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	v1
This version publication date	04 January 2018
First version publication date	04 January 2018

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
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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 wk	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 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	Investigator, Data analyst, Carer, Assessor, Subject

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	Solution 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	Solution 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	Solution 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	Solution 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	Solution 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	Solution 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	

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	
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 Vs. 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	superiority[1]
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:

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

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

Notes:

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

Statistical analysis title	Active-1 Vs. 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	superiority[3]
P-value	= 0.1391
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Notes:

[3] - The differences between groups were to be established by calculating the mean of the differences in the final-baseline score obtained individually (intrasubject) for each treatment group at 12 months (V16). However, many patients started with zero in the combined symptom and medication score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values between groups, the mean scores at V16 between the groups were 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.	
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 Vs Placebo
Comparison groups	Active-2, Year-1 v Placebo, Year-1
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [4]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[4] -

Statistical analysis title	Active-1 Vs Placebo
Comparison groups	Placebo, Year-1 v Active-1, Year-1
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
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

Statistical analysis title	Active-1 Vs 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	superiority
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

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	
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 Vs. 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	superiority
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

Statistical analysis title	Active-1 Vs. 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-1, Year-1 v Placebo, Year-1
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
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

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

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 Vs Placebo
Comparison groups	Active-2, Year-1 v Placebo, Year-1
Number of subjects included in analysis	51
Analysis specification	Post-hoc
Analysis type	superiority[5]
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:

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

Statistical analysis title	Active-1 Vs Placebo
Comparison groups	Placebo, Year-1 v Active-1, Year-1
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority[6]
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:

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

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 Vs. 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	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Statistical analysis title	Active-1 Vs. Placebo

Statistical analysis description:

ITT population

Comparison groups	Placebo, Year-1 v Active-1, Year-1

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

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 Vs. 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	superiority[7]
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:

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

Statistical analysis title	Active-1 Vs. 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	superiority[8]
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:

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

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 Vs. 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	superiority
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

Statistical analysis title	Active-1 Vs. Placebo
Statistical analysis description: ITT population	
Comparison groups	Placebo, Year-1 v Active-1, Year-1
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
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

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	
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 Vs. 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	superiority[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 differences between groups were to be established by calculating the mean of the differences in the final-baseline score obtained individually (intrasubject) for each treatment group at 12 months (V16). However, many patients started with zero in the combined symptom and medication score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values between groups, the mean scores at V16 between the groups were compared.

Statistical analysis title	Active-1 Vs. Placebo
Statistical analysis description: ITT population	
Comparison groups	Placebo, Year-1 v Active-1, Year-1
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority[10]
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:

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

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-2 Vs. Active-1
Comparison groups	Active 1, Year-2 v Active-2, Year-2
Number of subjects included in analysis	31
Analysis specification	Post-hoc
Analysis type	superiority[11]
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:

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

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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	36	21	
Units: mm2				
arithmetic mean (standard deviation)	20 (± 16.3)	19 (± 15.9)	21.6 (± 20.2)	

Statistical analyses

Statistical analysis title	Placebo in Year-1, Active-2 in Year-2 Vs. Placebo
Comparison groups	Placebo in Year-1, Active-2 in Year-2
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [12]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[12] - Placebo in Year-1, Active-2 in Year-2 vs Placebo in Year-1

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	
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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	36	21	
Units: µg/ml				
arithmetic mean (standard deviation)	1917.0 (± 3422.0)	2088.0 (± 1978.0)	1230.0 (± 984.6)	

Statistical analyses

Statistical analysis title	Placebo in Year-1, Active-2 in Year-2 Vs. Placebo
Comparison groups	Placebo in Year-1, Active-2 in Year-2
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [13]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[13] - Placebo in Year-1, Active-2 in Year-2 vs Placebo in Year-1

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	
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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	36	21	
Units: mm2				
arithmetic mean (standard deviation)	16.8 (± 11.9)	13.2 (± 12.3)	18.1 (± 14.2)	

Statistical analyses

Statistical analysis title	Placebo in Year-1, Active-2 in Year-2 Vs. Placebo
Comparison groups	Placebo in Year-1, Active-2 in Year-2

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05 [14]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[14] - Placebo in Year-1, Active-2 in Year-2 vs Placeb in Year-1 o

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 Year-2 Vs. Active-2 Year-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	superiority[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 differences between groups were to be established by calculating the mean of the differences in the final-baseline score obtained individually (intrasubject) for each treatment group. However, many patients started with zero in the combined symptom and medication score, which does not allow any intrasubject clinical improvement. As there was no statistically significant difference in baseline values between groups, the mean scores at V29 (24 months) between the groups were 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

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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	36	21	
Units: kU/l				
arithmetic mean (standard deviation)	17.3 (± 24.8)	12.9 (± 11.8)	15.6 (± 16.0)	

Statistical analyses

Statistical analysis title	Placebo in Year-1, Active-2 in Year-2 Vs. Placebo
Comparison groups	Placebo in Year-1, Active-2 in Year-2
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [16]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[16] - Placebo in Year-1, Active-2 in Year-2 vs Placebo in Year-1

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

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 Year-2 Vs. Active-2 Year-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	superiority[17]
P-value	= 0.4755
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Notes:

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