Clinical trial results:
A multicenter randomized double-blind placebo-controlled clinical trial for evaluation of efficacy and safety of specific immunotherapy with an aluminium hydroxide-adsorbed allergoid preparation of house dust mite (Dermatophagoides pteronyssinus) in patients with allergic bronchial asthma and with allergic rhinitis or rhinoconjunctivitis

Summary

EudraCT number	2015-000188-15
Trial protocol	PL LT DE ES LV AT HR
Global end of trial date	25 April 2019

Results information

Result version number	v1 (current)
This version publication date	11 November 2020
First version publication date	11 November 2020

Trial information

Trial identification

Sponsor protocol code	AL1402ac

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Allergopharma GmbH & Co. KG
Sponsor organisation address	Hermann-Körner-Straße 52, Reinbek, Germany, 21465
Public contact	Clinical Trials Information, Allergopharma GmbH & Co. KG, +49 40 727 65 - 0,
Scientific contact	Clinical Trials Information, Allergopharma GmbH & Co. KG, +49 40 727 65 - 0,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000835-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to demonstrate efficacy and to evaluate safety of AIT with an aluminium hydroxide adsorbed allergoid preparation of major allergens of D.p. in patients with allergic bronchial asthma (GINA 2016; steps 2 to 4) and allergic rhinitis or rhinoconjunctivitis caused by house dust mites.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) guidance for Good Clinical Practice (GCP) and the applicable regulatory requirements.

Data Safety Monitoring Board (DSMB) was in place throughout the trial; DSMB consisted of 3 independent experts, experienced in the field of allergy. The primary function of the DSMB was to ensure the subjects' safety. The DSMB team reviewed an update of the safety data from all treated subjects.

After each administration of the IMP, each subject in the study was kept under supervision of a qualified and trained investigator for at least 30 min. Safety evaluation during supervision after IMP administration consisted of: FEV1, Systolic BP, Diastolic BP, Heart rate (Pulse rate), Respiratory rate.

Background therapy:

-

Evidence for comparator:

-

Abbreviations used in this document:
ACQ=Asthma Quality of Life Questionnaire
AE=Adverse Event
AIT=Allergen Immunotherapy
ALAT=Alanine Aminotransferase
AQLQ=Asthma Quality of Life Questionnaire
ASAT=Aspartate Aminotransferase
BMI=Body Mass Index
BP=Blood Pressure
bpm=Beats per Minute
CS=Clinically Significant
CSMS=Combined Symptom Medication Score
D.f.=Dermatophagoides Farinae
D.p.=Dermatophagoides Pteronyssinus
DSMB=Data Safety Monitoring Board
dMS=Daily Medication Score
dSS=Daily Symptom Score
EAACI=European Academy of Allergy and Clinical Immunology
FEV1=Forced Expiratory Volume in 1 Second
γ-GT=Gamma Glutamyl Transferase
GCP=Good Clinical Practice
GINA=Global Initiative for Asthma
ICF=Informed Consent Form
ICS=Inhaled Corticosteroid
Ig=Immunoglobulin
kU/L=kilo Units per Litre

IMP=Investigational Medicinal Product
IS=Injection Site
MedDRA=Medical Dictionary for Regulatory Activities
NCS=Not Clincally Significant
PEF=Peakflow
PNU=Protein Nitrogen Unit
RBC=Red Blood Cells
rdss=Rhinitis Daily Symptom Score
SABA=Short Acting Beta Agonist
SPT=Skin Prickt Test
T=Treatment
TEAE=Treatment Emergent Adverse event
TU=Therapeutic Units
WAO=World Allergy Organization

Actual start date of recruitment	01 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 216
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Austria: 21
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Latvia: 40
Country: Number of subjects enrolled	Lithuania: 13
Country: Number of subjects enrolled	Romania: 27
Country: Number of subjects enrolled	Serbia: 50
Country: Number of subjects enrolled	Ukraine: 43
Country: Number of subjects enrolled	Russian Federation: 9
Worldwide total number of subjects	424
EEA total number of subjects	322

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)	122
Adults (18-64 years)	302
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 1038 male and female subjects (12 to 65 y) were screened for eligibility; of these, 426 were randomised to treatment according to the exclusion and inclusion criteria.

Pre-assignment

Screening details:

Study subjects (outpatients) were included if they were suffering from immunoglobulin (Ig) E-mediated allergic bronchial asthma according to GINA step 2-4, caused by house dust mite documented by skin prick test (SPT) wheal for Dermatophagoides pteronyssinus (D.p.) and specific IgE value of ≥ 1.50 kU/L to D.p.

Pre-assignment period milestones

Number of subjects started	1038[1]
Number of subjects completed	424

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Sponsor/DSMB decision: 10
Reason: Number of subjects	Consent withdrawn by subject: 49
Reason: Number of subjects	Pregnancy: 3
Reason: Number of subjects	Adverse event, non-fatal: 3
Reason: Number of subjects	Lost to follow-up: 4
Reason: Number of subjects	Missing reason: 1
Reason: Number of subjects	Other reasons: 7
Reason: Number of subjects	Inclusion/ exclusion criteria: 537

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects:

- enrolled worldwide is 1038
- subjects enrolled per country are given for the Safety Set of 424 patient

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Placebo: solution containing aluminium hydroxide (Al(OH)3) in normal saline (9 g/L sodium chloride) was applied.

Injection volume (0.1 mL at minimum 0.6 mL at maximum for matching Strength A placebo and 0.1 - 0.6 mL strength B placebo) was matching the volume of the corresponding active preparation.

The injections were administered slowly, strictly subcutaneously, under sterile precautionary measures, on the extensor side of the upper arm, a hand's breadth above the elbow, using a short-ground cannula. After each administration at the trial center, the patient was kept under close supervision for at least 30 minutes.

Arm title	Acaroid
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	D. pteronyssinus allergoid preparation 5400 PNU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

D. pteronyssinus allergoid preparation 5400 PNU

For the injection volume and administration details of the active treatment, please see the description above for Placebo.

PNU=Protein nitrogen unit

Number of subjects in period 1	Placebo	Acaroid
Started	134	290
Completed	127	272
Not completed	7	18
Consent withdrawn by subject	3	4
Adverse event, non-fatal	-	7
Pregnancy	2	1
Other reasons	1	3
Lost to follow-up	-	2
Sponsor/DSMB decision	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Acaroid
Reporting group description: -	

Reporting group values	Placebo	Acaroid	Total
Number of subjects	134	290	424
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)	36	86	122
Adults (18-64 years)	98	204	302
From 65-84 years	0	0	0
85 years and over	0	0	0
Adolescents	0	0	0
Age continuous Units: years			
arithmetic mean	28.5	27.1	
standard deviation	± 12.6	± 11.9	-
Gender categorical Units: Subjects			
Female	69	139	208
Male	65	151	216
Race Units: Subjects			
Caucasian	132	287	419
Asian descent	2	3	5

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Acaroid
Reporting group description: -	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

This was a multicenter, multinational, double-blind, placebo-controlled trial with 2 parallel groups. It was a confirmatory phase III pivotal trial with one primary efficacy endpoint to confirm the efficacy of Acaroid for the treatment of allergic asthma when comparing the dose of 5400 protein nitrogen unit (PNU) to placebo. Adolescent and adult patients with allergic bronchial asthma and allergic rhinitis or rhinoconjunctivitis caused by house dust mites were randomized 2:1 to treatment with Acaroid® or placebo for approximately 8 months.
The trial consisted of a screening period, a baseline period, a treatment period, and an eDiary period after treatment. In the baseline period, the necessity of inhaled corticosteroids (ICS) for treating asthma and the minimal dose of ICS required to achieve asthma control were evaluated.

Subject analysis set title	Acaroid
Subject analysis set type	Full analysis

Subject analysis set description:

This was a multicenter, multinational, double-blind, placebo-controlled trial with 2 parallel groups. It was a confirmatory phase III pivotal trial with one primary efficacy endpoint to confirm the efficacy of Acaroid for the treatment of allergic asthma when comparing the dose of 5400 protein nitrogen unit (PNU) to placebo. Adolescent and adult patients with allergic bronchial asthma and allergic rhinitis or rhinoconjunctivitis caused by house dust mites were randomized 2:1 to treatment with Acaroid® or placebo for approximately 8 months.
The trial consisted of a screening period, a baseline period, a treatment period, and an eDiary period after treatment. In the baseline period, the necessity of inhaled corticosteroids (ICS) for treating asthma and the minimal dose of ICS required to achieve asthma control were evaluated.

Primary: 1_Change of minimal controlled dose (multiple imputation)

End point title	1_Change of minimal controlled dose (multiple imputation)

End point description:

This was a confirmatory phase III pivotal trial: The primary objective was to confirm efficacy of Acaroid in the treatment of allergic asthma when comparing to placebo.

Primary endpoint was the change in dose steps of the minimum daily inhaled corticosteroid (ICS) dose required to ensure asthma control (well controlled or partly controlled [ACQ 6 score ≤ 1.00]) according to the Asthma Control Questionnaire (ACQ6) between baseline and after Allergen Immunotherapy.

End point type	Primary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Subjects				
Increase by 3 steps (+3)	0	1		
Increase by 2 steps (+2)	1	0		
Increase by 1 step (+1)	1	6		
No change	25	38		

Reduction by 1 step (-1)	33	64		
Reduction by 2 steps (-2)	37	97		
Reduction by 3 steps (-3)	24	46		
Reduction by 4 steps (-4)	2	12		
Missing (imputed)	9	22		

Statistical analyses

Statistical analysis title	Primary efficacy analysis

Statistical analysis description:

To derive the p-value for the hypothesis, the one-sided stratified Mann-Whitney U-test, also known as van-Elteren-test (van Elteren 1960)was performed with the stratification variables 'pooled country' and 'age group' (adolescents [12-17 years] and adults [≥18 years]). No continuity correction was to be done.

Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9311 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - One sided stratified Mann-Whitney U-test by pooled country and age group comparing active vs. placebo- multiple imputation.

Secondary: 2_1_Minimal controlled dose [µg] – summary statistics

End point title	2_1_Minimal controlled dose [µg] – summary statistics

End point description:

The change of the minimum daily ICS (Budesonide) dose required to ensure asthma control was analyzed as continuous variable.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	262		
Units: µg				
arithmetic mean (standard deviation)	-404.9 (± 309.1)	-455.0 (± 325.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: 2_2_Change of minimal controlled ICS dose [µg]

End point title	2_2_Change of minimal controlled ICS dose [µg]

End point description:

The requirement of the minimum daily ICS (Budesonide) dose to ensure asthma control was analyzed in categories of 200µg (range: -1200 to +800µg).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Subjects				
-1200	2	12		
-1000	2	7		
-800	24	45		
-600	11	27		
-400	41	110		
-200	16	18		
'0'	25	38		
400	1	5		
800	0	0		
Missing	10	24		

Statistical analyses

Statistical analysis title	Change of minimal controlled dose [µg]

Statistical analysis description:

The one-sided stratified Mann-Whitney U-test was used to compare the distributions of the change from baseline to post-treatment as categorical variable.

Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0297 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Frequency table

[3] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo - observed cases

Secondary: 3_1_ACQ6 score under the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point title	3_1_ACQ6 score under the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the mean score of all questions and ranges from 0 (no impairment) to 6 (maximum impairment). ACQ6 score was recorded as described in (Barnes P et al., Allergy 2014[69]: 1119-1140).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
arithmetic mean (standard deviation)	-1.142 (± 0.723)	-1.183 (± 0.701)		

Statistical analyses

No statistical analyses for this end point

Secondary: 3_2_ANCOVA for change of ACQ6 score under the highest daily ICS dose the patient was not controlled at baseline

End point title	3_2_ANCOVA for change of ACQ6 score under the highest daily ICS dose the patient was not controlled at baseline

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the mean score of all questions and ranges from 0 (no impairment) to 6 (maximum impairment).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
least squares mean (standard error)	-1.067 (± 0.053)	-1.155 (± 0.039)		

Statistical analyses

Statistical analysis title	ANCOVA change ACQ6 score at highest daily ICSdose
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1148 [4]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.199
upper limit	0.022

Notes:

[4] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 3_3_Categorical display of mean ACQ6 score under the lowest daily ICS dose the patient was controlled at post-treatment

End point title	3_3_Categorical display of mean ACQ6 score under the lowest daily ICS dose the patient was controlled at post-treatment

End point description:

Analysis of categorized ACQ6 score values.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Subjects				
ACQ6 = 0 for minimal controlled dose after AIT	37	92		
0<ACQ6≤0.5 for minimal controlled dose after AIT	49	103		
ACQ6 > 0.5 for minimal controlled dose after AIT	36	65		
Missing	10	26		

Statistical analyses

Statistical analysis title	Categorical display of mean ACQ6 score
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.8481 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Frequency table

[6] - One sided stratified Mann-Whitney U-test by pooled country and age group comparing active vs. placebo - observed cases

Secondary: 4_1_Night time awakening with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point title	4_1_Night time awakening with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (never) to 6 (unable to sleep because of asthma).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
arithmetic mean (standard deviation)	-1.04 (± 1.12)	-0.96 (± 1.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: 4_2_ANCOVA for change of night time awakening with the highest daily ICS dose the patient was not controlled at baseline

End point title	4_2_ANCOVA for change of night time awakening with the highest daily ICS dose the patient was not controlled at baseline

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (never) to 6 (unable to sleep because of asthma).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
least squares mean (standard error)	-0.88 (± 0.06)	-0.95 (± 0.04)		

Statistical analyses

Statistical analysis title	ANCOVA for change of night time awakening
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2723 [7]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.05

Notes:

[7] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 5_1_Severity of asthma symptoms with the highest daily ICS dose the patient was not controlled at baseline – summary statistics

End point title	5_1_Severity of asthma symptoms with the highest daily ICS dose the patient was not controlled at baseline – summary statistics

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the mean score of all questions and ranges from 0 (no symptoms) to 6 (very severe symptoms).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
arithmetic mean (standard deviation)	-1.31 (± 1.15)	-1.47 (± 1.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: 5_2_ANCOVA for change of severity of asthma symptoms with the highest daily ICS dose the patient was not controlled at baseline

End point title	5_2_ANCOVA for change of severity of asthma symptoms with the highest daily ICS dose the patient was not controlled at baseline

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (no symptoms) to 6 (very severe symptoms).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
least squares mean (standard error)	-1.39 (± 0.08)	-1.46 (± 0.06)		

Statistical analyses

Statistical analysis title	ANCOVA for change of severity of asthma symptoms
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4565 [8]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.1

Notes:

[8] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 6_1_Limitation of daily activities with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point title	6_1_Limitation of daily activities with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (not limited at all) to 6 (totally limited).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
arithmetic mean (standard deviation)	-1.34 (± 1.07)	-1.35 (± 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6_2_ANCOVA for change of limitation of daily activities with the highest daily ICS dose the patient was not controlled at baseline

End point title	6_2_ANCOVA for change of limitation of daily activities with the highest daily ICS dose the patient was not controlled at baseline

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (not limited at all) to 6 (totally limited).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
least squares mean (standard error)	-1.26 (± 0.08)	-1.31 (± 0.06)		

Statistical analyses

Statistical analysis title	ANCOVA change of limitation of daily activities
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5224 [9]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.11

Notes:

[9] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 7_1_Shortness of breath with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point title	7_1_Shortness of breath with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (none) to 6 (a very great deal).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
arithmetic mean (standard deviation)	-1.40 (± 1.10)	-1.48 (± 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: 7_2_ANCOVA for change of shortness of breath with the highest daily ICS dose the patient was not controlled at baseline

End point title	7_2_ANCOVA for change of shortness of breath with the highest daily ICS dose the patient was not controlled at baseline

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (none) to 6 (a very great deal).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
least squares mean (standard error)	-1.27 (± 0.08)	-1.45 (± 0.06)		

Statistical analyses

Statistical analysis title	ANCOVA for change of shortness of breath
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0222 [10]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.03

Notes:

[10] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 8_1_Wheezing with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point title	8_1_Wheezing with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (not at all) to 6 (all the time).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
arithmetic mean (standard deviation)	-1.09 (± 1.07)	-1.10 (± 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: 8_2_ANCOVA for change of wheezing with the highest daily ICS dose the patient was not controlled at baseline

End point title	8_2_ANCOVA for change of wheezing with the highest daily ICS dose the patient was not controlled at baseline

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (not at all) to 6 (all the time).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
least squares mean (standard error)	-0.99 (± 0.07)	-1.05 (± 0.05)		

Statistical analyses

Statistical analysis title	ANCOVA for change of wheezing
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4677 [11]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.09

Notes:

[11] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 9_1_Number of inhalations of bronchodilator rescue medication with the daily ICS highest dose the patient was not controlled at baseline - summary statistics

End point title	9_1_Number of inhalations of bronchodilator rescue medication with the daily ICS highest dose the patient was not controlled at baseline - summary statistics

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (none) to 6 (more than 16 puffs/inhalations most days).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
arithmetic mean (standard deviation)	-0.66 (± 0.89)	-0.74 (± 0.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: 9_2_ANCOVA for change of number of inhalations of bronchodilator rescue medication with the daily ICS highest dose the patient was not controlled at baseline

End point title	9_2_ANCOVA for change of number of inhalations of bronchodilator rescue medication with the daily ICS highest dose the patient was not controlled at baseline

End point description:

Analysis of ACQ6 score values. The outcome was calculated as the scores and ranged from 0 (none) to 6 (mor than 16 puffs/inhalations most days).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	245		
Units: Score				
least squares mean (standard error)	-0.60 (± 0.06)	-0.70 (± 0.04)		

Statistical analyses

Statistical analysis title	ANCOVA for change of number of inhalations
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1104 [12]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.02

Notes:

[12] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 10_1_Outcome of Mini-AQLQ with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point title	10_1_Outcome of Mini-AQLQ with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point description:

Change in outcome of the Quality of Life Questionnaire (Mini-AQLQ; Juniper et al., Eur Resp J 1999; 14(1): 32-38) with the highest daily ICS dose the patient was not controlled at baseline (was not available for Croatia and Romania). The outcome was calculated as the mean score of all questions and ranges from 1 (worse) to 7 (best).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78	169		
Units: Score				
arithmetic mean (standard deviation)	1.054 (± 1.008)	1.047 (± 0.961)		

Statistical analyses

No statistical analyses for this end point

Secondary: 10_2_ANCOVA for change of outcome of Mini-AQLQ with the highest daily ICS dose the patient was not controlled at baseline

End point title	10_2_ANCOVA for change of outcome of Mini-AQLQ with the highest daily ICS dose the patient was not controlled at

	baseline

End point description:

Change in outcome of the Quality of Life Questionnaire (Mini-AQLQ) with the highest daily ICS dose the patient was not controlled at baseline (was not available for Croatia and Romania). The outcome was calculated as the mean score of all questions and ranges from 1 (worse) to 7 (best).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78	169		
Units: Score				
least squares mean (standard error)	0.904 (± 0.089)	1.042 (± 0.063)		

Statistical analyses

Statistical analysis title	ANCOVA for change of outcome of Mini-AQLQ
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1171 [13]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	0.138
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	0.31

Notes:

[13] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 11_1_Mean pre-bronchodilator morning peak flow [L/min] with the highest daily ICS dose the patient was not controlled at baseline - summary statistcs

End point title	11_1_Mean pre-bronchodilator morning peak flow [L/min] with the highest daily ICS dose the patient was not controlled at baseline - summary statistcs

End point description:

Mean pre-bronchodilator morning peak flow [L/min]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112	233		
Units: L/min				
arithmetic mean (standard deviation)	17.85 (± 73.00)	11.16 (± 60.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: 11_2_ANCOVA for change of mean pre-bronchodilator morning peak flow [L/min] with the highest daily ICS dose the patient was not controlled at baseline

End point title	11_2_ANCOVA for change of mean pre-bronchodilator morning peak flow [L/min] with the highest daily ICS dose the patient was not controlled at baseline

End point description:

ANCOVA for change mean prebronchodilator morning peak flow [L/min]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112	233		
Units: L/min				
least squares mean (standard error)	15.59 (± 6.81)	10.24 (± 4.96)		

Statistical analyses

Statistical analysis title	ANCOVA for change of mean pre-bronchodilator
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4528 [14]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-5.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.36
upper limit	8.65

Notes:

[14] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 12_1_Patient's mean FEV1 [L/s] value with the highest daily dose ICS the patient was not controlled at baseline - summary statistics

End point title	12_1_Patient's mean FEV1 [L/s] value with the highest daily dose ICS the patient was not controlled at baseline - summary statistics

End point description:

Mean FEV1 value [L/s]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	20		
Units: L/s				
arithmetic mean (standard deviation)	-0.043 (± 0.580)	0.232 (± 0.401)		

Statistical analyses

No statistical analyses for this end point

Secondary: 12_2_ANCOVA for change of patient's mean FEV1 [L/s] value with the highest daily dose ICS the patient was not controlled at baseline

End point title	12_2_ANCOVA for change of patient's mean FEV1 [L/s] value with the highest daily dose ICS the patient was not controlled at baseline

End point description:

ANCOVA for change of mean FEV1 value [L/s]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	20		
Units: L/s				
least squares mean (standard error)	0.053 (± 0.214)	0.324 (± 0.130)		

Statistical analyses

Statistical analysis title	ANCOVA for change of patient's mean FEV1
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.185 [15]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	0.272
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.141
upper limit	0.685

Notes:

[15] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 13_1_Relative number of symptom free days with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point title	13_1_Relative number of symptom free days with the highest daily ICS dose the patient was not controlled at baseline - summary statistics

End point description:

A symptom free day was defined as a day where no asthma symptoms were entered into the Diary. The relative number of symptom free days was to be calculated as the number of symptom free days divided by the number of days where the corresponding questions were answered within the first week the highest uncontrolled ICS dose was administered.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	175		
Units: Number				
arithmetic mean (standard deviation)	0.376 (± 0.472)	0.509 (± 0.455)		

Statistical analyses

No statistical analyses for this end point

Secondary: 13_2_ANCOVA for change in relative number of symptom free days with the highest daily ICS dose the patient was not controlled at baseline

End point title	13_2_ANCOVA for change in relative number of symptom free days with the highest daily ICS dose the patient was not controlled at baseline

End point description:

A symptom free day was defined as a day where no asthma symptoms were entered into the eDiary. The relative number of symptom free days was to be calculated as the number of symptom free days divided by the number of days where the corresponding questions were answered within the first week the highest uncontrolled ICS dose was administered.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	175		
Units: Number				
least squares mean (standard error)	0.357 (± 0.052)	0.484 (± 0.038)		

Statistical analyses

Statistical analysis title	ANCOVA change relative number of symptom free days
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0218 [16]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.236

Notes:

[16] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 14_1_Rhinitis CSMS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point title	14_1_Rhinitis CSMS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point description:

Rhinitis and conjunctivitis symptoms and medication were recorded using daily eDiary questions at baseline, during and after treatment evaluated as described in: EAACI Position Paper (Pfaar et al. 2014; Allergy 69: 854–867).

The questionnaire consisted of 4 questions for rhinitis (itchy nose, sneezing, runny nose and blocked nose) and 2 questions for conjunctivitis (itchy/red eyes and watery eyes). Symptom scores (medication scores) each ranged from 0 to 3 (severe symptoms; highest medication category).

The outcome of the overall combined symptom and medication score (CSMS) ranged from 0 (no symptoms and no medication) to 6 (severe symptoms and highest category of medication).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
arithmetic mean (standard deviation)	-0.31 (± 0.80)	-0.45 (± 0.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: 14_2_ANCOVA for change of rhinitis CSMS under the lowest daily ICS dose required to ensure asthma control at baseline

End point title	14_2_ANCOVA for change of rhinitis CSMS under the lowest daily ICS dose required to ensure asthma control at baseline

End point description:

Analysis of rhinitis score values.

Symptom scores (medication scores) each ranged from 0 to 3 (severe symptoms; highest medication category). The outcome of the overall combined symptom and medication score (CSMS) ranged from 0 (no symptoms and no medication) to 6 (severe symptoms and highest category of medication).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
least squares mean (standard error)	-0.30 (± 0.07)	-0.48 (± 0.05)		

Statistical analyses

Statistical analysis title	ANCOVA for change of rhinitis CSMS

Statistical analysis description:

Rhinitis and conjunctivitis symptoms and medication were recorded using daily eDiary questions at baseline, during and after treatment evaluated as described in: EAACI Position Paper (Pfaar et al. 2014; Allergy 69: 854–867).

Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0147 [17]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	-0.04

Notes:

[17] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 14_3_Rhinitis and conjunctivitis CSMS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point title	14_3_Rhinitis and conjunctivitis CSMS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point description:

Analysis of rhinitis and conjunctivitis score values.

Symptom scores (medication scores) each ranged from 0 to 3 (severe symptoms; highest medication category). The outcome of the overall combined symptom and medication score (CSMS) ranged from 0 (no symptoms and no medication) to 6 (severe symptoms and highest category of medication).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
arithmetic mean (standard deviation)	-0.28 (± 0.74)	-0.40 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: 14_4_ANCOVA for change of rhinitis and conjunctivitis CSMS under the lowest daily ICS dose required to ensure asthma control at baseline

End point title	14_4_ANCOVA for change of rhinitis and conjunctivitis CSMS under the lowest daily ICS dose required to ensure asthma control at baseline

End point description:

Analysis of rhinitis and conjunctivitis score values.

Symptom scores (medication scores) each ranged from 0 to 3 (severe symptoms; highest medication category). The outcome of the overall combined symptom and medication score (CSMS) ranged from 0 (no symptoms and no medication) to 6 (severe symptoms and highest category of medication).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
least squares mean (standard error)	-0.28 (± 0.07)	-0.45 (± 0.05)		

Statistical analyses

Statistical analysis title	ANCOVA change of rhinitis and conjunctivitis CSMS
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0151 [18]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.03

Notes:

[18] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 14_5_Rhinitis dSS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point title	14_5_Rhinitis dSS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point description:

Analysis of rhitis daily symptom score values.

The rhinitis daily symptom score (rdSS) was calculated as the mean of the available rhinitis symptoms. The rdSS was calculated if at least 2 single rhinitis symptoms had been reported.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
arithmetic mean (standard deviation)	-0.10 (± 0.43)	-0.25 (± 0.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: 14_6_ANCOVA for change of rhinitis dSS under the lowest daily ICS dose required to ensure asthma control at baseline

End point title	14_6_ANCOVA for change of rhinitis dSS under the lowest daily ICS dose required to ensure asthma control at baseline

End point description:

Analysis of rhitis daily symptom score values.

The rhinitis daily symptom score (rdSS) was calculated as the mean of the available rhinitis symptoms. The rdSS was calculated if at least 2 single rhinitis symptoms had been reported.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
least squares mean (standard error)	-0.12 (± 0.04)	-0.24 (± 0.03)		

Statistical analyses

Statistical analysis title	ANCOVA for change of rhinitis dSS
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0033 [19]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	-0.04

Notes:

[19] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 14_7_Rhinitis and conjunctivitis dSS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point title	14_7_Rhinitis and conjunctivitis dSS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point description:

Analysis of rhitis and conjunctivitis daily symptom score values.

The overall daily symptoms score (dSS) were calculated as the mean symptom per day by summing up all available symptom scores and dividing by the number of the available symptoms. If less than 3 single symptoms were available, no dSS was to be calculated for the respective day.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
arithmetic mean (standard deviation)	-0.07 (± 0.35)	-0.20 (± 0.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: 14_8_ANCOVA for change of rhinitis and conjunctivitis dSS under the lowest daily ICS dose required to ensure asthma control at baseline

End point title	14_8_ANCOVA for change of rhinitis and conjunctivitis dSS under the lowest daily ICS dose required to ensure asthma control at baseline

End point description:

Analysis of rhitis and conjunctivitis daily symptom score values.

The overall daily symptoms score (dSS) was calculated as the mean symptom per day by summing up all available symptom scores and dividing by the number of the available symptoms. If less than 3 single symptoms were available, no dSS was to be calculated for the respective day.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
least squares mean (standard error)	-0.09 (± 0.03)	-0.21 (± 0.02)		

Statistical analyses

Statistical analysis title	ANCOVA change of rhinitis and conjunctivitis dSS
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0016 [20]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	-0.04

Notes:

[20] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 14_9_dMS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point title	14_9_dMS under the lowest daily ICS dose required to ensure asthma control at baseline - summary statistics

End point description:

Rescue medication used for symptom control.

The daily medication score (dMS) ranged from 0 (no medication taken) to 3 (corticosteroid tablets taken). Antihistamine tablets, eye drops, nasal drops or antihistamine sprays scored 1. Nasal corticoid spray scored 2. Corticoid tablets scored 3. If several questions for medications were answered with 'yes', the highest medication score category was to be taken. If more than one single category was missing or if all questions are not answered, the dMS was considered missing.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
median (standard deviation)	-0.21 (± 0.58)	-0.20 (± 0.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: 14_10_ANCOVA for change of dMS under the lowest daily ICS dose required to ensure asthma control at baseline

End point title	14_10_ANCOVA for change of dMS under the lowest daily ICS dose required to ensure asthma control at baseline

End point description:

Rescue medication used for symptom control.

The daily medication score (dMS) ranged from 0 (no medication taken) to 3 (corticosteroid tablets taken). If several questions for medications were answered with 'yes', the highest medication score category was to be taken. If more than one single category was missing or if all questions are not answered, the dMS was considered missing.

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	223		
Units: Score				
least squares mean (standard error)	-0.19 (± 0.05)	-0.24 (± 0.04)		

Statistical analyses

Statistical analysis title	ANCOVA for change of dMS
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3918 [21]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.06

Notes:

[21] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 15_1_Specific IgG4 of D p [kU/L] - summary statistics

End point title	15_1_Specific IgG4 of D p [kU/L] - summary statistics

End point description:

Serum specific IgG4 to D p (in kU/L).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to baseline

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	262		
Units: kU/L				
arithmetic mean (standard deviation)	0.06 (± 0.60)	4.70 (± 3.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: 15_2_ANCOVA for change of specific IgG4 of D p [kU/L]	
End point title	15_2_ANCOVA for change of specific IgG4 of D p [kU/L]
End point description:	
Change in specific IgG4 to D p (in kU/L).	
End point type	Secondary
End point timeframe:	
Change after Allergen Immunotherapy to baseline	

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	262		
Units: kU/L				
least squares mean (standard error)	0.49 (± 0.30)	5.05 (± 0.22)		

Statistical analyses

Statistical analysis title	ANCOVA for change of specific IgG4 of D p [kU/L]
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [22]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	4.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.93
upper limit	5.19

Notes:

[22] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 15_3_Specific IgG4 of D f [KU/L] - summary statistics	
End point title	15_3_Specific IgG4 of D f [KU/L] - summary statistics
End point description:	
Serum specific IgG4 to D f (in kU/L).	
End point type	Secondary
End point timeframe:	
Change after Allergen Immunotherapy to baseline	

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	262		
Units: KU/L				
arithmetic mean (standard deviation)	0.03 (± 0.37)	3.00 (± 2.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: 15_4_ANCOVA for change of specific IgG4 of D f [KU/L]

End point title	15_4_ANCOVA for change of specific IgG4 of D f [KU/L]
End point description: Change in specific IgG4 to D f (in kU/L).	
End point type	Secondary
End point timeframe: Change after Allergen Immunotherapy to baseline	

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	262		
Units: KU/L				
least squares mean (standard error)	0.27 (± 0.24)	3.21 (± 0.18)		

Statistical analyses

Statistical analysis title	ANCOVA for change of specific IgG4 of D f [KU/L]
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [23]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	2.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.44
upper limit	3.44

Notes:

[23] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 15_5_Eosinophils [10^9/L] - summary statistics	
End point title	15_5_Eosinophils [10^9/L] - summary statistics
End point description: Absolute eosinophil count.	
End point type	Secondary
End point timeframe: Change after Allergen Immunotherapy to baseline	

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	279		
Units: 10^9/L				
arithmetic mean (standard deviation)	-0.010 (± 0.181)	0.001 (± 0.204)		

Statistical analyses

No statistical analyses for this end point

Secondary: 15_6_ANCOVA for change of eosinophils [10^9/L]	
End point title	15_6_ANCOVA for change of eosinophils [10^9/L]
End point description: Absolute eosinophil count.	
End point type	Secondary
End point timeframe: Change after Allergen Immunotherapy to baseline	

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	279		
Units: 10^9/L				
least squares mean (standard error)	-0.011 (± 0.017)	0.008 (± 0.013)		

Statistical analyses

Statistical analysis title	ANCOVA for change of eosinophils [10^9/L]
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3033 [24]
Method	ANCOVA
Parameter estimate	LS mean difference (net)
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.054

Notes:

[24] - Acaroid vs. placebo
- ANCOVA analysis including treatment, pooled country, age group and baseline value

Secondary: 16_1_Time until the first moderate or severe asthma exacerbation during the diary phase after treatment

End point title	16_1_Time until the first moderate or severe asthma exacerbation during the diary phase after treatment

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Weeks after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Weeks				
median (confidence interval 95%)	25.4 (13.4 to 25.4)	22.9 (17.1 to 22.9)		

Statistical analyses

Statistical analysis title	Time to event Kaplan Meier [weeks]

Statistical analysis description:

Result of Kaplan-Meier did not give a valid parameter for CI. Median (confidence interval 95%): Placebo: 25.4 (13.4 to xx) Acaroid: 22.9 (17.1 to xx). EudraCT reporting system doesn't allow to enter a missing value for 'xx'. The missing parameters were therefore replaced by exiting parameters: Placebo: 25.4 (13.4 to 25.4) Acaroid: 22.9 (17.1 to 22.9).

Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.9954 [26]
Method	Log-rank test

Notes:

[25] - Time-to-event analysis using Kaplan-Meier and log-rank test

[26] - Log-rank test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_2_Time until the first moderate or severe asthma exacerbation from the time of first injection until the end of trial

End point title	16_2_Time until the first moderate or severe asthma exacerbation from the time of first injection until the end of trial

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Weeks after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Weeks				
median (confidence interval 95%)	34.0 (19.6 to 43.1)	36.9 (30.4 to 42.9)		

Statistical analyses

Statistical analysis title	Time to event Kaplan Meier [weeks]
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.6535 [28]
Method	Log-rank test

Notes:

[27] - Time-to-event analysis using Kaplan-Meier and log-rank test

[28] - Log-rank test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_3_Time until the first moderate or severe asthma exacerbation with the minimal ICS dose assessed after treatment

End point title	16_3_Time until the first moderate or severe asthma exacerbation with the minimal ICS dose assessed after treatment

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Weeks after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	262		
Units: Weeks				
median (confidence interval 95%)	22.0 (22.0 to 22.0)	20.9 (20.9 to 20.9)		

Statistical analyses

Statistical analysis title	Time to event Kaplan Meier [weeks]

Statistical analysis description:

Result of Kaplan-Meier did not give a valid parameter for CI. Median (confidence interval 95%): Placebo: xx (22.0 to xx) Acaroid: xx (20.9 to xx). EudraCT reporting system doesn't allow to enter a missing value for 'xx'. The missing parameters were therefore replaced by exiting parameters: Placebo: 22.0 (22.0 to 22.0) Acaroid: 20.9 (20.9 to 20.9).

Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.6964 [30]
Method	Log-rank test

Notes:

[29] - Time-to-event analysis using Kaplan-Meier and log-rank test

[30] - Log-rank test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_4_Number of asthma exacerbations (moderate or severe) during the diary phase after treatment - summary statistics

End point title	16_4_Number of asthma exacerbations (moderate or severe) during the diary phase after treatment - summary statistics

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number				
arithmetic mean (standard deviation)	1.4 (± 2.0)	1.2 (± 1.7)		

Statistical analyses

Statistical analysis title	Number of asthma moderate or severe exacerbations
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.5572 [32]
Method	Wilcoxon (Mann-Whitney)

Notes:

[31] - Descriptive statistics

[32] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs.

placebo

Secondary: 16_5_Number of asthma exacerbations (moderate or severe) during the diary phase after treatment

End point title	16_5_Number of asthma exacerbations (moderate or severe) during the diary phase after treatment

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number of exacerbation				
'0'	69	141		
'1'	23	64		
'2'	13	28		
'3'	7	21		
'4'	6	9		
'5'	4	14		
'6'	6	4		
'7'	3	3		
'8'	1	1		
'9'	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: 16_6_Number of asthma exacerbations (moderate or severe) from the time of first injection until the end of trial - summary statistics

End point title	16_6_Number of asthma exacerbations (moderate or severe) from the time of first injection until the end of trial - summary statistics

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number				
arithmetic mean (standard deviation)	2.9 (± 3.8)	2.4 (± 3.2)		

Statistical analyses

Statistical analysis title	Number of moderate or severe asthma exacerbations
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.8345 [34]
Method	Wilcoxon (Mann-Whitney)

Notes:

[33] - Descriptive statistics

[34] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_7_Number of asthma exacerbations (moderate or severe) from the time of first injection until the end of trial

End point title	16_7_Number of asthma exacerbations (moderate or severe) from the time of first injection until the end of trial

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per

day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number of exacerbation				
'0'	47	98		
'1'	25	66		
'2'	9	27		
'3'	12	23		
'4'	7	20		
'5'	4	9		
'6'	8	9		
'7'	4	7		
'8'	4	7		
'9'	2	5		
'10'	3	6		
'11'	1	3		
'12'	1	1		
'13'	0	0		
'14'	1	4		
'15'	3	1		
'16'	0	0		
'17'	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: 16_8_Number of asthma exacerbations (moderate or severe) with the minimal ICS dose assessed after treatment - summary statistics

End point title	16_8_Number of asthma exacerbations (moderate or severe) with the minimal ICS dose assessed after treatment - summary statistics

End point description:

Number of moderate or severe asthma exacerbations with the minmal ICS dose after treatment

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	262		
Units: Number				
arithmetic mean (standard deviation)	0.9 (± 1.6)	0.7 (± 1.2)		

Statistical analyses

Statistical analysis title	Number of moderate or severe asthma exacerbations
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.7037 [36]
Method	Wilcoxon (Mann-Whitney)

Notes:

[35] - Descriptive statistics

[36] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_9_Number of asthma exacerbations (moderate or severe) with the minimal ICS dose assessed after treatment

End point title	16_9_Number of asthma exacerbations (moderate or severe) with the minimal ICS dose assessed after treatment

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	262		
Units: Number of exacerbation				
'0'	77	167		
'1'	18	51		
'2'	11	18		
'3'	9	13		
'4'	1	8		
'5'	1	2		
'6'	3	2		
'7'	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: 16_10_Number of severe asthma exacerbations during the diary phase after treatment - summary statistics

End point title	16_10_Number of severe asthma exacerbations during the diary phase after treatment - summary statistics

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number				
arithmetic mean (standard deviation)	0.0 (± 0.1)	0.0 (± 0.1)		

Statistical analyses

Statistical analysis title	Number of severe asthma exacerbations
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.7142 [38]
Method	Wilcoxon (Mann-Whitney)

Notes:

[37] - Descriptive statistics

[38] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_11_Number of severe asthma exacerbations during the diary phase after treatment

End point title	16_11_Number of severe asthma exacerbations during the diary phase after treatment

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number of exacerbation				
'0'	131	285		
'1'	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: 16_12_Number of severe asthma exacerbations from the time of first injection until the end of trial - summary statistics

End point title	16_12_Number of severe asthma exacerbations from the time of first injection until the end of trial - summary statistics

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number				
arithmetic mean (standard deviation)	0.0 (± 0.1)	0.0 (± 0.1)		

Statistical analyses

Statistical analysis title	Number of severe asthma exacerbations
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.7893 [40]
Method	Wilcoxon (Mann-Whitney)

Notes:

[39] - Descriptive statistics

[40] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_13_Number of severe asthma exacerbations from the time of first injection until the end of trial

End point title	16_13_Number of severe asthma exacerbations from the time of first injection until the end of trial

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number of exacerbation				
'0'	130	284		
'1'	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: 16_14_Number of severe asthma exacerbations with the minimal ICS dose assessed after treatment - summary statistics

End point title	16_14_Number of severe asthma exacerbations with the minimal ICS dose assessed after treatment - summary statistics

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	262		
Units: Number				
arithmetic mean (standard deviation)	0.0 (± 0.0)	0.0 (± 0.0)		

Statistical analyses

Statistical analysis title	Number of severe asthma exacerbations
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.5 [42]
Method	Wilcoxon (Mann-Whitney)

Notes:

[41] - Descriptive statistics

[42] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_15_Number of severe asthma exacerbations with the minimal ICS dose assessed after treatment

End point title	16_15_Number of severe asthma exacerbations with the minimal ICS dose assessed after treatment

End point description:

Severe asthma exacerbation:

One or more of the following criteria had to be fulfilled: use of systemic corticosteroids (tablets, suspension, or injection); increase from a stable maintenance dose of systemic corticosteroids for at least 3 days; hospitalization or emergency room visit due to the requirement of systemic corticosteroids for asthma treatment.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	262		
Units: Number of exacerbation				
'0'	122	262		

Statistical analyses

No statistical analyses for this end point

Secondary: 16_16_Number of moderate asthma exacerbations during the diary phase after treatment - summary statistics

End point title	16_16_Number of moderate asthma exacerbations during the diary phase after treatment - summary statistics

End point description:

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number				
arithmetic mean (standard deviation)	1.3 (± 2.0)	1.2 (± 1.7)		

Statistical analyses

Statistical analysis title	Number of moderate asthma exacerbations
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.5398 [44]
Method	Wilcoxon (Mann-Whitney)

Notes:

[43] - Descriptive statistics

[44] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_17_Number of moderate asthma exacerbations during the diary phase after treatment

End point title	16_17_Number of moderate asthma exacerbations during the diary phase after treatment

End point description:

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number of exacerbation				
'0'	70	141		
'1'	22	65		
'2'	13	27		
'3'	7	21		
'4'	6	9		
'5'	4	14		
'6'	6	4		
'7'	3	3		
'8'	1	1		
'9'	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: 16_18_Number of moderate asthma exacerbations from the time of first injection until the end of trial - summary statistics

End point title	16_18_Number of moderate asthma exacerbations from the time of first injection until the end of trial - summary statistics

End point description:

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number				
arithmetic mean (standard deviation)	2.9 (± 3.8)	2.4 (± 3.2)		

Statistical analyses

Statistical analysis title	Number of moderate asthma exacerbations
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.8301 [46]
Method	Wilcoxon (Mann-Whitney)

Notes:

[45] - Descriptive statistics

[46] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_19_Number of moderate asthma exacerbations from the time of first injection until the end of trial

End point title	16_19_Number of moderate asthma exacerbations from the time of first injection until the end of trial

End point description:

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	286		
Units: Number of exacerbation				
'0'	47	98		
'1'	26	67		
'2'	8	26		
'3'	12	23		
'4'	7	20		
'5'	5	9		
'6'	7	9		
'7'	4	7		
'8'	4	8		
'9'	2	4		
'10'	3	6		
'11'	1	3		
'12'	1	1		
'13'	0	0		
'14'	1	4		
'15'	3	1		
'16'	0	0		
'17'	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: 16_20_Number of moderate asthma exacerbations with the minimal ICS dose assessed after treatment - summary statistics

End point title	16_20_Number of moderate asthma exacerbations with the minimal ICS dose assessed after treatment - summary statistics

End point description:

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	262		
Units: Number				
arithmetic mean (standard deviation)	0.9 (± 1.6)	0.7 (± 1.2)		

Statistical analyses

Statistical analysis title	Number of moderate asthma exacerbations
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.7037 [48]
Method	Wilcoxon (Mann-Whitney)

Notes:

[47] - Descriptive statistics

[48] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Secondary: 16_21_Number of moderate asthma exacerbations with the minimal ICS dose assessed after treatment

End point title	16_21_Number of moderate asthma exacerbations with the minimal ICS dose assessed after treatment

End point description:

Moderate asthma exacerbation:

One or more of the following criteria had to be fulfilled: > 50% increase in SABA use and > 8 puffs per day on 2 of 3 consecutive days compared to baseline; ≥ 20% decrease in morning PEF from baseline on 2 of 3 consecutive days compared to baseline; Night time awakenings requiring SABA use on at least 2 of 3 consecutive nights.

End point type	Secondary

End point timeframe:

Number of asthma exacerbations after Allergen Immunotherapy categorized

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	262		
Units: Number of exacerbation				
'0'	77	167		
'1'	18	51		
'2'	11	18		
'3'	9	13		
'4'	1	8		
'5'	1	2		
'6'	3	2		
'7'	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: 17_1_Clinical chemistry: Creatinine [µmol/L]: absolute values and change

End point title	17_1_Clinical chemistry: Creatinine [µmol/L]: absolute values and change
End point description: Creatinine [µmol/L]	
End point type	Secondary
End point timeframe: Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)	

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[49]	290[50]		
Units: µmol/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	4.00 (± 12.52)	4.14 (± 11.42)		
Last treatment visit - Baseline (T1)	4.31 (± 8.19)	4.40 (± 8.20)		

Notes:

[49] - Safety Set

[50] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.983 [52]
Method	Wilcoxon (Mann-Whitney)

Notes:

[51] - Descriptive statistics

[52] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.937 [54]
Method	Wilcoxon (Mann-Whitney)

Notes:

[53] - Descriptive statistics

[54] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 17_2_Clinical chemistry: Bilirubin, total [µmol/L]: absolute values and change

End point title	17_2_Clinical chemistry: Bilirubin, total [µmol/L]: absolute values and change

End point description:

Bilirubin, total [µmol/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[55]	290[56]		
Units: µmol/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	-1.80 (± 6.21)	-1.44 (± 5.23)		
Last treatment visit - Baseline (T1)	0.46 (± 5.12)	-0.50 (± 4.57)		

Notes:

[55] - Safety Set

[56] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	= 0.6087 [58]
Method	Wilcoxon (Mann-Whitney)

Notes:

[57] - Descriptive statistics

[58] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0.0207 [60]
Method	Wilcoxon (Mann-Whitney)

Notes:

[59] - Descriptive statistics

[60] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 17_3_Clinical chemistry: ASAT (Aspartate Aminotransferase) [U/L]: absolute values and change

End point title	17_3_Clinical chemistry: ASAT (Aspartate Aminotransferase) [U/L]: absolute values and change

End point description:

ASAT (Aspartate Aminotransferase) [U/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[61]	290[62]		
Units: U/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	2.90 (± 11.14)	2.96 (± 8.00)		
Last treatment visit - Baseline (T1)	7.16 (± 8.94)	5.33 (± 21.38)		

Notes:

[61] - Safety Set

[62] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	= 0.7378 [64]
Method	Wilcoxon (Mann-Whitney)

Notes:

[63] - Descriptive statistics

[64] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	= 0.4345 [66]
Method	Wilcoxon (Mann-Whitney)

Notes:

[65] - Descriptive statistics

[66] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 17_4_Clinical chemistry: ALAT (Alanine Aminotransferase) [U/L]: absolute values and change

End point title	17_4_Clinical chemistry: ALAT (Alanine Aminotransferase) [U/L]: absolute values and change

End point description:

ALAT (Alanine Aminotransferase) [U/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[67]	290[68]		
Units: U/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	2.82 (± 13.53)	5.62 (± 14.52)		
Last treatment visit - Baseline (T1)	3.12 (± 13.42)	-1.81 (± 21.94)		

Notes:

[67] - Safety Set

[68] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	= 0.0067 [70]
Method	Wilcoxon (Mann-Whitney)

Notes:

[69] - Descriptive statistics

[70] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	= 0.0138 [72]
Method	Wilcoxon (Mann-Whitney)

Notes:

[71] - Descriptive statistics

[72] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 17_5_Clinical chemistry: γ-GT (Gamma Glutamyl Transferase) [U/L]: absolute values and change

End point title	17_5_Clinical chemistry: γ-GT (Gamma Glutamyl Transferase) [U/L]: absolute values and change

End point description:

γ-GT (Gamma Glutamyl Transferase) [U/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[73]	290[74]		
Units: U/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.08 (± 16.95)	-0.08 (± 10.82)		
Last treatment visit - Baseline (T1)	0.46 (± 14.84)	0.00 (± 9.57)		

Notes:

[73] - Safety Set

[74] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[75]
P-value	= 0.3629 [76]
Method	Wilcoxon (Mann-Whitney)

Notes:

[75] - Descriptive statistics

[76] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[77]
P-value	= 0.0742 [78]
Method	Wilcoxon (Mann-Whitney)

Notes:

[77] - Descriptive statistics

[78] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 17_6_Clinical chemistry: Glucose [mmol/L]: absolute values and change

End point title	17_6_Clinical chemistry: Glucose [mmol/L]: absolute values and change

End point description:

Glucose [mmol/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[79]	290[80]		
Units: mmol/L]				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	-0.17 (± 0.78)	-0.10 (± 0.83)		
Last treatment visit - Baseline (T1)	-0.35 (± 0.79)	-0.19 (± 0.93)		

Notes:

[79] - Safety Set

[80] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[81]
P-value	= 0.5011 [82]
Method	Wilcoxon (Mann-Whitney)

Notes:

[81] - Descriptive statistics

[82] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[83]
P-value	= 0.1691 [84]
Method	Wilcoxon (Mann-Whitney)

Notes:

[83] - Descriptive statistics

[84] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_1_Hematology: Hemoglobin [mmol/L]: absolute values and change

End point title	18_1_Hematology: Hemoglobin [mmol/L]: absolute values and change

End point description:

Hemoglobin [mmol/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[85]	290[86]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	-0.01 (± 0.53)	0.02 (± 0.56)		
Last treatment visit - Baseline (T1)	-0.08 (± 0.52)	-0.11 (± 0.44)		

Notes:

[85] - Safety Set

[86] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[87]
P-value	= 0.762 [88]
Method	Wilcoxon (Mann-Whitney)

Notes:

[87] - Descriptive statistics

[88] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[89]
P-value	= 0.4341 [90]
Method	Wilcoxon (Mann-Whitney)

Notes:

[89] - Descriptive statistics

[90] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_2_Hematology: Leukocytes [10^9/L]: absolute values and change

End point title	18_2_Hematology: Leukocytes [10^9/L]: absolute values and change

End point description:

Leukocytes [10^9/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[91]	290[92]		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.39 (± 1.90)	0.43 (± 1.86)		
Last treatment visit - Baseline (T1)	0.13 (± 1.63)	0.06 (± 1.76)		

Notes:

[91] - Safety Set

[92] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[93]
P-value	= 0.6216 [94]
Method	Wilcoxon (Mann-Whitney)

Notes:

[93] - Descriptive statistics

[94] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[95]
P-value	= 0.8715 [96]
Method	Wilcoxon (Mann-Whitney)

Notes:

[95] - Descriptive statistics

[96] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_3_Hematology: Basophils [10^9/L]: absolute values and change

End point title	18_3_Hematology: Basophils [10^9/L]: absolute values and change

End point description:

Basophils [10^9/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[97]	290[98]		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.03 (± 0.06)	0.03 (± 0.05)		
Last treatment visit - Baseline (T1)	0.01 (± 0.04)	0.00 (± 0.04)		

Notes:

[97] - Safety Set

[98] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[99]
P-value	= 0.6571 [100]
Method	Wilcoxon (Mann-Whitney)

Notes:

[99] - Descriptive statistics

[100] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[101]
P-value	= 0.1964 [102]
Method	Wilcoxon (Mann-Whitney)

Notes:

[101] - Descriptive statistics

[102] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_4_Hematology: Basophils/Leukocytes [%]: absolute values and change

End point title	18_4_Hematology: Basophils/Leukocytes [%]: absolute values and change

End point description:

Basophils/Leukocytes [%]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[103]	290[104]		
Units: [%]				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.31 (± 0.59)	0.28 (± 0.35)		
Last treatment visit - Baseline (T1)	0.11 (± 0.22)	0.07 (± 0.32)		

Notes:

[103] - Safety Set

[104] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[105]
P-value	= 0.7356 [106]
Method	Wilcoxon (Mann-Whitney)

Notes:

[105] - Descriptive statistics

[106] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[107]
P-value	= 0.1312 [108]
Method	Wilcoxon (Mann-Whitney)

Notes:

[107] - Descriptive statistics

[108] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_5_Hematology: Eosinophils [10^9/L]: absolute values and change

End point title	18_5_Hematology: Eosinophils [10^9/L]: absolute values and change

End point description:

Eosinophils [10^9/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[109]	290[110]		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	-0.04 (± 0.22)	-0.05 (± 0.27)		
Last treatment visit - Baseline (T1)	0.01 (± 0.20)	-0.01 (± 0.18)		

Notes:

[109] - Safety Set

[110] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[111]
P-value	= 0.7385 [112]
Method	Wilcoxon (Mann-Whitney)

Notes:

[111] - Descriptive statistics

[112] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[113]
P-value	= 0.29 [114]
Method	Wilcoxon (Mann-Whitney)

Notes:

[113] - Descriptive statistics

[114] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_6_Hematology: Eosinophils/Leukocytes [%]: absolute values and change

End point title	18_6_Hematology: Eosinophils/Leukocytes [%]: absolute values and change

End point description:

Eosinophils/Leukocytes [%]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[115]	290[116]		
Units: [%]				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	-0.95 (± 3.26)	-0.97 (± 3.61)		
Last treatment visit - Baseline (T1)	0.18 (± 2.62)	-0.29 (± 2.87)		

Notes:

[115] - Safety Set

[116] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[117]
P-value	= 0.7898 [118]
Method	Wilcoxon (Mann-Whitney)

Notes:

[117] - Descriptive statistics

[118] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[119]
P-value	= 0.1483 [120]
Method	Wilcoxon (Mann-Whitney)

Notes:

[119] - Descriptive statistics

[120] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_7_Hematology: Lymphocytes [10^9/L]: absolute values and change

End point title	18_7_Hematology: Lymphocytes [10^9/L]: absolute values and change

End point description:

Lymphocytes [10^9/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[121]	290[122]		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.10 (± 0.56)	0.14 (± 0.60)		
Last treatment visit - Baseline (T1)	-0.06 (± 0.62)	-0.03 (± 0.54)		

Notes:

[121] - Safety Set

[122] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Acaroid v Placebo
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[123]
P-value	= 0.4392 [124]
Method	Wilcoxon (Mann-Whitney)

Notes:

[123] - Descriptive statistics

[124] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[125]
P-value	= 0.3844 [126]
Method	Wilcoxon (Mann-Whitney)

Notes:

[125] - Descriptive statistics

[126] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_8_Hematology: Lymphocytes/Leukocytes [%]: absolute values and change

End point title	18_8_Hematology: Lymphocytes/Leukocytes [%]: absolute values and change

End point description:

Lymphocytes/Leukocytes [%]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[127]	290[128]		
Units: [%]				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	-0.67 (± 9.47)	0.43 (± 7.50)		
Last treatment visit - Baseline (T1)	-1.54 (± 8.38)	-0.55 (± 7.45)		

Notes:

[127] - Safety Set

[128] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[129]
P-value	= 0.1111 [130]
Method	Wilcoxon (Mann-Whitney)

Notes:

[129] - Descriptive statistics

[130] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[131]
P-value	= 0.2056 [132]
Method	Wilcoxon (Mann-Whitney)

Notes:

[131] - Descriptive statistics

[132] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_9_Hematology: Monocytes [10^9/L]: absolute values and change

End point title	18_9_Hematology: Monocytes [10^9/L]: absolute values and change

End point description:

Monocytes [10^9/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[133]	290[134]		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.05 (± 0.21)	0.05 (± 0.16)		
Last treatment visit - Baseline (T1)	-0.03 (± 0.15)	-0.05 (± 0.17)		

Notes:

[133] - Safety Set

[134] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[135]
P-value	= 0.9355 [136]
Method	Wilcoxon (Mann-Whitney)

Notes:

[135] - Descriptive statistics

[136] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[137]
P-value	= 0.286 [138]
Method	Wilcoxon (Mann-Whitney)

Notes:

[137] - Descriptive statistics

[138] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_10_Hematology: Monocytes/Leukocytes [%]: absolute values and change

End point title	18_10_Hematology: Monocytes/Leukocytes [%]: absolute values and change

End point description:

Monocytes/Leukocytes [%]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[139]	290[140]		
Units: [%]				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.37 (± 2.47)	0.27 (± 2.19)		
Last treatment visit - Baseline (T1)	-0.69 (± 1.92)	-0.73 (± 2.16)		

Notes:

[139] - Safety Set

[140] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[141]
P-value	= 0.8945 [142]
Method	Wilcoxon (Mann-Whitney)

Notes:

[141] - Descriptive statistics

[142] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[143]
P-value	= 0.6391 [144]
Method	Wilcoxon (Mann-Whitney)

Notes:

[143] - Descriptive statistics

[144] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_11_Hematology: Neutrophils [10^9/L]: absolute values and change

End point title	18_11_Hematology: Neutrophils [10^9/L]: absolute values and change

End point description:

Neutrophils [10^9/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[145]	290[146]		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.26 (± 1.77)	0.26 (± 1.53)		
Last treatment visit - Baseline (T1)	0.23 (± 1.40)	0.11 (± 1.49)		

Notes:

[145] - Safety Set

[146] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[147]
P-value	= 0.5462 [148]
Method	Wilcoxon (Mann-Whitney)

Notes:

[147] - Descriptive statistics

[148] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[149]
P-value	= 0.7094 [150]
Method	Wilcoxon (Mann-Whitney)

Notes:

[149] - Descriptive statistics

[150] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_12_Hematology: Neutrophils/Leukocytes [%]: absolute values and change

End point title	18_12_Hematology: Neutrophils/Leukocytes [%]: absolute values and change

End point description:

Neutrophils/Leukocytes [%]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[151]	290[152]		
Units: [%]				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.88 (± 11.44)	-0.10 (± 9.54)		
Last treatment visit - Baseline (T1)	1.93 (± 9.46)	1.76 (± 9.81)		

Notes:

[151] - Safety Set

[152] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[153]
P-value	= 0.2342 [154]
Method	Wilcoxon (Mann-Whitney)

Notes:

[153] - Descriptive statistics

[154] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Acaroid v Placebo

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[155]
P-value	= 0.6848 [156]
Method	Wilcoxon (Mann-Whitney)

Notes:

[155] - Descriptive statistics

[156] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 18_13_Hematology: Platelets [10^9/L]: absolute values and change

End point title	18_13_Hematology: Platelets [10^9/L]: absolute values and change

End point description:

Platelets [10^9/L]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[157]	290[158]		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	6.05 (± 41.16)	10.26 (± 47.72)		
Last treatment visit - Baseline (T1)	11.06 (± 41.31)	4.34 (± 40.58)		

Notes:

[157] - Safety Set

[158] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[159]
P-value	= 0.319 [160]
Method	Wilcoxon (Mann-Whitney)

Notes:

[159] - Descriptive statistics

[160] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[161]
P-value	= 0.1039 [162]
Method	Wilcoxon (Mann-Whitney)

Notes:

[161] - Descriptive statistics

[162] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 19_Urinalysis

End point title	19_Urinalysis

End point description:

The absolute and relative numbers of patients with urinalysis parameter values at normal or abnormal range (clinically significant or not) are displayed. At the last treatment visit, no patients were reported with abnormal clinically significant values for any urinalysis parameter. At the final visit, patients with abnormal clinically significant values were identified for urine occult blood (placebo: 1 patient [0.7%]; Acaroid: 0 patients) and urine glucose (placebo: 0 patients; Acaroid: 1 patient [0.3%]).

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[163]	290[164]		
Units: Number				
1a_Blood: S1: Normal	134	288		
1a_Blood: S1: Abnormal NCS	0	2		
1a_Blood: S1: Abnormal CS	0	0		
1b_Blood: FV: Normal	132	279		
1b_Blood: FV: Abnormal NCS	0	4		
1b_Blood: FV: Abnormal CS	1	0		
2a_Glucose: S1: Normal	134	290		
2a_Glucose: S1: Abnormal NCS	0	0		
2a_Glucose: S1: Abnormal CS	0	0		
2b_Glucose: FV: Normal	133	282		
2b_Glucose: FV: Abnormal NCS	0	0		
2b_Glucose: FV: Abnormal CS	0	1		

Notes:

[163] - Safety Set

[164] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: 20_1_Vital signs: Systolic blood pressure [mmHg]

End point title	20_1_Vital signs: Systolic blood pressure [mmHg]

End point description:

Systolic blood pressure [mmHg]

End point type	Secondary

End point timeframe:
Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[165]	290[166]		
Units: mmHg				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.7 (± 9.3)	0.4 (± 9.9)		
Last treatment visit - Baseline (T1)	-0.3 (± 9.6)	-0.6 (± 9.6)		

Notes:
[165] - Safety Set
[166] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[167]
P-value	= 0.4265 [168]
Method	Wilcoxon (Mann-Whitney)

Notes:
[167] - Descriptive statistics
[168] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[169]
P-value	= 0.6831 [170]
Method	Wilcoxon (Mann-Whitney)

Notes:
[169] - Descriptive statistics
[170] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 20_2_Vital signs: Diastolic blood pressure [mmHg]

End point title	20_2_Vital signs: Diastolic blood pressure [mmHg]

End point description:
Diastolic blood pressure [mmHg]

End point type	Secondary

End point timeframe:
Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[171]	290[172]		
Units: mmHg				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.4 (± 7.5)	0.2 (± 7.9)		
Last treatment visit - Baseline (T1)	0.5 (± 7.6)	0.2 (± 7.7)		

Notes:

[171] - Safety Set

[172] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[173]
P-value	= 0.7274 [174]
Method	Wilcoxon (Mann-Whitney)

Notes:

[173] - Descriptive statistics

[174] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[175]
P-value	= 0.7094 [176]
Method	Wilcoxon (Mann-Whitney)

Notes:

[175] - Descriptive statistics

[176] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 20_3_Vital signs: Heart rate [beats/min]

End point title	20_3_Vital signs: Heart rate [beats/min]

End point description:

Heart rate [beats/min]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[177]	290[178]		
Units: beats/min				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.3 (± 8.4)	0.4 (± 8.3)		
Last treatment visit - Baseline (T1)	-0.7 (± 7.2)	-0.1 (± 7.4)		

Notes:

[177] - Safety Set

[178] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[179]
P-value	= 0.5775 [180]
Method	Wilcoxon (Mann-Whitney)

Notes:

[179] - Descriptive statistics

[180] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[181]
P-value	= 0.4971 [182]
Method	Wilcoxon (Mann-Whitney)

Notes:

[181] - Descriptive statistics

[182] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 20_4_Vital signs: Respiratory rate [breaths/min]

End point title	20_4_Vital signs: Respiratory rate [breaths/min]

End point description:

Respiratory rate [breaths/min]

End point type	Secondary

End point timeframe:

Change after Allergen Immunotherapy to screening (S1) / to baseline (T1)

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[183]	290[184]		
Units: breaths/min				
arithmetic mean (standard deviation)				
Final visit – Screening (S1)	0.0 (± 1.6)	-0.1 (± 1.6)		
Last treatment visit - Baseline (T1)	0.1 (± 1.5)	0.0 (± 1.4)		

Notes:

[183] - Safety Set

[184] - Safety Set

Statistical analyses

Statistical analysis title	Change final visit to screening visit (S1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[185]
P-value	= 0.3422 [186]
Method	Wilcoxon (Mann-Whitney)

Notes:

[185] - Descriptive statistics

[186] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Statistical analysis title	Change last treatment visit to baseline visit (T1)
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[187]
P-value	= 0.9453 [188]
Method	Wilcoxon (Mann-Whitney)

Notes:

[187] - Descriptive statistics

[188] - Two-sided Mann-Whitney U-test comparing the active treatment group vs. placebo

Secondary: 21_Tolerability assessments of investigator and patient

End point title	21_Tolerability assessments of investigator and patient

End point description:

Assessment of the overall tolerability by the investigator and the patient using a 5 point Likert scale (1=very bad; 5=very good)

End point type	Secondary

End point timeframe:

At trial termination

End point values	Placebo	Acaroid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134[189]	290[190]		
Units: Scale				
arithmetic mean (standard deviation)				
Investigator's assessment	4.5 (± 0.7)	4.4 (± 0.8)		
Patient's assessment	4.5 (± 0.7)	4.3 (± 0.8)		

Notes:

[189] - Safety set

[190] - Safety set

Statistical analyses

Statistical analysis title	Tolerability assessments of investigator
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[191]
P-value	= 0.9753 [192]
Method	Wilcoxon (Mann-Whitney)

Notes:

[191] - Descriptive statistics

[192] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Statistical analysis title	Tolerability assessments of patient
Comparison groups	Placebo v Acaroid
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other[193]
P-value	= 0.9987 [194]
Method	Wilcoxon (Mann-Whitney)

Notes:

[193] - Descriptive statistics

[194] - One-sided Mann-Whitney U-test stratified by pooled country and age group comparing active vs. placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events occuring from the first screening visit (including trial-related procedures) until 30 days after final visit.
Non-serious adverse events are presented in the Safety Set (SAF) from the onset of treatment to 30 d after final visit.

Adverse event reporting additional description:

SAEs were reported with similar frequency on active and placebo treatment (placebo: 5 events in 5 patients [3.7%]; Acaroid: 11 events in 8 patients [2.8%].
One SAE in 1 patient in the active treatment group (0.3%; none with placebo) was assessed as related to IMP (active treatment, hypersensitivity systemic adverse event).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

One patient 0904-032 was not included in the analysis of SAEs because the patient withdrew from study before treatment started. The patient did not have an adverse event / SAE.

Reporting group title	Acaroid

Reporting group description:

One patient 0908-004 was not included in the analysis of SAEs because the patient withdrew from study before treatment started. The patient did not have an adverse event / SAE.

Serious adverse events	Placebo	Acaroid	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 134 (3.73%)	8 / 290 (2.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lip injury			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 134 (0.75%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Foetal death			
subjects affected / exposed	1 / 134 (0.75%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
High risk pregnancy			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 134 (0.75%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 134 (0.75%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			

subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus infection			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 134 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Acaroid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 134 (53.73%)	214 / 290 (73.79%)	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 134 (5.22%)	10 / 290 (3.45%)	
occurrences (all)	13	16	

General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	15 / 134 (11.19%)	124 / 290 (42.76%)	
occurrences (all)	37	628	
Injection site pain			
subjects affected / exposed	1 / 134 (0.75%)	16 / 290 (5.52%)	
occurrences (all)	1	33	
Injection site pruritus			
subjects affected / exposed	3 / 134 (2.24%)	36 / 290 (12.41%)	
occurrences (all)	9	113	
Injection site swelling			
subjects affected / exposed	4 / 134 (2.99%)	133 / 290 (45.86%)	
occurrences (all)	6	586	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	14 / 134 (10.45%)	36 / 290 (12.41%)	
occurrences (all)	16	44	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 134 (2.24%)	15 / 290 (5.17%)	
occurrences (all)	3	16	
Pharyngitis			
subjects affected / exposed	13 / 134 (9.70%)	15 / 290 (5.17%)	
occurrences (all)	17	23	
Viral upper respiratory tract infection			
subjects affected / exposed	20 / 134 (14.93%)	48 / 290 (16.55%)	
occurrences (all)	26	76	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2017	The initial Trial Protocol final 1.0, dated 03 Aug 2016, was amended twice after the enrolment of patients (first patient, first screening was on 22 Mar 2017), leading to final Trial Protocol 2.0, dated 04 Aug 2017, and to final Trial Protocol 3.0, dated 29 Nov 2017.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported