences (all)	9	0	10
Discomfort			
subjects affected / exposed	0 / 37 (0.00%)	1 / 45 (2.22%)	1 / 29 (3.45%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 45 (2.22%)	2 / 29 (6.90%)
occurrences (all)	2	1	2
Odynophagia			
subjects affected / exposed	2 / 37 (5.41%)	4 / 45 (8.89%)	2 / 29 (6.90%)
occurrences (all)	2	5	2
Abdominal pain upper			
subjects affected / exposed	0 / 37 (0.00%)	1 / 45 (2.22%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
Dental discomfort			
subjects affected / exposed	0 / 37 (0.00%)	3 / 45 (6.67%)	1 / 29 (3.45%)
occurrences (all)	0	5	2
Vomiting			
subjects affected / exposed	0 / 37 (0.00%)	0 / 45 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	4 / 37 (10.81%)	6 / 45 (13.33%)	0 / 29 (0.00%)
occurrences (all)	14	15	0
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	3 / 37 (8.11%)	4 / 45 (8.89%)	3 / 29 (10.34%)
occurrences (all)	5	17	5
Cough			
subjects affected / exposed	2 / 37 (5.41%)	6 / 45 (13.33%)	3 / 29 (10.34%)
occurrences (all)	2	7	7
Nasal congestion			
subjects affected / exposed	2 / 37 (5.41%)	0 / 45 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	4 / 37 (10.81%)	7 / 45 (15.56%)	0 / 29 (0.00%)
occurrences (all)	7	11	0
Bronchospasm			
subjects affected / exposed	1 / 37 (2.70%)	3 / 45 (6.67%)	2 / 29 (6.90%)
occurrences (all)	1	4	2
Dyspnoea			
subjects affected / exposed	0 / 37 (0.00%)	2 / 45 (4.44%)	2 / 29 (6.90%)
occurrences (all)	0	2	4
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 45 (0.00%)	0 / 29 (0.00%)
occurrences (all)	6	0	0
Pruritus			
subjects affected / exposed	3 / 37 (8.11%)	5 / 45 (11.11%)	2 / 29 (6.90%)
occurrences (all)	4	6	4
Musculoskeletal and connective tissue disorders			
Contusion			
subjects affected / exposed	2 / 37 (5.41%)	1 / 45 (2.22%)	1 / 29 (3.45%)
occurrences (all)	2	1	1
Back pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 45 (2.22%)	1 / 29 (3.45%)
occurrences (all)	0	2	2
Muscle contracture			
subjects affected / exposed	0 / 37 (0.00%)	2 / 45 (4.44%)	1 / 29 (3.45%)
occurrences (all)	0	4	1
Pain in extremity			

subjects affected / exposed	1 / 37 (2.70%)	1 / 45 (2.22%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 37 (8.11%)	0 / 45 (0.00%)	2 / 29 (6.90%)
occurrences (all)	4	0	2
Conjunctivitis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 45 (0.00%)	1 / 29 (3.45%)
occurrences (all)	2	0	1
Influenza			
subjects affected / exposed	2 / 37 (5.41%)	4 / 45 (8.89%)	2 / 29 (6.90%)
occurrences (all)	2	5	3
Nasopharyngitis			
subjects affected / exposed	3 / 37 (8.11%)	7 / 45 (15.56%)	3 / 29 (10.34%)
occurrences (all)	4	9	3
Pharyngitis			
subjects affected / exposed	4 / 37 (10.81%)	1 / 45 (2.22%)	3 / 29 (10.34%)
occurrences (all)	5	2	4
Pharyngotonsillitis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 45 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
Respiratory tract infection			
subjects affected / exposed	4 / 37 (10.81%)	8 / 45 (17.78%)	3 / 29 (10.34%)
occurrences (all)	6	10	4
Sinusitis			
subjects affected / exposed	4 / 37 (10.81%)	0 / 45 (0.00%)	1 / 29 (3.45%)
occurrences (all)	5	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 37 (2.70%)	1 / 45 (2.22%)	1 / 29 (3.45%)
occurrences (all)	1	1	1
Hordeolum			
subjects affected / exposed	0 / 37 (0.00%)	3 / 45 (6.67%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
Tonsillitis			
subjects affected / exposed	1 / 37 (2.70%)	5 / 45 (11.11%)	0 / 29 (0.00%)
occurrences (all)	1	6	0

Ear infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 45 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Active-1, Year-2	Active-2, Year-2	Placebo in Year-1, Active-2 in Year-2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 32 (75.00%)	32 / 40 (80.00%)	13 / 22 (59.09%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 32 (18.75%)	12 / 40 (30.00%)	4 / 22 (18.18%)
occurrences (all)	21	52	14
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 32 (0.00%)	2 / 40 (5.00%)	0 / 22 (0.00%)
occurrences (all)	0	5	0
Injection site pruritus			
subjects affected / exposed	1 / 32 (3.13%)	2 / 40 (5.00%)	1 / 22 (4.55%)
occurrences (all)	1	2	1
Injection site oedema			
subjects affected / exposed	0 / 32 (0.00%)	2 / 40 (5.00%)	0 / 22 (0.00%)
occurrences (all)	0	5	0
Injection site reaction			
subjects affected / exposed	2 / 32 (6.25%)	1 / 40 (2.50%)	3 / 22 (13.64%)
occurrences (all)	6	1	6
Asthenia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 40 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injection site inflammation			
subjects affected / exposed	0 / 32 (0.00%)	2 / 40 (5.00%)	0 / 22 (0.00%)
occurrences (all)	0	4	0
Injection site pain			
subjects affected / exposed	1 / 32 (3.13%)	3 / 40 (7.50%)	0 / 22 (0.00%)
occurrences (all)	6	5	0
Discomfort			
subjects affected / exposed	1 / 32 (3.13%)	3 / 40 (7.50%)	0 / 22 (0.00%)
occurrences (all)	2	3	0

Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	2 / 32 (6.25%)	3 / 40 (7.50%)	0 / 22 (0.00%)
occurrences (all)	2	3	0
Odynophagia			
subjects affected / exposed	1 / 32 (3.13%)	5 / 40 (12.50%)	2 / 22 (9.09%)
occurrences (all)	1	5	2
Abdominal pain upper			
subjects affected / exposed	2 / 32 (6.25%)	0 / 40 (0.00%)	1 / 22 (4.55%)
occurrences (all)	5	0	1
Dental discomfort			
subjects affected / exposed	2 / 32 (6.25%)	1 / 40 (2.50%)	1 / 22 (4.55%)
occurrences (all)	2	1	2
Vomiting			
subjects affected / exposed	0 / 32 (0.00%)	4 / 40 (10.00%)	0 / 22 (0.00%)
occurrences (all)	0	6	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 32 (6.25%)	2 / 40 (5.00%)	0 / 22 (0.00%)
occurrences (all)	18	5	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 32 (9.38%)	4 / 40 (10.00%)	2 / 22 (9.09%)
occurrences (all)	7	13	2
Cough			
subjects affected / exposed	1 / 32 (3.13%)	4 / 40 (10.00%)	1 / 22 (4.55%)
occurrences (all)	1	5	1
Nasal congestion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 40 (2.50%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	4 / 32 (12.50%)	4 / 40 (10.00%)	2 / 22 (9.09%)
occurrences (all)	8	8	2
Bronchospasm			
subjects affected / exposed	1 / 32 (3.13%)	1 / 40 (2.50%)	1 / 22 (4.55%)
occurrences (all)	5	1	1

Dyspnoea			
subjects affected / exposed	2 / 32 (6.25%)	3 / 40 (7.50%)	1 / 22 (4.55%)
occurrences (all)	6	4	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 40 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 32 (0.00%)	1 / 40 (2.50%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
Contusion			
subjects affected / exposed	0 / 32 (0.00%)	2 / 40 (5.00%)	0 / 22 (0.00%)
occurrences (all)	0	3	0
Back pain			
subjects affected / exposed	2 / 32 (6.25%)	3 / 40 (7.50%)	0 / 22 (0.00%)
occurrences (all)	3	4	0
Muscle contracture			
subjects affected / exposed	1 / 32 (3.13%)	3 / 40 (7.50%)	0 / 22 (0.00%)
occurrences (all)	1	4	0
Pain in extremity			
subjects affected / exposed	2 / 32 (6.25%)	2 / 40 (5.00%)	1 / 22 (4.55%)
occurrences (all)	3	2	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 32 (0.00%)	3 / 40 (7.50%)	0 / 22 (0.00%)
occurrences (all)	0	3	0
Conjunctivitis			
subjects affected / exposed	1 / 32 (3.13%)	3 / 40 (7.50%)	0 / 22 (0.00%)
occurrences (all)	2	4	0
Influenza			
subjects affected / exposed	3 / 32 (9.38%)	4 / 40 (10.00%)	0 / 22 (0.00%)
occurrences (all)	4	5	0
Nasopharyngitis			
subjects affected / exposed	6 / 32 (18.75%)	8 / 40 (20.00%)	6 / 22 (27.27%)
occurrences (all)	9	11	9

Pharyngitis			
subjects affected / exposed	1 / 32 (3.13%)	3 / 40 (7.50%)	3 / 22 (13.64%)
occurrences (all)	1	3	4
Pharyngotonsillitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 40 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	4 / 32 (12.50%)	5 / 40 (12.50%)	3 / 22 (13.64%)
occurrences (all)	8	6	5
Sinusitis			
subjects affected / exposed	3 / 32 (9.38%)	0 / 40 (0.00%)	1 / 22 (4.55%)
occurrences (all)	4	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 32 (6.25%)	3 / 40 (7.50%)	1 / 22 (4.55%)
occurrences (all)	2	4	1
Hordeolum			
subjects affected / exposed	1 / 32 (3.13%)	0 / 40 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	2 / 32 (6.25%)	1 / 40 (2.50%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Ear infection			
subjects affected / exposed	2 / 32 (6.25%)	0 / 40 (0.00%)	1 / 22 (4.55%)
occurrences (all)	2	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2012	Increase in the number of participant sites due to low recruitment rate.
13 May 2013	Increase in the number of participant sites due to low recruitment rate.
15 July 2013	Change of the Principal Investigator for the "Hospital del Sureste" , Madrid

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported