



Clinical trial results:

A multicentre randomised placebo-controlled double-blind clinical trial for evaluation of safety and efficacy of specific immunotherapy with an aluminium hydroxide-adsorbed Allergoid Preparation of house dust mite (*Dermatophagoides pteronyssinus*) in patients with allergic asthma bronchiale +/- rhinitis / rhinoconjunctivitis

Summary

EudraCT number	2004-003892-35
Trial protocol	DE
Global end of trial date	29 March 2011

Results information

Result version number	v1 (current)
This version publication date	24 June 2018
First version publication date	24 June 2018

Trial information

Trial identification

Sponsor protocol code	AL 0104 av
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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., 0049 40427650,
Scientific contact	Clinical Trials Information, ALLERGOPHARMA GMBH & CO. KG., 0049 40427650,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
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	14 September 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 March 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate efficacy and tolerability of specific immunotherapy (SIT) with an aluminium hydroxide-adsorbed allergoid preparation of the major allergens from *Dermatophagoides pteronyssinus* (D. pteronyssinus).

This trial was random., double-blind, placebo-contr. phase III, in 2 parallel groups of patients over 18 y of age; children and adolesc less than 18 y in the control group received UC with study-specific pharmacotherapy, instead of placebo.

Before randomisation to treatment, patient's minimal requirement of the inhaled corticosteroid dose to achieve asthma control was determined (patient diary, baseline). After randomisation to SIT, the study duration was 2 y for each patient (2 annual assessments).

After the analysis of the 2 y results, a decision was made to complete a full 3 year course of SIT in all actively treated patients (as recommended by the World Health Organisation) and do an open-label 3 y follow-up in children.

SIT=Specific Immunotherapy

UC=Usual Care

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that 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. The study was conducted multinationally in accordance with the respective national legal requirements.

Children and adolescents under 18 years in the control group did not receive placebo, but instead received usual care with study-specific pharmacotherapy; 'usual care' consisted of a reliever and controller asthma medication.

Other than routine care, no specific measures were implemented for the protection of trial subjects.

Background therapy:

Treatment of asthma in this study was by an inhaled corticosteroid: fluticasone propionate 100 – 1000 µg per day in adults (50 – 500 µg per day in children) dry powder inhalation from a disk device. The corticosteroid dose was adjusted during the baseline phase at the beginning of the study and during assessment phases (15 September to 15 February each study year) until one dose step below the threshold dose of asthma control criteria (according to GINA) was met.

Acute symptomatic treatment of lower airways symptoms was with salbutamol metered dose inhaler (MDI; 100 µg per dose) used only as required. Other medication (including long acting-agonists, inhaled corticosteroids in the form of combination products was not permitted during the study.

Treatment of allergic rhinitis / rhinoconjunctivitis and other concomitant diseases was on the investigators' discretion. Long-term use of oral or other systemic corticosteroids (i.e. depot corticosteroids), immunoregulatory substances or medication that could influence the efficacy of SIT were exclusion criteria and their use was not permitted during the study.

If further treatments (i.e. oral corticosteroids) were required for the treatment of asthma exacerbations, these could be used; the duration of those therapies was to be kept as short as possible and their use documented.

DBP=Double Blind Phase
FU=Follow up Phase
GINA=Global Initiative for Asthma
MDI=Metered Dose Inhaler
OLP=Open Label Phase
SIT=Specific Immunotherapy

Evidence for comparator: -

Actual start date of recruitment	23 May 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Poland: 107
Worldwide total number of subjects	130
EEA total number of subjects	130

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)	39
Adolescents (12-17 years)	27
Adults (18-64 years)	64
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 235 subjects [111 children and adolescents (2-17 y); 124 adults (18-64 y)] were screened for eligibility. Of these, 130 subjects (66 children and adolescents; 64 adults) were randomised to treatment, according to the exclusion and inclusion criteria.

Pre-assignment

Screening details:

Screened and randomised to treatment according to the exclusion and inclusion criteria.

Asthma was treated by inhaled Fluticasone propionate (FP); 100 - 1000 µg/day adults; 50 - 500 µg/day children, dry powder inhalation, disks. FP dose was adjusted during the baseline until 1 dose step below the threshold dose of asthma control criteria (GINA).

Period 1

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

Blinding implementation details:

Following a baseline assessment, all patients received either placebo (usual care in patients under 18 y) or the treatment allergoid preparation from D. pteronyssinus allergens for 2 years. This represents the double-blind, placebo-controlled treatment phase.

To minimise bias, different project leaders and monitors handled the 2 age groups of the study (adults and children), with a strict separation of information between these groups as well as between the participating centers

Arms

Are arms mutually exclusive?	Yes
Arm title	Children - Allergoid treatment (BDP)

Arm description:

Children randomised to allergoid treatment during the double-blind phase of the study.

Arm type	Experimental
Investigational medicinal product name	D. pteronyssinus allergoid preparation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

House dust mite allergens were extracted from purified mite bodies (D. pteronyssinus) with buffered saline, partially purified by diafiltration, characterised, chemically modified by treatment with aldehydes and adsorbed onto aluminium hydroxide. The concentration was specified in PNU.

Two concentrations of the preparation were provided:

strength A: 300 PNU/mL being a 1:10 dilution of strength B (3000 PNU/mL).

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.

PNU=Protein nitrogen unit

Arm title	Children - Usual care (BDP)
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Arm description:

Children randomised to usual care during the double-blind phase of the study.

Arm type	Usual care in children, instead of placebo
Investigational medicinal product name	Usual care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Patients under 18 years of age at the time of enrollment who were randomised to control group did not receive a placebo preparation. Pharmacotherapy according to the study specific medication was used instead in the control group (usual care).

The 'usual care' consisted of a reliever and controller asthma medication.

Arm title	Adults - Allergoid treatment (BDP)
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Arm description:

Adults randomised to Allergoid treatment during the double-blind phase of the study..

Arm type	Experimental
Investigational medicinal product name	D. pteronyssinus allergoid preparation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

House dust mite allergens were extracted from purified mite bodies (D. pteronyssinus) with buffered saline, partially purified by diafiltration, characterised, chemically modified by treatment with aldehydes and adsorbed onto aluminium hydroxide. The concentration was specified in PNU.

Two concentrations of the preparation were provided:

strength A: 300 PNU/mL being a 1:10 dilution of strength B (3000 PNU/mL).

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.

PNU=Protein nitrogen unit

Arm title	Adults - Placebo (DBP)
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Arm description:

Adults randomised to placebo during the double-blind phase of the study.

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

Dosage and administration details:

A placebo solution was supplied as comparator for patients over 18 years of age, containing histamine-dihydrochloride (0.0125 mg/mL corresponding to strength A and 0.125 mg/mL corresponding to strength B) and caramel as a colouring agent, to ensure blinding by the physician and patient.

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

For the injection volume and administration details of the placebo solution, please see the description above for the allergoid treatment arm.

Number of subjects in period 1	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)
Started	33	33	30
Completed	33	29	23
Not completed	0	4	7
Consent withdrawn by subject	-	3	5
Pregnancy	-	-	1
Lost to follow-up	-	1	1
Protocol deviation	-	-	-

Number of subjects in period 1	Adults - Placebo (DBP)
Started	34
Completed	25
Not completed	9
Consent withdrawn by subject	3
Pregnancy	-
Lost to follow-up	5
Protocol deviation	1

Period 2

Period 2 title	2_Open label phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Children - Allergoid treatment (OLP)

Arm description:

Children randomised to Allergoid treatment during the double-blind phase entered into a 3rd year of open-label SIT.

Arm type	Experimental
Investigational medicinal product name	D. pteronyssinus allergoid preparation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

House dust mite allergens were extracted from purified mite bodies (D. pteronyssinus) with buffered saline, partially purified by diafiltration, characterised, chemically modified by treatment with aldehydes and adsorbed onto aluminium hydroxide. The concentration was specified in PNU.

Two concentrations of the preparation were provided:
strength A: 300 PNU/mL being a 1:10 dilution of strength B (3000 PNU/mL).

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.

PNU=Protein nitrogen unit

Arm title	Adults - Allergoid treatment (OLP)
Arm description: Adults randomised to Allergoid treatment during the double-blind phase entered into a 3rd year of open-label SIT.	
Arm type	Experimental
Investigational medicinal product name	D. pteronyssinus allergoid preparation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

House dust mite allergens were extracted from purified mite bodies (D. pteronyssinus) with buffered saline, partially purified by diafiltration, characterised, chemically modified by treatment with aldehydes and adsorbed onto aluminium hydroxide. The concentration was specified in PNU.

Two concentrations of the preparation were provided:
strength A: 300 PNU/mL being a 1:10 dilution of strength B (3000 PNU/mL).

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.

PNU=Protein nitrogen unit

Number of subjects in period 2^[1]	Children - Allergoid treatment (OLP)	Adults - Allergoid treatment (OLP)
Started	33	22
Completed	30	19
Not completed	3	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-
Lost to follow-up	2	1
Decision by sponsor	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Several trial subjects did not continue the study after the double blind phase in the active treatment, in the 'usual care', or the placebo treatment groups.

Period 3

Period 3 title	3_Follow-up phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Children - Allergoid treatment (FU)
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Arm description:

Children from the control treatment group who were in the double-blind phase of the study and received the 'usual care' for 2 years were offered to enter an open-label SIT for 3 years, as a follow-up phase of the study.

Arm type	Experimental
Investigational medicinal product name	D. pteronyssinus allergoid preparation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

House dust mite allergens were extracted from purified mite bodies (D. pteronyssinus) with buffered saline, partially purified by diafiltration, characterised, chemically modified by treatment with aldehydes and adsorbed onto aluminium hydroxide. The concentration was specified in PNU.

Two concentrations of the preparation were provided:

strength A: 300 PNU/mL being a 1:10 dilution of strength B (3000 PNU/mL).

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.

PNU=Protein nitrogen unit

Number of subjects in period 3^[2]	Children - Allergoid treatment (FU)
Started	23
Completed	21
Not completed	2
Lost to follow-up	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Several trial subjects did not continue the study after the double blind phase in the active treatment, in the 'usual care', or the placebo treatment groups.

Baseline characteristics

Reporting groups

Reporting group title	Children - Allergoid treatment (BDP)
Reporting group description: Children randomised to allergoid treatment during the double-blind phase of the study.	
Reporting group title	Children - Usual care (BDP)
Reporting group description: Children randomised to usual care during the double-blind phase of the study.	
Reporting group title	Adults - Allergoid treatment (BDP)
Reporting group description: Adults randomised to Allergoid treatment during the double-blind phase of the study..	
Reporting group title	Adults - Placebo (DBP)
Reporting group description: Adults randomised to placebo during the double-blind phase of the study.	

Reporting group values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)
Number of subjects	33	33	30
Age categorical Units: Subjects			
Children (2-11 years)	22	17	0
Adolescents (12-17 years)	11	16	0
Adults (18-64 years)	0	0	30
Gender categorical Units: Subjects			
Female	11	10	14
Male	22	23	16
Race Units: Subjects			
White	33	33	30

Reporting group values	Adults - Placebo (DBP)	Total	
Number of subjects	34	130	
Age categorical Units: Subjects			
Children (2-11 years)	0	39	
Adolescents (12-17 years)	0	27	
Adults (18-64 years)	34	64	
Gender categorical Units: Subjects			
Female	17	52	
Male	17	78	
Race Units: Subjects			
White	34	130	

End points

End points reporting groups

Reporting group title	Children - Allergoid treatment (BDP)
Reporting group description: Children randomised to allergoid treatment during the double-blind phase of the study.	
Reporting group title	Children - Usual care (BDP)
Reporting group description: Children randomised to usual care during the double-blind phase of the study.	
Reporting group title	Adults - Allergoid treatment (BDP)
Reporting group description: Adults randomised to Allergoid treatment during the double-blind phase of the study..	
Reporting group title	Adults - Placebo (DBP)
Reporting group description: Adults randomised to placebo during the double-blind phase of the study.	
Reporting group title	Children - Allergoid treatment (OLP)
Reporting group description: Children randomised to Allergoid treatment during the double-blind phase entered into a 3rd year of open-label SIT.	
Reporting group title	Adults - Allergoid treatment (OLP)
Reporting group description: Adults randomised to Allergoid treatment during the double-blind phase entered into a 3rd year of open-label SIT.	
Reporting group title	Children - Allergoid treatment (FU)
Reporting group description: Children from the control treatment group who were in the double-blind phase of the study and received the 'usual care' for 2 years were offered to enter an open-label SIT for 3 years, as a follow-up phase of the study.	

Primary: 1_DBP_Minimum dose of inhaled corticosteroid to achieve asthma control, after 2 years of treatment

End point title	1_DBP_Minimum dose of inhaled corticosteroid to achieve asthma control, after 2 years of treatment
End point description: The minimum FP dose for asthma control according to GINA, was assessed before SIT therapy (baseline) and after the 2nd year of treatment, using predefined dose steps. Asthma control assessment (based on the nature and severity of asthma symptoms and the use of rescue medication) was based on patient diary entries: night-time awakenings; morning peak flow; daytime asthma symptoms; use of salbutamol rescue medication; exacerbations of asthma; emergency visits/unscheduled visits to the investigator due to asthma. Good asthma control was achieved if all of the following were fulfilled in each of the last 2 weeks of the 4 week diary phase: no night-time awakenings; no exacerbations; no emergency visit. FP dose: Children=50 to 500 µg/day, Adults=100 to 1000 µg/day FP dose steps: 1=50µg; 2=100µg; 3=250µg; 4=500µg; 5=1000µg. Results represent the change in minimum asthma control dose of FP in children/adults, as dose steps; scale -4 to +3. FP=Fluticasone propionate	
End point type	Primary

End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after 2 years of double-blind treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[1]	32	27	29
Units: subjects				
Improvement (-4)	0	0	0	1
Improvement (-3)	10	5	4	4
Improvement (-2)	6	1	0	6
Improvement (-1)	9	12	5	2
No change (0)	3	9	9	7
Deterioration (+1)	2	3	6	5
Deterioration (+2)	3	1	2	3
Deterioration (+3)	0	1	1	1

Notes:

[1] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
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Statistical analysis description:

Children: changes from baseline in FP dose steps after 2 years of treatment with SIT.

FP=Fluticasone propionate

SIT=Specific immunotherapy

Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.0487
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - This study was designed to demonstrate superiority of allergoid vs. placebo with regard to the inhalative dose of fluticasone propionate needed to ensure asthma control according to GINA recommendation.

Statistical analysis title	2_Difference between treatment groups (adults)
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Statistical analysis description:

Adults: changes from baseline in fluticasone dose steps after 2 years of treatment with SIT.

SIT=Specific immunotherapy

Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
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Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.4533
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - This study was designed to demonstrate superiority of allergoid vs. placebo with regard to the inhalative dose of fluticasone propionate needed to ensure asthma control according to GINA recommendation.

Secondary: 2_DBP_Minimum dose of inhaled corticosteroid to achieve asthma control, after 1 year of treatment

End point title	2_DBP_Minimum dose of inhaled corticosteroid to achieve asthma control, after 1 year of treatment
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End point description:

Please see the description provided for end point #1.

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after 1 year of double-blind treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[4]	32	27	29
Units: subjects				
Improvement (-3)	3	2	4	5
Improvement (-2)	9	0	2	2
Improvement (-1)	11	8	4	3
No change (0)	6	11	10	9
Deterioration (+1)	4	8	5	7
Deterioration (+2)	0	2	2	3
Deterioration (+3)	0	1	0	0

Notes:

[4] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
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Statistical analysis description:

Please see description provided for end point 1.

Comparison groups	Children - Usual care (BDP) v Children - Allergoid treatment (BDP)
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Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0006
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Please see description provided for end point 1.

Statistical analysis title	2_Difference between treatment groups (adults)
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Statistical analysis description:

Please see description provided for end point 1.

Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.7051
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Please see description provided for end point 1.

Secondary: 3_DBP_Mean peak flow (L/min) during asthma control phases, after 2 year of treatment

End point title	3_DBP_Mean peak flow (L/min) during asthma control phases, after 2 year of treatment
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End point description:

Mean peak flow values were assessed during the last 2 weeks of asthma control phases.

Results show the changes from baseline in the pre-bronchodilator morning PEF [L/min] post treatment after 2 years of double-blind treatment.

Results are based on the daily measurement of morning PEF documented in the diaries; the mean PEF during the last 2 weeks, when GINA ASTHMA CONTROL DOSE was determined.

Evaluation was also performed after 1 year of treatment; results were similar to the 2 year assessment.

PEF=Peak expiratory flow

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after 2 years of double-blind treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[7]	32	27	29
Units: L/min				
median (full range (min-max))	50.70 (-38.5 to 155.7)	23.55 (-81.4 to 171.4)	13.20 (-42.8 to 138.6)	5.00 (-40.0 to 89.3)

Notes:

[7] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
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Statistical analysis description:

Changes from baseline in peak flow (children) after 1 year of treatment with SIT.

PEF=Peak expiratory flow

SIT=Specific immunotherapy

Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0315
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
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Statistical analysis description:

Changes from baseline in peak flow (children) after 1 year of treatment with SIT.

PEF=Peak expiratory flow

SIT=Specific immunotherapy

Comparison groups	Adults - Placebo (DBP) v Adults - Allergoid treatment (BDP)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4036
Method	Wilcoxon (Mann-Whitney)

Secondary: 4_DBP_Mean peak flow (% of predicted normal) during asthma control phases, after 2 years of treatment

End point title	4_DBP_Mean peak flow (% of predicted normal) during asthma control phases, after 2 years of treatment
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End point description:

Please see the description provided for end point 3_DBP.

Evaluation was also performed after 1 year of treatment; results were similar to the 2 year assessment.

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after 2 years of double-blind treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[8]	32	27	29
Units: % of predicted normal				
median (full range (min-max))	4.00 (-27.8 to 44.2)	-4.10 (-27.9 to 32.0)	3.50 (-7.0 to 27.4)	1.0 (-7.7 to 15.8)

Notes:

[8] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1584
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2908
Method	Wilcoxon (Mann-Whitney)

Secondary: 5_DBP_Changes from baseline in the asthma control parameters, after 1 and 2 years of treatment

End point title	5_DBP_Changes from baseline in the asthma control parameters, after 1 and 2 years of treatment
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End point description:

Changes from baseline in the asthma control parameters.

The following items were documented daily for 4 to 5 periods of 4 weeks during each diary phase: 1) night-time awakenings; 2) morning PEF <80% of predicted normal; 3) daytime cough/dry cough; 4) daytime chest tightness; 5) daytime wheeze; 6) daytime dyspnoea; 7) asthma control phases with asthma summary score > 1; 8) use of salbutamol rescue medication; 9) exacerbations of asthma; 10) emergency visits/unscheduled visits to the investigator due to asthma.

Note: No relevant differences were seen between allergoid preparation and comparator in any of the evaluated items or age group, after 1 year or 2 years of treatment.

Thus, only a representative entry of data is made for the item: all asthma symptoms. Data are shown

as the difference between the baseline and the end of treatment (after 2 years of double-blind treatment phase).

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after 1 and 2 years of double-blind treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[9]	32	27	29
Units: score				
median (full range (min-max))	0.0 (-64 to 14)	-0.5 (-24 to 26)	-2.0 (-14 to 60)	-2.0 (-34 to 29)

Notes:

[9] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4106
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9967
Method	Wilcoxon (Mann-Whitney)

Secondary: 6_DBP_Changes from baseline in FEV1 after 1 and 2 years of treatment

End point title	6_DBP_Changes from baseline in FEV1 after 1 and 2 years of treatment
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End point description:

Changes from baseline in the pre-bronchodilator morning FEV1 [L] post treatment, after 1 and 2 years of double-blind treatment. Determination of the Lung function tests FEV1 was performed by spirometry. For enrollment into the study the patients had to have a lung function of at least 80%.

Note: No clinically relevant or statistically significant differences between allergoid and comparator were

seen with regard to FEV1 in either of the 2 age groups, after 1 and 2 years of double-blind treatment. Thus, results are shown only for those obtained after 2 years of double-blind treatment.

FEV1=forced expiratory volume in one second

End point type	Secondary
End point timeframe:	
Assessment period of approx. 6 months before treatment (baseline assessment) and at each visit during the diary assessment phases.	

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[10]	31	25	27
Units: litre(s)				
median (full range (min-max))	0.35 (-0.10 to 1.60)	0.41 (-0.01 to 1.10)	-0.08 (-1.46 to 0.46)	-0.16 (-1.40 to 0.16)

Notes:

[10] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
Comparison groups	Children - Usual care (BDP) v Children - Allergoid treatment (BDP)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.311
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1449
Method	Wilcoxon (Mann-Whitney)

Secondary: 7_DBP_Changes from baseline in maximal expiratory flow (MEF), after 1 and 2 years of treatment

End point title	7_DBP_Changes from baseline in maximal expiratory flow (MEF), after 1 and 2 years of treatment
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End point description:

Determination of the lung function test MEF [Litres/sec] was performed by spirometry. Changes from baseline after 1 and 2 years of treatment were analysed for MEF25, MEF50, and MEF75.

Note: Results are shown only for MEF75, obtained after 2 years of double-blind treatment. Results from MEF25 and MEF50 showed similar trend as the results for MEF75.

MEF=Maximal expiratory flow at 25%, 50%, and 75% of vital capacity

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and at each visit during the diary assessment phases.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 ^[11]	31	18	20
Units: L/sec				
median (full range (min-max))	0.50 (-1.04 to 2.02)	0.70 (-0.40 to 4.60)	0.15 (-1.50 to 2.09)	-0.55 (-2.51 to 0.90)

Notes:

[11] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4563
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0057
Method	Wilcoxon (Mann-Whitney)

Secondary: 8_DBP_Changes from baseline in the non-specific bronchial hyperactivity provocative concentration of methacholine required to produce a 20% fall in FEV1 (PC20FEV1), after 2 years of treatment

End point title	8_DBP_Changes from baseline in the non-specific bronchial hyperactivity provocative concentration of methacholine required to produce a 20% fall in FEV1 (PC20FEV1), after 2
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End point description:

Changes from baseline in the non-specific bronchial hyperactivity provocative concentration of methacholine required to produce a 20% fall in FEV1 (PC20FEV1) after 2 years of treatment.

The methacholine bronchial provocation test (MBPT) was performed to assess the bronchial hyperresponsiveness (BHR) during the course of study. The test was carried out according to the standardised and published 'short provocation protocol'.

FEV1=Forced expiratory volume in one second

PC20FEV1=Provocative concentration of methacholine required to produce a 20% fall in FEV1

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after 2 years of double-blind treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32 ^[12]	28	23	25
Units: ln(PC20FEV1)				
median (full range (min-max))	0.708 (-4.27 to 4.74)	0.000 (-5.25 to 4.53)	0.000 (-2.19 to 2.96)	0.000 (-2.59 to 1.95)

Notes:

[12] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5716
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8923
Method	Wilcoxon (Mann-Whitney)

Secondary: 9_DBP_Changes from baseline in the immunological profile of sIgE, after 1 and 2 years of treatment

End point title	9_DBP_Changes from baseline in the immunological profile of sIgE, after 1 and 2 years of treatment
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End point description:

Changes from baseline in the immunological profile of serum sIgE (mite-specific), after 1 and 2 years of treatment.

Serum sIgE was determined using the RAST/CAP method. For inclusion in the study, patient had to have a positive RAST/CAP to D. pteronyssinus $\geq$ CAP class II (i.e. ≥ 0.70 kUIgE/L (kU = kilo-units)).

Results are presented in percent, as a change from baseline after treatment.

Note: Results are presented only for data obtained after 2 years of treatment.

Results obtained after 1 year of SIT were similar to those after 2 years of treatment.

CAP=ImmunoCAP sIgE blood test

sIgE=Specific immunoglobulin E

RAST=Radio-allergo-sorbent test

SIT=Specific immunotherapy

End point type	Secondary
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End point timeframe:

At baseline (before treatment), after 1 year and 2 years of double-blind of treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29 ^[13]	27	24	24
Units: percent				
number (not applicable)	-22.9	2.0	-29.3	-11.3

Notes:

[13] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0217
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3278
Method	Wilcoxon (Mann-Whitney)

Secondary: 10_DBP_Changes from baseline in the immunological profile of sIgG1, after 1 and 2 years treatment

End point title	10_DBP_Changes from baseline in the immunological profile of sIgG1, after 1 and 2 years treatment
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End point description:

Changes from baseline in the immunological profile of serum sIgG1 (specific for D. pteronyssinus-induced house dust mite), after 1 and 2 years SIT.

Allergen specific ELISA was used to determine the sIgG1.

Results are presented in percent, as a change from baseline after treatment.

Results are presented here only for data obtained after 2 years of treatment; results obtained after 2 years of SIT were similar to those after 1 year.

sIgG1=specific immunoglobulin G1 (specific for D. pteronyssinus-induced house dust mite)

End point type	Secondary
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End point timeframe:

At baseline (before treatment), after 1 year, and 2 years of double-blind of treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29 ^[14]	27	24	24
Units: percent				
number (not applicable)	85.2	-15.5	90.9	-11.6

Notes:

[14] - Full Analysis Set for all treatment groups

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: 11_DBP_Changes from baseline in the immunological profile of sIgG4, after 1 and 2 years of treatment

End point title	11_DBP_Changes from baseline in the immunological profile of sIgG4, after 1 and 2 years of treatment
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End point description:

Changes from baseline in the immunological profile of serum sIgG4 (specific for D. pteronyssinus-induced house dust mite), after 1 and 2 years of treatment.

Allergen specific ELISA was used to determine the sIgG4.

Results are presented in percent, as a change from baseline after treatment.

Note: Results are presented here only for data obtained after 2 years of treatment; results obtained after 2 years of SIT were similar to those after 1 year.

sIgG4=specific immunoglobulin G4 (specific for D. pteronyssinus-induced house dust mite)

End point type	Secondary
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End point timeframe:

At baseline (before treatment), after 1 year and 2 years of double-blind treatment.

End point values	Children - Allergoid treatment (BDP)	Children - Usual care (BDP)	Adults - Allergoid treatment (BDP)	Adults - Placebo (DBP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	27	24	24
Units: percent				
number (not applicable)	1146.9	3.8	541.5	-0.7

Statistical analyses

Statistical analysis title	1_Difference between treatment groups (children)
Comparison groups	Children - Allergoid treatment (BDP) v Children - Usual care (BDP)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	2_Difference between treatment groups (adults)
Comparison groups	Adults - Allergoid treatment (BDP) v Adults - Placebo (DBP)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: 12_OLP_Minimum dose of inhaled corticosteroid to achieve asthma control, after the 3rd year of SIT

End point title	12_OLP_Minimum dose of inhaled corticosteroid to achieve asthma control, after the 3rd year of SIT
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End point description:

During the 3rd year of the study, patients received SIT in an open-label manner.
For further details, please refer to the description for the endpoint #1_BDP.

Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority
1_Change from baseline in PEF (children); $p < 0.0001$
2_Change from baseline in PEF (adults); $p < 0.0001$

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after the 3rd year of open-label SIT with allergoid preparation.

End point values	Children - Allergoid treatment (OLP)	Adults - Allergoid treatment (OLP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[15]	21		
Units: subjects				
Improvement (-3)	10	1		
Improvement (-2)	4	1		
Improvement (-1)	13	6		
No change (0)	1	6		
Deterioration (+1)	5	5		
Deterioration (+2)	0	1		
Deterioration (+3)	0	1		

Notes:

[15] - Full Analysis Set for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 13_OLP_Mean peak flow (L/min) during asthma control phases, after the 3rd year of SIT

End point title	13_OLP_Mean peak flow (L/min) during asthma control phases, after the 3rd year of SIT
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End point description:

During the 3rd year of the study, patients received SIT in an open-label manner.

For further details, please refer to the description for endpoint 3_DBP.

Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority

1_Change from baseline in PEF (children); $p < 0.0001$

2_Change from baseline in PEF (adults); $p = 0.0094$

SIT=Specific immunotherapy

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after the 3rd year of open-label SIT with allergoid preparation.

End point values	Children - Allergoid treatment (OLP)	Adults - Allergoid treatment (OLP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[16]	21		
Units: L/min				
median (full range (min-max))	63.60 (5.8 to 163.6)	17.20 (-25.8 to 122.2)		

Notes:

[16] - Full Analysis Set for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 14_OLP_Mean peak flow (% predicted) during asthma control phases, after the 3rd year of SIT

End point title	14_OLP_Mean peak flow (% predicted) during asthma control phases, after the 3rd year of SIT
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End point description:

During the 3rd year of the study, patients received SIT in an open-label manner.

For further details, please refer to the description for endpoint 3_DBP.

Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority

1_Change from baseline in PEF (children); $p = 0.9096$

2_Change from baseline in PEF (adults); $p = 0.0024$

SIT=Specific immunotherapy

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after the 3rd year of open-label SIT with allergoid preparation.

End point values	Children - Allergoid treatment (OLP)	Adults - Allergoid treatment (OLP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[17]	21		
Units: % of predicted normal				
median (full range (min-max))	1.70 (-34.8 to 38.6)	4.40 (-3.6 to 28.9)		

Notes:

[17] - Full Analysis Set for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 15_OLP_Changes from baseline in the asthma control parameters, after the 3rd year of SIT

End point title	15_OLP_Changes from baseline in the asthma control parameters, after the 3rd year of SIT
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End point description:

During the 3rd year of the study, patients received SIT in an open-label manner.
For further details, please refer to the description for endpoint #5_DBP.

Note: No clinically relevant or statistically significant differences were seen between allergoid preparation and comparator in any of the evaluated items or age group, after the 3rd year of SIT. Thus, only a representative entry of data is made for the item: all asthma symptoms. Data are shown as the difference between the baseline and the end of treatment (after the 3rd year of double-blind treatment phase).

Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority
1_Change from baseline in PEF (children); p = 0.2987
2_Change from baseline in PEF (adults); p = 0.5048

SIT=Specific immunotherapy

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after the 3rd year of double-blind SIT with allergoid preparation.

End point values	Children - Allergoid treatment (OLP)	Adults - Allergoid treatment (OLP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[18]	21		
Units: score				
median (full range (min-max))	-1.0 (-64 to 36)	3.0 (-15 to 60)		

Notes:

[18] - Full Analysis Set for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 16_OLP_Changes from baseline in FEV1 after the 3rd year of SIT

End point title	16_OLP_Changes from baseline in FEV1 after the 3rd year of SIT
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End point description:

During the 3rd year of the study, patients received SIT in an open-label manner.
For further details, please refer to the description for endpoint #6_DBP.

Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority
1_Change from baseline in PEF (children); $p < 0.0001$
2_Change from baseline in PEF (adults); $p < 0.0014$

SIT=Specific immunotherapy

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after the 3rd year of open-label SIT with allergoid preparation.

FEV1=forced expiratory volume in one second

SIT=Specific immunotherapy

End point values	Children - Allergoid treatment (OLP)	Adults - Allergoid treatment (OLP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[19]	21		
Units: litre(s)				
median (full range (min-max))	0.59 (-0.50 to 2.05)	-0.22 (-0.91 to 0.45)		

Notes:

[19] - Full Analysis Set for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 17_OLP_Changes from baseline in maximal expiratory flow (MEF), after the 3rd year of SIT

End point title	17_OLP_Changes from baseline in maximal expiratory flow (MEF), after the 3rd year of SIT
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End point description:

During the 3rd year of the study, patients received SIT in an open-label manner.

For further details, please refer to the description for the endpoint #7_DBP.

Note: Results are shown only for MEF75, obtained after the 3rd year of treatment.
Results from MEF25 and MEF50 showed similar trend as the results for MEF75.

Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority
1_Change from baseline in PEF (children); $p < 0.0001$
2_Change from baseline in PEF (adults); $p = 0.7917$

MEF=Maximal expiratory flow at 25%, 50%, and 75% of vital capacity
SIT=Specific immunotherapy

End point type	Secondary
End point timeframe:	
Assessment period of approx. 6 months before treatment (baseline assessment) and after the 3rd year of open-label SIT with allergoid preparation.	

End point values	Children - Allergoid treatment (OLP)	Adults - Allergoid treatment (OLP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[20]	16		
Units: L/sec				
median (full range (min-max))	0.89 (-0.80 to 2.40)	-0.03 (-2.77 to 1.38)		

Notes:

[20] - Full Analysis Set for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 18_OLP_Changes from baseline in the non-specific bronchial hyperactivity provocative concentration of methacholine required to produce a 20% fall in FEV1 (PC20FEV1), after the 3rd year of SIT

End point title	18_OLP_Changes from baseline in the non-specific bronchial hyperactivity provocative concentration of methacholine required to produce a 20% fall in FEV1 (PC20FEV1), after the 3rd year of SIT
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End point description:

During the 3rd year of the study, patients received SIT in an open-label manner.
For further details, please refer to the description for the endpoint #8_DBP.

Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority
1_Change from baseline in PEF (children); $p = 0.0213$
2_Change from baseline in PEF (adults); $p = 0.0977$

FEV1=Forced expiratory volume in one second
PC20FEV1=Provocative concentration of methacholine required to produce a 20% fall in FEV1

End point type	Secondary
End point timeframe:	
Assessment period of approx. 6 months before treatment (baseline assessment) and after the 3rd year of open-label SIT with allergoid preparation.	

End point values	Children - Allergoid treatment (OLP)	Adults - Allergoid treatment (OLP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31 ^[21]	16		
Units: ln(PC20FEV1)				
median (full range (min-max))	0.722 (-3.35 to 4.74)	0.413 (-2.25 to 4.83)		

Notes:

[21] - Full Analysis Set for all treatment groups

Statistical analyses

No statistical analyses for this end point

Secondary: 19_FU_Changes from baseline in FEV1 (L) after 3 years of SIT

End point title	19_FU_Changes from baseline in FEV1 (L) after 3 years of SIT
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End point description:

During the follow-up 3 years of the study, patients received SIT in an open-label manner. For further details, please refer to the description for the endpoint #6_DBP.

Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority 1_Change from baseline in PEF (children); p = 0.0327

SIT=Specific immunotherapy

End point type	Secondary
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End point timeframe:

Assessment period of approx. 6 months before treatment (baseline assessment) and after 3 years of open-label SIT with allergoid preparation.

End point values	Children - Allergoid treatment (FU)			
Subject group type	Reporting group			
Number of subjects analysed	22 ^[22]			
Units: litre(s)				
median (full range (min-max))	0.440 (-1.29 to 1.77)			

Notes:

[22] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: 20_FU_Changes from baseline in maximal expiratory flow (MEF), after 3 years of SIT

End point title	20_FU_Changes from baseline in maximal expiratory flow (MEF), after 3 years of SIT
End point description:	
During the follow-up 3 years of the study, patients received SIT in an open-label manner. For further details, please refer to the description for the endpoint #7_DBP.	
Note: Results are shown only for MEF75, obtained after 3 years of treatment with SIT. Results from MEF25 and MEF50 showed similar trend as the results for MEF75.	
Statistical evaluation was performed using Wilcoxon (Mann-Whitney) method; Analysis type: superiority 1_Change from baseline in PEF (children); p = 0.1019	
MEF=Maximal expiratory flow at 25%, 50%, and 75% of vital capacity	
End point type	Secondary
End point timeframe:	
Assessment period of approx. 6 months before treatment (baseline assessment) and after 3 years of open-label SIT with allergoid preparation.	

End point values	Children - Allergoid treatment (FU)			
Subject group type	Reporting group			
Number of subjects analysed	22 ^[23]			
Units: L/sec				
median (full range (min-max))	0.53 (-3.19 to 2.57)			

Notes:

[23] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of the study (signing of the informed consent) until the end of the study (last study visit i.e. 2 years after study start for open-label phase, and 3 years for the follow-up phase).

Adverse event reporting additional description:

Some AEs were reported during the 'bridging' phase of the study. This phase occurred between the 'blind-label' phase and 'open-label' phase, when no treatment was given. AEs that were reported during the 'bridging' phase were included in the 'blind-label' phase.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	8.0
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Reporting groups

Reporting group title	Screening/Baseline: Children - Allergoid treatment
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Reporting group description:

Children during the screening/baseline phase of the study, randomised to Allergoid treatment group.

Reporting group title	Screening/Baseline: Children - Usual care
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Reporting group description:

Children during the screening/baseline phase of the study, randomised to 'usual care' treatment group.

Reporting group title	Screening/Baseline: Adults - Allergoid treatment
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Reporting group description:

Adults during the screening/baseline phase of the study, randomised to Allergoid treatment group.

Reporting group title	Screening/Baseline: Adults - Placebo
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Reporting group description:

Adults during the screening/baseline phase of the study, randomised to placebo treatment group.

Reporting group title	DBP: Children - Allergoid treatment
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Reporting group description:

Children randomised to allergoid treatment, during the double-blind treatment phase.

Reporting group title	DBP: Children - Usual care
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Reporting group description:

Children randomised to usual care, during the double-blind treatment phase..

Reporting group title	DBP: Adults - Allergoid treatment
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Reporting group description:

Adults randomised to Allergoid treatment, during the double-blind treatment phase.

Reporting group title	DBP: Adults - Placebo
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Reporting group description:

Adults randomised to placebo, during the double-blind treatment phase.

Reporting group title	OLP: Children - Allergoid treatment
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Reporting group description:

Children receiving Allergoid treatment during the open-label phase (OLP).

Reporting group title	OLP: Adults - Allergoid treatment
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Reporting group description:

Adults receiving Allergoid treatment during the open-label phase (OLP).

Reporting group title	FU: Children - Allergoid treatment
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Reporting group description:

Children receiving Allergoid treatment during the follow-up phase (FU).

Serious adverse events	Screening/Baseline: Children - Allergoid treatment	Screening/Baseline: Children - Usual care	Screening/Baseline: Adults - Allergoid treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Lumbar vertebral fracture	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic dysregulation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Anorexia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma exacerbation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis acute			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			

subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria generalised			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acne pustular			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute appendicitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
Additional description: This SAE occurred during the 'bridging' phase of the study.			

subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Screening/Baseline: Adults - Placebo	DBP: Children - Allergoid treatment	DBP: Children - Usual care
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	4 / 32 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Lumbar vertebral fracture	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic dysregulation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Anorexia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma exacerbation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis acute			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			

subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria generalised			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acne pustular			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute appendicitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection			

subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess	Additional description: This SAE occurred during the 'bridging' phase of the study.		
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DBP: Adults - Allergoid treatment	DBP: Adults - Placebo	OLP: Children - Allergoid treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	3 / 31 (9.68%)	5 / 33 (15.15%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Lumbar vertebral fracture	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	0 / 28 (0.00%)	1 / 31 (3.23%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic dysregulation			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cyanosis			

subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Anorexia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 31 (3.23%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma exacerbation			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis acute			
subjects affected / exposed	0 / 28 (0.00%)	1 / 31 (3.23%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			

subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria generalised			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acne pustular			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Acute appendicitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess	Additional description: This SAE occurred during the 'bridging' phase of the study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	OLP: Adults - Allergoid treatment	FU: Children - Allergoid treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	9 / 23 (39.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Lumbar vertebral fracture	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic dysregulation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rehabilitation therapy			

subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Anorexia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma exacerbation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis acute			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			

subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria generalised			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acne pustular			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			

subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute appendicitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
	Additional description: This SAE occurred during the 'bridging' phase of the study.		
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Screening/Baseline: Children - Allergoid treatment	Screening/Baseline: Children - Usual care	Screening/Baseline: Adults - Allergoid treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 33 (75.76%)	23 / 32 (71.88%)	5 / 28 (17.86%)
Injury, poisoning and procedural complications			
Meniscus lesion			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection site pain			
	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		

subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Injection site pruritus subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Injection site swelling	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Social circumstances Family stress subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 32 (3.13%) 1	0 / 28 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 32 (3.13%) 1	0 / 28 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0	0 / 28 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			

Asthma	Additional description: Three occurrences of this AE were during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	7 / 33 (21.21%)	9 / 32 (28.13%)	0 / 28 (0.00%)
occurrences (all)	7	9	0
Rhinitis allergic			
subjects affected / exposed	2 / 33 (6.06%)	2 / 32 (6.25%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Cough			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Urticaria generalised			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Tenosynovitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 32 (6.25%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Bronchitis acute	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group)		
subjects affected / exposed	6 / 33 (18.18%)	3 / 32 (9.38%)	0 / 28 (0.00%)
occurrences (all)	6	3	0
Gastroenteritis			
subjects affected / exposed	1 / 33 (3.03%)	2 / 32 (6.25%)	0 / 28 (0.00%)
occurrences (all)	1	2	0

Nasopharyngitis		Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group). One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	11 / 33 (33.33%)	13 / 32 (40.63%)	4 / 28 (14.29%)	
occurrences (all)	11	13	4	
Pharyngitis				
subjects affected / exposed	3 / 33 (9.09%)	6 / 32 (18.75%)	1 / 28 (3.57%)	
occurrences (all)	3	6	1	
Rhinitis		Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	6 / 33 (18.18%)	4 / 32 (12.50%)	0 / 28 (0.00%)	
occurrences (all)	6	4	0	
Sinusitis				
subjects affected / exposed	3 / 33 (9.09%)	0 / 32 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	3	0	1	
Smallpox				
subjects affected / exposed	2 / 33 (6.06%)	0 / 32 (0.00%)	0 / 28 (0.00%)	
occurrences (all)	2	0	0	
Tonsillitis				
subjects affected / exposed	1 / 33 (3.03%)	1 / 32 (3.13%)	1 / 28 (3.57%)	
occurrences (all)	1	1	1	
Acute tonsillitis				
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)	
occurrences (all)	0	0	0	
Ear infection				
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)	
occurrences (all)	0	0	0	
Laryngitis				
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)	
occurrences (all)	0	0	0	
Pneumonia				
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)	
occurrences (all)	0	0	0	
Viral infection		Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	1 / 33 (3.03%)	1 / 32 (3.13%)	0 / 28 (0.00%)	
occurrences (all)	1	1	0	
Herpes simplex		Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		

subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis	Additional description: Two occurrences of this AE were during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 33 (0.00%)	0 / 32 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Screening/Baseline: Adults - Placebo	DBP: Children - Allergoid treatment	DBP: Children - Usual care
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 31 (22.58%)	32 / 33 (96.97%)	31 / 32 (96.88%)
Injury, poisoning and procedural complications			
Meniscus lesion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injection site pain	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	0 / 31 (0.00%)	4 / 33 (12.12%)	0 / 32 (0.00%)
occurrences (all)	0	4	0
Injection site pruritus			
subjects affected / exposed	0 / 31 (0.00%)	5 / 33 (15.15%)	0 / 32 (0.00%)
occurrences (all)	0	5	0
Injection site swelling	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	0 / 31 (0.00%)	9 / 33 (27.27%)	0 / 32 (0.00%)
occurrences (all)	0	9	0
Pyrexia			

subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0	2 / 32 (6.25%) 2
Social circumstances			
Family stress			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Conjunctivitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Three occurrences of this AE were during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 31 (0.00%)	15 / 33 (45.45%)	14 / 32 (43.75%)
occurrences (all)	0	15	17
Rhinitis allergic			
subjects affected / exposed	0 / 31 (0.00%)	4 / 33 (12.12%)	4 / 32 (12.50%)
occurrences (all)	0	4	4
Cough			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	4 / 32 (12.50%)
occurrences (all)	1	2	4

Wheezing subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0	1 / 32 (3.13%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0	2 / 32 (6.25%) 2
Skin and subcutaneous tissue disorders Urticaria generalised subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1	0 / 32 (0.00%) 0
Musculoskeletal and connective tissue disorders Tenosynovitis subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 33 (0.00%) 0	0 / 32 (0.00%) 0
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	3 / 33 (9.09%) 3	2 / 32 (6.25%) 2
Bronchitis acute subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	11 / 33 (33.33%) 11	10 / 32 (31.25%) 10
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1	0 / 32 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3	20 / 33 (60.61%) 20	15 / 32 (46.88%) 16
Pharyngitis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	18 / 33 (54.55%) 18	11 / 32 (34.38%) 11
Rhinitis	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		

subjects affected / exposed	2 / 31 (6.45%)	4 / 33 (12.12%)	7 / 32 (21.88%)
occurrences (all)	2	4	7
Sinusitis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Smallpox			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 31 (0.00%)	3 / 33 (9.09%)	0 / 32 (0.00%)
occurrences (all)	0	3	0
Acute tonsillitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	3 / 32 (9.38%)
occurrences (all)	0	2	3
Ear infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Laryngitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	2 / 32 (6.25%)
occurrences (all)	0	2	2
Viral infection			
	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 31 (0.00%)	4 / 33 (12.12%)	1 / 32 (3.13%)
occurrences (all)	0	4	1
Herpes simplex			
	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0

Oral candidiasis	Additional description: Two occurrences of this AE were during the 'bridging' phase (children, usual care treatment group).			
	subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 32 (6.25%)
	occurrences (all)	0	0	2

Non-serious adverse events	DBP: Adults - Allergoid treatment	DBP: Adults - Placebo	OLP: Children - Allergoid treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 28 (53.57%)	18 / 31 (58.06%)	25 / 33 (75.76%)
Injury, poisoning and procedural complications			
Meniscus lesion			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 28 (3.57%)	1 / 31 (3.23%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Injection site pain	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	3 / 28 (10.71%)	2 / 31 (6.45%)	2 / 33 (6.06%)
occurrences (all)	3	2	2
Injection site pruritus			
subjects affected / exposed	3 / 28 (10.71%)	1 / 31 (3.23%)	1 / 33 (3.03%)
occurrences (all)	3	1	1
Injection site swelling	Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
subjects affected / exposed	6 / 28 (21.43%)	5 / 31 (16.13%)	1 / 33 (3.03%)
occurrences (all)	6	5	1
Pyrexia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Social circumstances			
Family stress			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 28 (3.57%)	1 / 31 (3.23%)	2 / 33 (6.06%)
occurrences (all)	1	1	2

Conjunctivitis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 31 (3.23%) 1	0 / 33 (0.00%) 0
Gastrointestinal disorders			
Dyspepsia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Three occurrences of this AE were during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	0 / 31 (0.00%) 0	7 / 33 (21.21%) 7
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	2 / 31 (6.45%) 2	5 / 33 (15.15%) 5
Cough subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	4 / 31 (12.90%) 4	2 / 33 (6.06%) 2
Wheezing subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 31 (3.23%) 1	2 / 33 (6.06%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	2 / 31 (6.45%) 2	0 / 33 (0.00%) 0
Skin and subcutaneous tissue disorders			

Urticaria generalised subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 31 (0.00%) 0	2 / 33 (6.06%) 2
Musculoskeletal and connective tissue disorders Tenosynovitis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 31 (0.00%) 0	2 / 33 (6.06%) 2
Bronchitis acute subjects affected / exposed occurrences (all)	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group)		
	0 / 28 (0.00%) 0	1 / 31 (3.23%) 1	5 / 33 (15.15%) 5
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group). One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
	6 / 28 (21.43%) 6	6 / 31 (19.35%) 6	6 / 33 (18.18%) 6
Pharyngitis subjects affected / exposed occurrences (all)	6 / 28 (21.43%) 6	9 / 31 (29.03%) 9	4 / 33 (12.12%) 4
Rhinitis subjects affected / exposed occurrences (all)	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
	2 / 28 (7.14%) 2	1 / 31 (3.23%) 1	1 / 33 (3.03%) 1
Sinusitis subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1
Smallpox subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0
Tonsillitis			

subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Acute tonsillitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 31 (3.23%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Ear infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	2 / 28 (7.14%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Pneumonia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Viral infection	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Herpes simplex	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	2 / 28 (7.14%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Tracheitis			
subjects affected / exposed	4 / 28 (14.29%)	1 / 31 (3.23%)	0 / 33 (0.00%)
occurrences (all)	4	1	0
Oral candidiasis	Additional description: Two occurrences of this AE were during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 28 (0.00%)	0 / 31 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	OLP: Adults - Allergoid treatment	FU: Children - Allergoid treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)	17 / 23 (73.91%)	
Injury, poisoning and procedural complications			

Meniscus lesion subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 23 (4.35%) 1	
General disorders and administration site conditions			
Injection site pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Injection site pruritus subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Injection site swelling subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 23 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Social circumstances Family stress subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 23 (4.35%) 1	
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 23 (4.35%) 1	
Vomiting			

Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).

Additional description: One occurrence of this AE was during the 'bridging' phase (adults, placebo group).

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Three occurrences of this AE were during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 23 (8.70%) 2	
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 23 (8.70%) 2	
Cough subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Wheezing subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 23 (4.35%) 1	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 23 (8.70%) 2	
Dyspnoea subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Urticaria generalised subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 23 (4.35%) 1	
Musculoskeletal and connective tissue disorders			
Tenosynovitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	

Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 23 (8.70%) 2	
Bronchitis acute subjects affected / exposed occurrences (all)	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group)		
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	3 / 23 (13.04%) 3	
Nasopharyngitis subjects affected / exposed occurrences (all)	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group). One occurrence of this AE was during the 'bridging' phase (adults, placebo group).		
Pharyngitis subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	10 / 23 (43.48%) 10	
Rhinitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	6 / 23 (26.09%) 6	
Sinusitis subjects affected / exposed occurrences (all)	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
Smallpox subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Tonsillitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Acute tonsillitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 23 (8.70%) 2	
Ear infection subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 23 (0.00%) 0	
Laryngitis			

subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Viral infection	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Herpes simplex	Additional description: One occurrence of this AE was during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 21 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Influenza			
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Tracheitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis	Additional description: Two occurrences of this AE were during the 'bridging' phase (children, usual care treatment group).		
subjects affected / exposed	0 / 21 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2005	Non-substantial amendment: Administrative and operative amendments. • A second project manager responsible for the open investigation in patients < 18 years of age was appointed, and a Blind Data Review Board was established. • To ensure confidentiality of information gained in the open part of this study from the double-blind investigation in adults, regulations pertaining to the separation of both study parts were established. • The randomisation procedure and the number of (randomised) patients per center were clarified. • For patients who received other than the permitted asthma medication, the assessment of medication for efficacy analysis was defined. • Two repeats of house dust sampling for the determination of house dust mite allergens were made obligatory. • The method (chi-squared test) of group comparison in case of only few steps of changes from baseline was added. • For the assessment of the primary endpoint (asthma control), the data from the last two weeks of every 4-week diary had to be available. The randomisation procedure and the number of (randomised) patients per center had to be available.
04 May 2005	Non-substantial amendment: Administrative and operative amendment. Adjust study administrative items.
30 August 2005	Substantial amendment Adjust study procedures in the study protocol: • Omit the determination of unspecific bronchial provocation testing and nitric oxide determination in exhaled air at screening. • While recording the lung function data during the assessment phases of the study, also include the assessment of MEF25, 50, and 75 (MEF25, MEF50, MEF75=maximal expiratory flow at 25% – 50% – 75% of vital capacity).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported