Clinical trial results:
Multicenter, placebo-controlled, long-term study of Depigoid Birch 5000 in adults and adolescents with allergic rhinitis and/or rhinoconjunctivitis with or without intermittent asthma

Summary

EudraCT number	2012-000414-11
Trial protocol	DE LT CZ FI PL LV
Global end of trial date	30 July 2018

Results information

Result version number	v1 (current)
This version publication date	02 January 2020
First version publication date	02 January 2020

Trial information

Trial identification

Sponsor protocol code	603-PG-PSC-191

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01694836
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LETI Pharma GmbH
Sponsor organisation address	Stockumer Str. 28, Witten, Germany, 58453
Public contact	Medical Department, LETI Pharma GmbH, 0049 2302202860, info@leti.de
Scientific contact	Medical Department, LETI Pharma GmbH, 0049 2302202860, info@leti.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000630-PIP02-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 July 2018
Global end of trial reached?	Yes
Global end of trial date	30 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the long-term efficacy and safety of depigmented and glutaraldehyde polymerized allergenic extract of 100% birch pollen (Depigoid Birch) at a concentration of 5000 DPP/mL applied according to the perennial treatment regimen in comparison to placebo in adult and adolescent patients with birch pollen-induced allergic rhinitis and/or rhinoconjunctivitis.

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 protocol, all amendments, informed consent forms (ICF) were approved by an independent ethics committee (IEC) and health authorities; ICF was explained to and consent obtained from each patient before participation. To minimize risks, stopping criteria were defined and an independent Data Monitoring Committee (DMC) was created to assess the progress, safety and critical efficacy endpoints of the study. Three interim analyses were planned to assess efficacy of the treatment and the study futility. In addition, patients were permitted to use rescue medication (RM) to alleviate allergic symptoms; these medications are also used as symptomatic RM in daily clinical routine for allergic rhino-conjunctivitis and allergic intermittent asthma; after the study ended, the placebo-treated patients were also offered a 3-year perennial specific immunotherapy (SIT) with Depigoid Birch as a follow-up treatment in countries where legally possible. The sponsor issued a global protocol amendment requiring the withdrawal of all co-sensitized patients and continuing only with patients mono-sensitized to birch (according to the skin prick test at screening), because statistically significant differences in favor of Depigoid Birch 5000 over placebo for the treatment of allergic rhinitis and/or rhino-conjunctivitis, with or without intermittent asthma, could only be shown in mono-sensitized patients (demonstrated by results of planned 2nd-year interim analysis, the additional analyses of 3rd-year data and the post-hoc analyses of 2nd and 3rd year data performed by the DMC).

Background therapy:

Country-specific RMs were used in the study for treatment of potentially occurring characteristic symptoms related to the underlying disease (allergic rhinitis/rhinoconjunctivitis with or without asthma due to birch pollen).

Evidence for comparator:

Placebo control was used in this study. It was appropriate as the European Medicines Agency (EMA) guideline on clinical development of products for SIT for the treatment of allergic diseases (CHMP/EWP/18504/2006) recommends that Phase III studies in immunotherapy should show superiority of test drugs to placebo.

Actual start date of recruitment	17 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 215
Country: Number of subjects enrolled	Czech Republic: 50
Country: Number of subjects enrolled	Finland: 48
Country: Number of subjects enrolled	Germany: 217
Country: Number of subjects enrolled	Latvia: 30
Country: Number of subjects enrolled	Lithuania: 55
Country: Number of subjects enrolled	Russian Federation: 34
Worldwide total number of subjects	649
EEA total number of subjects	615

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	49
Adults (18-64 years)	592
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients (12-70 y) from 7 countries were enrolled and screened over 2 recruitment periods (started Sep-2012, ended Jan-2014). 649 of 973 (66.7%) enrolled patients were randomized to treatment (434 to Depigoid Birch; 215 to placebo).

Pre-assignment

Screening details:

Subjects were included if they had immunoglobulin E (IgE)-mediated seasonal allergic rhinitis and/or rhinoconjunctivitis with or without intermittent asthma due to birch pollen allergy verified by specific IgE reactivity (CAP-RAST ≥2) and positive Skin Prick Test (SPT) (wheal diameter of at least 3.0 mm) within one month prior to screening (SCR).

Period 1

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

Blinding implementation details:

The matching placebo had similar appearance to Depigoid Birch 5000. The Sponsor remained blinded to the study treatment during the study. Sealed emergency cards (containing the study code, the randomization number and the information about the therapy regimen) were available at the study site and could be opened if knowledge of the study therapy regimen was necessary to provide optimal treatment to the patient in case of an emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Mono-sensitized Year 1-3/Depigoid Birch

Arm description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with Depigoid Birch 5000 and completed all 3 years of treatment phase.

Arm type	Experimental
Investigational medicinal product name	Depigoid Birch 5000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The initial rush build-up treatment phase (V1-1) comprised subcutaneous administration of 2 injections of Depigoid Birch 5000, a 0.2 mL injection followed by a 0.3 mL injection 30 minutes later in the upper left arm and upper right arm, respectively. The maintenance treatment phase comprised subcutaneous administration of 0.5 mL injection of Depigoid Birch in 4- to 6-week intervals over 3 pollen seasons. In total, 29 subcutaneous injections were administered for the maintenance phase of approximately 3 years including 3 pollen seasons. The total volume of 0.5 mL of injection was administered in the upper arm, preferably alternating between left and right arm from visit to visit. Patient were observed at the site for at least 30 minutes after the injections.

Arm title	Co-sensitized Year 1-3/Depigoid Birch

Arm description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were co-sensitized according to the Skin Prick Test results at screening (against grass and/or weed pollen and/or perennial allergens). They were randomized to treatment with Depigoid Birch 5000 and completed all 3 years of treatment phase.

Arm type	Experimental

Investigational medicinal product name	Depigoid Birch 5000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The initial rush build-up treatment phase (V1-1) comprised subcutaneous administration of 2 injections of Depigoid Birch 5000, a 0.2 mL injection followed by a 0.3 mL injection 30 minutes later in the upper left arm and upper right arm, respectively. The maintenance treatment phase comprised subcutaneous administration of 0.5 mL injection of Depigoid Birch in 4- to 6-week intervals over 3 pollen seasons. In total, 29 subcutaneous injections were administered for the maintenance phase of approximately 3 years including 3 pollen seasons. The total volume of 0.5 mL of injection was administered in the upper arm, preferably alternating between left and right arm from visit to visit. Patient were observed at the site for at least 30 minutes after the injections.

Arm title	Mono-sensitized Year 1-3/Placebo

Arm description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with placebo and completed all 3 years of treatment phase.

Arm type	Experimental
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:

The initial rush build-up treatment phase (V1-1) comprised subcutaneous administration of 2 injections of placebo, a 0.2 mL injection followed by a 0.3 mL injection 30 minutes later in the upper left arm and upper right arm, respectively. The maintenance treatment phase comprised subcutaneous administration of 0.5 mL injection of placebo in 4- to 6-week intervals over 3 pollen seasons. In total, 29 subcutaneous injections were administered for the maintenance phase of approximately 3 years including 3 pollen seasons. The total volume of 0.5 mL of injection was administered in the upper arm, preferably alternating between left and right arm from visit to visit. Patient were observed at the site for at least 30 minutes after the injections.

Arm title	Co-sensitized Year 1-3/Placebo

Arm description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were co-sensitized according to the Skin Prick Test results at screening (against grass and/or weed pollen and/or perennial allergens). They were randomized to treatment with placebo and completed all 3 years of treatment phase.

Arm type	Experimental
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:

The initial rush build-up treatment phase (V1-1) comprised subcutaneous administration of 2 injections of placebo, a 0.2 mL injection followed by a 0.3 mL injection 30 minutes later in the upper left arm and upper right arm, respectively. The maintenance treatment phase comprised subcutaneous administration of 0.5 mL injection of placebo in 4- to 6-week intervals over 3 pollen seasons. In total, 29 subcutaneous injections were administered for the maintenance phase of approximately 3 years including 3 pollen seasons. The total volume of 0.5 mL of injection was administered in the upper arm, preferably alternating between left and right arm from visit to visit. Patient were observed at the site for at least 30 minutes after the injections.

Number of subjects in period 1	Mono-sensitized Year 1-3/Depigoid Birch	Co-sensitized Year 1-3/Depigoid Birch	Mono-sensitized Year 1-3/Placebo
Started	174	260	85
Completed	134	212	66
Not completed	40	48	19
Consent withdrawn by subject	13	16	5
Adverse event, non-fatal	6	8	1
Discontinued treatment but remained in the study	4	2	-
Pregnancy	-	2	-
Other reason	12	8	7
Lack of compliance	1	1	-
Lost to follow-up	2	4	4
Lack of efficacy	2	2	1
Protocol deviation	-	5	1

Number of subjects in period 1	Co-sensitized Year 1-3/Placebo
Started	130
Completed	103
Not completed	27
Consent withdrawn by subject	8
Adverse event, non-fatal	3
Discontinued treatment but remained in the study	4
Pregnancy	1
Other reason	5
Lack of compliance	2
Lost to follow-up	2
Lack of efficacy	1
Protocol deviation	1

Period 2

Period 2 title	Treatment-free follow-up phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Only Mono-sensitized patients completed the follow-up phase in the study. No treatment was administered in this phase. The Sponsor remained blinded to the study treatment. Sealed emergency cards (containing the study code, the randomization number and the information about the therapy

regimen) were available at the study site and could be opened if knowledge of the study therapy regimen was necessary to provide optimal treatment to the patient in an emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Mono-sensitized Year 1-5/Depigoid Birch

Arm description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with Depigoid Birch 5000 and completed all 5 years of study duration (3 years treatment and 2 years treatment-free follow-up).

Arm type	Follow-up
Investigational medicinal product name	Depigoid Birch 5000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The patients in the Mono-sensitized Year 1-3/Depigoid Birch 5000 group were followed up for 2 years post-treatment. No treatment was administered during the follow-up period.

Arm title	Mono-sensitized Year 1-5/Placebo

Arm description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with placebo and completed all 5 years of study duration (3 years treatment and 2 years treatment-free follow-up).

Arm type	Follow-up
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:

The patients in the Mono-sensitized Year 1-3/Placebo group were followed up for 2 years post-treatment. No treatment was administered during the follow-up period.

Number of subjects in period 2[1]	Mono-sensitized Year 1-5/Depigoid Birch	Mono-sensitized Year 1-5/Placebo
Started	174	85
Completed	128	64
Not completed	46	21
Consent withdrawn by subject	18	7
Adverse event, non-fatal	7	1
Other reason	12	7
Lack of compliance	1	-
Lost to follow-up	5	4
Lack of efficacy	2	1
Protocol deviation	1	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: Data analysis for Mono-sensitized patients were conducted for periods Year 1-3 (treatment phase; Period 1) and Year 1-5 (treatment + follow-up phase; Period 2). No separate analysis was conducted for the follow-up phase (Year 4-5). Therefore, the number of subjects starting the follow-up phase (Period 2) is derived from the number of subjects starting the treatment phase (Year 1 in the treatment phase).

Baseline characteristics

Reporting groups	
Reporting group title	Mono-sensitized Year 1-3/Depigoid Birch
Reporting group description:	
Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with Depigoid Birch 5000 and completed all 3 years of treatment phase.	
Reporting group title	Co-sensitized Year 1-3/Depigoid Birch
Reporting group description:	
Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were co-sensitized according to the Skin Prick Test results at screening (against grass and/or weed pollen and/or perennial allergens). They were randomized to treatment with Depigoid Birch 5000 and completed all 3 years of treatment phase.	
Reporting group title	Mono-sensitized Year 1-3/Placebo
Reporting group description:	
Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with placebo and completed all 3 years of treatment phase.	
Reporting group title	Co-sensitized Year 1-3/Placebo
Reporting group description:	
Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were co-sensitized according to the Skin Prick Test results at screening (against grass and/or weed pollen and/or perennial allergens). They were randomized to treatment with placebo and completed all 3 years of treatment phase.	

Reporting group values	Mono-sensitized Year 1-3/Depigoid Birch	Co-sensitized Year 1-3/Depigoid Birch	Mono-sensitized Year 1-3/Placebo
Number of subjects	174	260	85
Age categorical Units: Subjects			
Adolescents (12-17 years)	11	24	3
Adults (18-70 years)	163	236	82
Age continuous Units: years			
arithmetic mean	38.8	37.3	41.0
standard deviation	± 12.96	± 13.60	± 12.84
Gender categorical Units: Subjects			
Female	98	138	48
Male	76	122	37
Race Units: Subjects			
White	174	259	84
Other	0	1	1
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes	50	69	28
No	124	191	57
Asthmatic status at baseline Units: Subjects			

Yes	59	88	31
No	115	172	54
Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes	174	260	85
No	0	0	0
Weight Units: kilogram(s)			
arithmetic mean	73.5	74.8	73.1
standard deviation	± 17.77	± 16.03	± 13.99
Height Units: centimeter(s)			
arithmetic mean	171.7	172.3	169.2
standard deviation	± 9.50	± 10.18	± 8.75
BMI Units: kilogram(s)/square meter			
arithmetic mean	24.7	25.1	25.5
standard deviation	± 4.59	± 4.34	± 4.24
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean	12.1	12.7	10.8
standard deviation	± 9.45	± 9.60	± 8.02

Reporting group values	Co-sensitized Year 1-3/Placebo	Total	
Number of subjects	130	649	
Age categorical Units: Subjects			
Adolescents (12-17 years)	11	49	
Adults (18-70 years)	119	600	
Age continuous Units: years			
arithmetic mean	35.9		
standard deviation	± 13.25	-	
Gender categorical Units: Subjects			
Female	73	357	
Male	57	292	
Race Units: Subjects			
White	129	646	
Other	1	3	
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes	38	185	
No	92	464	
Asthmatic status at baseline Units: Subjects			
Yes	46	224	
No	84	425	

Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes	130	649	
No	0	0	
Weight Units: kilogram(s)			
arithmetic mean	73.3		
standard deviation	± 15.91	-	
Height Units: centimeter(s)			
arithmetic mean	171.8		
standard deviation	± 9.91	-	
BMI Units: kilogram(s)/square meter			
arithmetic mean	24.6		
standard deviation	± 3.99	-	
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean	13.7		
standard deviation	± 10.48	-	

Subject analysis sets

Subject analysis set title	Mono-sensitized FAS/Depigoid Birch 5000
Subject analysis set type	Full analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Full Analysis Set (FAS)/Depigoid Birch 5000 contained all randomized mono-sensitized patients who received Depigoid Birch 5000 and provide at least one primary efficacy assessment after start of treatment. This was equivalent to a modified intention-to-treat (mITT) population.

Subject analysis set title	Mono-sensitized SAF/Depigoid Birch 5000
Subject analysis set type	Safety analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Safety Analysis Set (SAF)/Depigoid Birch 5000 contained all randomized mono-sensitized patients who received at least one dose of Depigoid Birch 5000. Patients were assigned to treatment groups as treated.

Subject analysis set title	Mono-sensitized PP Year 3/Depigoid Birch 5000
Subject analysis set type	Per protocol

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Per Protocol (PP) Year 3/Depigoid Birch 5000 contained all mono-sensitized patients of the FAS in Year 3 who received Depigoid Birch 5000 without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Mono-sensitized PP Year 5/Depigoid Birch 5000
Subject analysis set type	Per protocol

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Per Protocol (PP) Year 5/Depigoid Birch 5000 contained all mono-sensitized patients of the FAS in Year 5 who received Depigoid Birch 5000 without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Mono-sensitized AI PK set/Depigoid Birch 5000
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Aluminium Pharmacokinetic (Al PK) set/Depigoid Birch 5000 contained randomized mono-sensitized patients who received Depigoid Birch 5000 and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Co-sensitized FAS/Depigoid Birch 5000
Subject analysis set type	Full analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening, and were subsequently enrolled in the study by signing the ICF. The Co-sensitized Full Analysis Set (FAS)/Depigoid Birch 5000 contained all randomized co-sensitized patients who received Depigoid Birch 5000 and provide at least one primary efficacy assessment after start of treatment. This was equivalent to a modified intention-to-treat (mITT) population.

Subject analysis set title	Co-sensitized SAF/Depigoid Birch 5000
Subject analysis set type	Safety analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Safety Analysis Set (SAF)/Depigoid Birch 5000 contained all randomized co-sensitized patients who received at least one dose of Depigoid Birch 5000. Patients were assigned to treatment groups as treated.

Subject analysis set title	Co-sensitized PP Year 3/Depigoid Birch 5000
Subject analysis set type	Per protocol

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Per Protocol (PP) Year 3/Depigoid Birch 5000 contained all co-sensitized patients of the FAS in Year 3 who received Depigoid Birch 5000 without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Co-sensitized Al PK set/Depigoid Birch 5000
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Aluminium Pharmacokinetic (Al PK) set/Depigoid Birch 5000 contained all randomized co-sensitized patients who received Depigoid Birch 5000 and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Mono-sensitized FAS/Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Full Analysis Set (FAS)/Placebo contained all randomized mono-sensitized patients who received placebo and provide at least one primary efficacy assessment after start of treatment. This was equivalent to a modified intention-to-treat (mITT) population.

Subject analysis set title	Mono-sensitized SAF/Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Safety Analysis Set (SAF)/Placebo contained all randomized mono-sensitized patients who received at least one dose of placebo. Patients were assigned to treatment groups as treated.

Subject analysis set title	Mono-sensitized PP Year 3/Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Per Protocol (PP) Year 3/Placebo contained all mono-sensitized patients of the FAS in Year 3 who received placebo without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Mono-sensitized PP Year 5/Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Per Protocol (PP) Year 5/Placebo contained all mono-sensitized patients of the FAS in Year 5 who received placebo without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Mono-sensitized Al PK set/Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Aluminium Pharmacokinetic (Al PK) set/Placebo contained randomized mono-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Co-sensitized FAS/Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening, and were subsequently enrolled in the study by signing the ICF. The Co-sensitized Full Analysis Set (FAS)/Placebo contained all randomized co-sensitized patients who received placebo and provide at least one primary efficacy assessment after start of treatment. This was equivalent to a modified intention-to-treat (mITT) population.

Subject analysis set title	Co-sensitized SAF/Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Safety Analysis Set (SAF)/Placebo contained all randomized co-sensitized patients who received at least one dose of placebo. Patients were assigned to treatment groups as treated.

Subject analysis set title	Co-sensitized PP Year 3/Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Per Protocol (PP) Year 3/Placebo contained all co-sensitized patients of the FAS in Year 3 who received placebo without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Co-sensitized Al PK set/Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Aluminium Pharmacokinetic (Al PK) set/Placebo contained all randomized co-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Mono- and Co-sensitized Al PK set/Depigoid Birch
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Mono- and Co-sensitized Aluminium Pharmacokinetic (Al PK) set/Depigoid Birch contained all randomized mono- and co-sensitized patients who received Depigoid Birch and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Mono- and Co-sensitized Al PK set/Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Mono- and Co-sensitized Aluminium Pharmacokinetic (Al PK) set/Placebo contained all randomized mono- and co-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Reporting group values	Mono-sensitized FAS/Depigoid Birch 5000	Mono-sensitized SAF/Depigoid Birch 5000	Mono-sensitized PP Year 3/Depigoid Birch 5000
Number of subjects	161	174	130

Age categorical Units: Subjects			
Adolescents (12-17 years)	10	11	7
Adults (18-70 years)	151	163	123
Age continuous Units: years			
arithmetic mean	38.4	38.8	39.5
standard deviation	± 12.71	± 12.96	± 12.59
Gender categorical Units: Subjects			
Female	92	98	75
Male	69	76	55
Race Units: Subjects			
White	161	174	130
Other	0	0	0
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes	49	50	
No	112	124	
Asthmatic status at baseline Units: Subjects			
Yes	58	59	
No	103	115	
Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes	161	174	
No	0	0	
Weight Units: kilogram(s)			
arithmetic mean	73.5	73.5	73.3
standard deviation	± 17.81	± 17.77	± 16.51
Height Units: centimeter(s)			
arithmetic mean	171.9	171.7	171.5
standard deviation	± 9.58	± 9.50	± 9.64
BMI Units: kilogram(s)/square meter			
arithmetic mean	24.7	24.7	24.9
standard deviation	± 4.60	± 4.59	± 4.27
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean	12.1	12.1	
standard deviation	± 9.56	± 9.45	±

Reporting group values	Mono-sensitized PP Year 5/Depigoid Birch 5000	Mono-sensitized Al PK set/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000
Number of subjects	116	18	245

Age categorical Units: Subjects			
Adolescents (12-17 years)	7	0	24
Adults (18-70 years)	109	18	221
Age continuous Units: years			
arithmetic mean	38.6	41.6	37.1
standard deviation	± 12.08	± 10.48	± 13.85
Gender categorical Units: Subjects			
Female	67	9	128
Male	49	9	117
Race Units: Subjects			
White	116	18	244
Other	0	0	1
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes			65
No			180
Asthmatic status at baseline Units: Subjects			
Yes			84
No			161
Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes			245
No			0
Weight Units: kilogram(s)			
arithmetic mean	73.3	76.3	74.8
standard deviation	± 16.53	± 17.84	± 16.21
Height Units: centimeter(s)			
arithmetic mean	171.7	172.8	172.4
standard deviation	± 9.41	± 10.60	± 10.34
BMI Units: kilogram(s)/square meter			
arithmetic mean	24.7	25.3	25.1
standard deviation	± 4.55	± 4.39	± 4.42
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean			12.8
standard deviation	±	±	± 9.60

Reporting group values	Co-sensitized SAF/Depigoid Birch 5000	Co-sensitized PP Year 3/Depigoid Birch 5000	Co-sensitized Al PK set/Depigoid Birch 5000
Number of subjects	260	206	14

Age categorical Units: Subjects			
Adolescents (12-17 years)	24	23	0
Adults (18-70 years)	236	183	14
Age continuous Units: years			
arithmetic mean	37.3	37.3	37.9
standard deviation	± 13.60	± 13.86	± 11.91
Gender categorical Units: Subjects			
Female	138	101	8
Male	122	105	6
Race Units: Subjects			
White	259	205	14
Other	1	1	0
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes	69		
No	191		
Asthmatic status at baseline Units: Subjects			
Yes	88		
No	172		
Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes	260		
No	0		
Weight Units: kilogram(s)			
arithmetic mean	74.8	75.2	71.1
standard deviation	± 16.03	± 16.73	± 15.91
Height Units: centimeter(s)			
arithmetic mean	172.3	172.6	170.6
standard deviation	± 10.18	± 10.58	± 10.82
BMI Units: kilogram(s)/square meter			
arithmetic mean	24.9	25.1	24.2
standard deviation	± 4.23	± 4.61	± 3.68
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean	12.7		
standard deviation	± 9.60	±	±

Reporting group values	Mono-sensitized FAS/Placebo	Mono-sensitized SAF/Placebo	Mono-sensitized PP Year 3/Placebo
Number of subjects	79	85	66

Age categorical Units: Subjects			
Adolescents (12-17 years)	3	3	2
Adults (18-70 years)	76	82	64
Age continuous Units: years			
arithmetic mean	40.8	41.0	40.6
standard deviation	± 12.99	± 12.84	± 12.67
Gender categorical Units: Subjects			
Female	45	48	37
Male	34	37	29
Race Units: Subjects			
White	78	84	65
Other	1	1	1
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes	27	28	
No	52	57	
Asthmatic status at baseline Units: Subjects			
Yes	30	31	
No	49	54	
Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes	79	85	
No	0	0	
Weight Units: kilogram(s)			
arithmetic mean	72.7	73.1	71.6
standard deviation	± 13.75	± 13.99	± 13.24
Height Units: centimeter(s)			
arithmetic mean	169.2	169.2	168.8
standard deviation	± 8.80	± 8.75	± 8.86
BMI Units: kilogram(s)/square meter			
arithmetic mean	25.4	25.5	25.1
standard deviation	± 4.30	± 4.24	± 3.97
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean	10.7	10.8	
standard deviation	± 7.58	± 8.02	±

Reporting group values	Mono-sensitized PP Year 5/Placebo	Mono-sensitized AI PK set/Placebo	Co-sensitized FAS/Placebo
Number of subjects	63	5	123

Age categorical Units: Subjects			
Adolescents (12-17 years)	2	0	11
Adults (18-70 years)	61	5	112
Age continuous Units: years			
arithmetic mean	40.9	48.8	35.6
standard deviation	± 12.76	± 10.66	± 13.06
Gender categorical Units: Subjects			
Female	34	3	68
Male	29	2	55
Race Units: Subjects			
White	62	5	122
Other	1	0	1
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes			36
No			87
Asthmatic status at baseline Units: Subjects			
Yes			44
No			79
Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes			123
No			0
Weight Units: kilogram(s)			
arithmetic mean	71.7	75.0	73.0
standard deviation	± 13.54	± 11.66	± 15.97
Height Units: centimeter(s)			
arithmetic mean	168.9	167.4	171.5
standard deviation	± 9.05	± 10.81	± 9.85
BMI Units: kilogram(s)/square meter			
arithmetic mean	25.1	27.0	24.7
standard deviation	± 4.06	± 5.29	± 4.01
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean			13.7
standard deviation	±	±	± 10.64

Reporting group values	Co-sensitized SAF/Placebo	Co-sensitized PP Year 3/Placebo	Co-sensitized AI PK set/Placebo
Number of subjects	130	95	11

Age categorical Units: Subjects			
Adolescents (12-17 years)	11	10	0
Adults (18-70 years)	119	85	11
Age continuous Units: years			
arithmetic mean	35.9	35.2	41.8
standard deviation	± 13.25	± 12.98	± 12.99
Gender categorical Units: Subjects			
Female	73	52	6
Male	57	43	5
Race Units: Subjects			
White	129	94	11
Other	1	1	0
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes	38		
No	92		
Asthmatic status at baseline Units: Subjects			
Yes	46		
No	84		
Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes	130		
No	0		
Weight Units: kilogram(s)			
arithmetic mean	73.3	73.5	84.4
standard deviation	± 15.91	± 16.83	± 15.38
Height Units: centimeter(s)			
arithmetic mean	171.8	171.5	173.7
standard deviation	± 9.91	± 10.16	± 8.74
BMI Units: kilogram(s)/square meter			
arithmetic mean	24.6	24.8	27.9
standard deviation	± 3.99	± 4.22	± 4.44
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean	13.7		
standard deviation	± 10.48	±	±

Reporting group values	Mono- and Co-sensitized AI PK set/Depigoid Birch	Mono- and Co-sensitized AI PK set/Placebo	
Number of subjects	32	16	

Age categorical Units: Subjects			
Adolescents (12-17 years)	0	0	
Adults (18-70 years)	32	16	
Age continuous Units: years			
arithmetic mean	40.0	44.0	
standard deviation	± 11.09	± 12.41	
Gender categorical Units: Subjects			
Female	17	9	
Male	15	7	
Race Units: Subjects			
White	32	16	
Other	0	0	
Asthmatic reaction to birch pollen in the past Units: Subjects			
Yes			
No			
Asthmatic status at baseline Units: Subjects			
Yes			
No			
Patients with nasal/ocular symptoms with at least moderate intensity Units: Subjects			
Yes			
No			
Weight Units: kilogram(s)			
arithmetic mean	74.0	81.4	
standard deviation	± 16.95	± 14.63	
Height Units: centimeter(s)			
arithmetic mean	171.8	171.8	
standard deviation	± 10.58	± 9.55	
BMI Units: kilogram(s)/square meter			
arithmetic mean	24.9	27.6	
standard deviation	± 4.07	± 4.56	
Time (years) since the first allergic reaction to birch pollen Units: Years			
arithmetic mean			
standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Mono-sensitized Year 1-3/Depigoid Birch

Reporting group description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with Depigoid Birch 5000 and completed all 3 years of treatment phase.

Reporting group title	Co-sensitized Year 1-3/Depigoid Birch

Reporting group description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were co-sensitized according to the Skin Prick Test results at screening (against grass and/or weed pollen and/or perennial allergens). They were randomized to treatment with Depigoid Birch 5000 and completed all 3 years of treatment phase.

Reporting group title	Mono-sensitized Year 1-3/Placebo

Reporting group description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with placebo and completed all 3 years of treatment phase.

Reporting group title	Co-sensitized Year 1-3/Placebo

Reporting group description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were co-sensitized according to the Skin Prick Test results at screening (against grass and/or weed pollen and/or perennial allergens). They were randomized to treatment with placebo and completed all 3 years of treatment phase.

Reporting group title	Mono-sensitized Year 1-5/Depigoid Birch

Reporting group description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with Depigoid Birch 5000 and completed all 5 years of study duration (3 years treatment and 2 years treatment-free follow-up).

Reporting group title	Mono-sensitized Year 1-5/Placebo

Reporting group description:

Treatment arms are defined here according to the evaluation of the data in the final analysis. Patients in this arm were mono-sensitized according to the Skin Prick Test results at screening. They were randomized to treatment with placebo and completed all 5 years of study duration (3 years treatment and 2 years treatment-free follow-up).

Subject analysis set title	Mono-sensitized FAS/Depigoid Birch 5000
Subject analysis set type	Full analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Full Analysis Set (FAS)/Depigoid Birch 5000 contained all randomized mono-sensitized patients who received Depigoid Birch 5000 and provide at least one primary efficacy assessment after start of treatment. This was equivalent to a modified intention-to-treat (mITT) population.

Subject analysis set title	Mono-sensitized SAF/Depigoid Birch 5000
Subject analysis set type	Safety analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Safety Analysis Set (SAF)/Depigoid Birch 5000 contained all randomized mono-sensitized patients who received at least one dose of Depigoid Birch 5000. Patients were assigned to treatment groups as treated.

Subject analysis set title	Mono-sensitized PP Year 3/Depigoid Birch 5000
Subject analysis set type	Per protocol

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Per Protocol (PP) Year 3/Depigoid Birch 5000 contained all mono-sensitized patients of the FAS in Year 3 who received Depigoid Birch 5000

without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Mono-sensitized PP Year 5/Depigoid Birch 5000
Subject analysis set type	Per protocol

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Per Protocol (PP) Year 5/Depigoid Birch 5000 contained all mono-sensitized patients of the FAS in Year 5 who received Depigoid Birch 5000 without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Mono-sensitized Al PK set/Depigoid Birch 5000
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Aluminium Pharmacokinetic (Al PK) set/Depigoid Birch 5000 contained randomized mono-sensitized patients who received Depigoid Birch 5000 and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Co-sensitized FAS/Depigoid Birch 5000
Subject analysis set type	Full analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening, and were subsequently enrolled in the study by signing the ICF. The Co-sensitized Full Analysis Set (FAS)/Depigoid Birch 5000 contained all randomized co-sensitized patients who received Depigoid Birch 5000 and provide at least one primary efficacy assessment after start of treatment. This was equivalent to a modified intention-to-treat (mITT) population.

Subject analysis set title	Co-sensitized SAF/Depigoid Birch 5000
Subject analysis set type	Safety analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Safety Analysis Set (SAF)/Depigoid Birch 5000 contained all randomized co-sensitized patients who received at least one dose of Depigoid Birch 5000. Patients were assigned to treatment groups as treated.

Subject analysis set title	Co-sensitized PP Year 3/Depigoid Birch 5000
Subject analysis set type	Per protocol

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Per Protocol (PP) Year 3/Depigoid Birch 5000 contained all co-sensitized patients of the FAS in Year 3 who received Depigoid Birch 5000 without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Co-sensitized Al PK set/Depigoid Birch 5000
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Aluminium Pharmacokinetic (Al PK) set/Depigoid Birch 5000 contained all randomized co-sensitized patients who received Depigoid Birch 5000 and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Mono-sensitized FAS/Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Full Analysis Set (FAS)/Placebo contained all randomized mono-sensitized patients who received placebo and provide at least one primary efficacy assessment after start of treatment. This was equivalent to a modified intention-to-treat (mITT) population.

Subject analysis set title	Mono-sensitized SAF/Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Safety Analysis Set (SAF)/Placebo contained all randomized mono-sensitized patients who received at least one dose of placebo. Patients were assigned to treatment groups as treated.

Subject analysis set title	Mono-sensitized PP Year 3/Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Per Protocol (PP) Year 3/Placebo contained all mono-sensitized patients of the FAS in Year 3 who received placebo without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Mono-sensitized PP Year 5/Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Per Protocol (PP) Year 5/Placebo contained all mono-sensitized patients of the FAS in Year 5 who received placebo without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Mono-sensitized Al PK set/Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Mono-sensitized patients were those who were identified through a positive skin prick test (SPT) at screening as allergic to birch pollen only. The Mono-sensitized Aluminium Pharmacokinetic (Al PK) set/Placebo contained randomized mono-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Co-sensitized FAS/Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening, and were subsequently enrolled in the study by signing the ICF. The Co-sensitized Full Analysis Set (FAS)/Placebo contained all randomized co-sensitized patients who received placebo and provide at least one primary efficacy assessment after start of treatment. This was equivalent to a modified intention-to-treat (mITT) population.

Subject analysis set title	Co-sensitized SAF/Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Safety Analysis Set (SAF)/Placebo contained all randomized co-sensitized patients who received at least one dose of placebo. Patients were assigned to treatment groups as treated.

Subject analysis set title	Co-sensitized PP Year 3/Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Per Protocol (PP) Year 3/Placebo contained all co-sensitized patients of the FAS in Year 3 who received placebo without major protocol deviations relevant for the statistical evaluation.

Subject analysis set title	Co-sensitized Al PK set/Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Aluminium Pharmacokinetic (Al PK) set/Placebo contained all randomized co-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Mono- and Co-sensitized Al PK set/Depigoid Birch
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Mono- and Co-sensitized Aluminium Pharmacokinetic (Al PK) set/Depigoid Birch contained all randomized mono- and co-sensitized patients who received Depigoid Birch and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Subject analysis set title	Mono- and Co-sensitized Al PK set/Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Mono- and Co-sensitized Aluminium Pharmacokinetic (Al PK) set/Placebo contained all randomized mono- and co-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH)3 plasma and/or urine measurements.

Primary: Mean integrated Symptoms and Medication Score (SMS)

End point title	Mean integrated Symptoms and Medication Score (SMS)

End point description:

Based on the planned second interim analysis for futility, the DMC (agreed with the sponsor and the PEI) recommended to discontinue the Co-sensitized patients from the study. Only the Mono-sensitized patients continued with the follow-up phase. Therefore, full results (Year 1-5) are presented for the Mono-sensitized patients, while only results in the treatment phase (Year 1-3) are presented for the Co-sensitized patients. The primary efficacy endpoint of the study was the mean integrated SMS on nasal and ocular symptoms and their RM score (RMS) per pollen season. The mean integrated SMS per year were compared between treatment groups by means of Wilcoxon-Mann-Whitney (two-sided) and Hodges-Lehmann two-sided 95% CI of the median difference between the treatments. Exploratory analysis based on logistic regression model for superiority testing, with treatment arm and age group as factors accounting for the stratification variables applied for randomization was performed in the FAS.

End point type	Primary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1-5 in the Mono-sensitized patients and Year 1-3 in the Co-sensitized patients.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	148[1]	235[2]	77[3]	116[4]
Units: score				
arithmetic mean (standard deviation)				
Year 1	7.80 (± 4.669)	8.38 (± 4.381)	9.01 (± 5.222)	7.79 (± 4.679)
Year 2	7.37 (± 4.131)	7.77 (± 4.215)	8.93 (± 5.317)	7.31 (± 4.814)
Year 3	6.49 (± 4.166)	7.28 (± 4.526)	8.21 (± 4.538)	7.06 (± 4.207)
Year 4	5.82 (± 3.942)	0 (± 0)	7.26 (± 5.036)	0 (± 0)
Year 5	6.27 (± 4.224)	0 (± 0)	7.88 (± 5.222)	0 (± 0)

Notes:

[1] - No. of subjects analyzed:
Year 1: 148; Year 2: 148; Year 3: 137; Year 4: 123; Year 5: 124
[2] - No. of subjects analyzed:
Year 1: 235; Year 2: 218; Year 3: 214
[3] - No. of subjects analyzed:
Year 1: 77; Year 2: 71; Year 3: 66; Year 4: 63; Year 5: 63
[4] - No. of subjects analyzed:
Year 1: 116; Year 2: 111; Year 3: 108

Statistical analyses

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 1)

Statistical analysis description:

Depigoid Birch was considered superior to placebo if lower scores of the primary endpoint were more likely in the active treatment group than in the control group, i.e. if the probability of any random scores recorded per pollen season (1, 2, 3, or 5) for Depigoid Birch being lower than that for placebo was above 0.5. The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo

Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.105
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	0.714

Notes:

[5] - The mean integrated SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 2)

Statistical analysis description:

Depigoid Birch was considered superior to placebo if lower scores of the primary endpoint were more likely in the active treatment group than in the control group, i.e. if the probability of any random scores recorded per pollen season (1, 2, 3, or 5) for Depigoid Birch being lower than that for placebo was above 0.5. The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0389
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	0.663

Notes:

[6] - The mean integrated SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 3)

Statistical analysis description:

Depigoid Birch was considered superior to placebo if lower scores of the primary endpoint were more likely in the active treatment group than in the control group, i.e. if the probability of any random scores recorded per pollen season (1, 2, 3, or 5) for Depigoid Birch being lower than that for placebo was above 0.5. The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo

Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.004
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	0.612

Notes:

[7] - The mean integrated SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 4)

Statistical analysis description:

Depigoid Birch was considered superior to placebo if lower scores of the primary endpoint were more likely in the active treatment group than in the control group, i.e. if the probability of any random scores recorded per pollen season (1, 2, 3, or 5) for Depigoid Birch being lower than that for placebo was above 0.5. The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0974
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	0.663

Notes:

[8] - The mean integrated SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 5)

Statistical analysis description:

Depigoid Birch was considered superior to placebo if lower scores of the primary endpoint were more likely in the active treatment group than in the control group, i.e. if the probability of any random scores recorded per pollen season (1, 2, 3, or 5) for Depigoid Birch being lower than that for placebo was above 0.5. The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo

Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0556
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2.8
Variability estimate	Standard error of the mean
Dispersion value	0.714

Notes:

[9] - The mean integrated SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 1)

Statistical analysis description:

Depigoid Birch was considered superior to placebo if lower scores of the primary endpoint were more likely in the active treatment group than in the control group, i.e. if the probability of any random scores recorded per pollen season (1, 2, 3, or 5) for Depigoid Birch being lower than that for placebo was above 0.5. The number of subjects analyzed for both Depigoid Birch 5000 and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Placebo v Co-sensitized FAS/Depigoid Birch 5000
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.1284
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.485

Notes:

[10] - The mean integrated SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 2)

Statistical analysis description:

Depigoid Birch was considered superior to placebo if lower scores of the primary endpoint were more likely in the active treatment group than in the control group, i.e. if the probability of any random scores recorded per pollen season (1, 2, 3, or 5) for Depigoid Birch being lower than that for placebo was above 0.5. The number of subjects analyzed for both Depigoid Birch 5000 and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.2329
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[11] - The mean integrated SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 3)

Statistical analysis description:

Depigoid Birch was considered superior to placebo if lower scores of the primary endpoint were more likely in the active treatment group than in the control group, i.e. if the probability of any random scores recorded per pollen season (1, 2, 3, or 5) for Depigoid Birch being lower than that for placebo was above 0.5. The number of subjects analyzed for both Depigoid Birch 5000 and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.9454
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.485

Notes:

[12] - The mean integrated SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Secondary: Mean Integrated Symptoms and Medication Score (SMS) (0-6)

End point title	Mean Integrated Symptoms and Medication Score (SMS) (0-6)

End point description:

Based on the planned second interim analysis for futility, the DMC (agreed with the sponsor and the PEI) recommended to discontinue the Co-sensitized patients from the study. Only Mono-sensitized patients continued with the follow-up phase. Therefore, full results (Year 1-5) are presented for the Mono-sensitized patients, while only results in the treatment phase (Year 1-3) are presented for the Co-sensitized patients. The mean integrated SMS (0-6) was calculated as the sum of SS for rhinoconjunctivitis and the RMS according to the EAACI criteria for equal weight of both SS and RMS.

The values of the SMS (0-6) for rhinoconjunctivitis range from 0 to 6, whereby higher values indicate worse outcome.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1-5 in the Mono-sensitized patients and Year 1-3 in the Co-sensitized patients.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	148[13]	235[14]	77[15]	116[16]
Units: score				
arithmetic mean (standard deviation)				
Year 1	1.66 (± 0.928)	1.73 (± 0.841)	1.93 (± 1.002)	1.67 (± 0.959)
Year 2	1.55 (± 0.877)	1.64 (± 0.876)	1.89 (± 1.001)	1.54 (± 0.923)
Year 3	1.36 (± 0.882)	1.49 (± 0.912)	1.74 (± 0.868)	1.47 (± 0.812)
Year 4	1.22 (± 0.854)	0 (± 0)	1.52 (± 0.985)	0 (± 0)
Year 5	1.30 (± 0.871)	0 (± 0)	1.68 (± 1.012)	0 (± 0)

Notes:

[13] - No. of subjects analyzed:
Year 1-2: 148; Year 3: 137; Year 4: 123; Year 5: 124
[14] - No. of subjects analyzed:
Year 1: 235; Year 2: 218; Year 3: 214
[15] - No. of subjects analyzed:
Year 1: 77; Year 2: 71; Year 3: 66; Year 4-5: 63
[16] - No. of subjects analyzed:
Year 1: 116; Year 2: 111; Year 3: 108

Statistical analyses

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0616
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.153

Notes:

[17] - The mean integrated SMS (0-6) between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0119
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.128

Notes:

[18] - The mean integrated SMS (0-6) between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.128

Notes:

[19] - The mean integrated SMS (0-6) between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 4)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.0482
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.128

Notes:

[20] - The mean integrated SMS (0-6) between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 5)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.013
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.153

Notes:

[21] - The mean integrated SMS (0-6) between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized

	FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.2612
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.102

Notes:

[22] - The mean integrated SMS (0-6) between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.3477
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.102

Notes:

[23] - The mean integrated SMS (0-6) between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.9
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.102

Notes:

[24] - The mean integrated SMS (0-6) between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Secondary: Mean Integrated Symptom Score (SS)

End point title	Mean Integrated Symptom Score (SS)

End point description:

Only the Mono-sensitized patients continued with the follow-up phase. Therefore, full results (Year 1-5) are presented for the Mono-sensitized patients, while only results in the treatment phase (Year 1-3) are presented for the Co-sensitized patients. Mean integrated SS was an integrated part of the primary efficacy endpoint but was assessed as secondary efficacy endpoint separately. The daily SS was defined as the mean of the symptoms' severity scorings per day during a pollen season and was derived from the patient's eDiary entries. The SS scores ranged from 0 to 18 points derived from 4 nasal (itching, sneezing, rhinorrhea, and obstruction) and 2 ocular (itching/grittiness/redness and tearing) symptoms, each assessed by the patient on 4-point-Likert scale ranging from 0 to 3. Calculations of the SS according to the EAACI criteria were used for statistical analyses.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1-5 in the Mono-sensitized patients and Year 1-3 in the Co-sensitized patients.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	148[25]	235[26]	77[27]	116[28]
Units: score				
arithmetic mean (standard deviation)				
Year 1	5.79 (± 3.299)	6.47 (± 3.159)	6.51 (± 3.479)	5.85 (± 3.494)
Year 2	5.73 (± 2.960)	6.24 (± 3.053)	6.51 (± 3.442)	5.61 (± 3.544)
Year 3	5.18 (± 2.964)	5.83 (± 3.339)	6.06 (± 3.079)	5.61 (± 3.128)
Year 4	4.64 (± 2.691)	0 (± 0)	5.53 (± 3.580)	0 (± 0)
Year 5	5.02 (± 3.009)	0 (± 0)	5.88 (± 3.763)	0 (± 0)

Notes:

[25] - No. of subjects analyzed:
Year 1-2: 148; Year 3: 137; Year 4: 123; Year 5: 124

[26] - No. of subjects analyzed:
Year 1: 235; Year 2: 218; Year 3: 214
[27] - No. of subjects analyzed:
Year 1: 77; Year 2: 71; Year 3: 66, Year 4-5: 63
[28] - No. of subjects analyzed:
Year 1: 116; Year 2: 111; Year 3: 108

Statistical analyses

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.1114
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[29] - The mean integrated SS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.0715
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	0.459

Notes:

[30] - The mean integrated SS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.0292
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.485

Notes:

[31] - The mean integrated SS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 4)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.1585
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[32] - The mean integrated SS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 5)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.1885
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.536

Notes:

[33] - The mean integrated SS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.0442
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.383

Notes:

[34] - The mean integrated SS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized

	FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.0585
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.383

Notes:

[35] - The mean integrated SS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.8259
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.383

Notes:

[36] - The mean integrated SS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Secondary: Mean Integrated Rescue Medication Score (RMS)

End point title	Mean Integrated Rescue Medication Score (RMS)

End point description:

Only the Mono-sensitized patients continued with the follow-up phase. Therefore, full results (Year 1-5) are presented for the Mono-sensitized patients, while only results in the treatment phase (Year 1-3) are presented for the Co-sensitized patients. Mean integrated RMS excluding RM for asthmatic patients was an integrated part of the primary efficacy endpoint but was also assessed separately as secondary efficacy endpoint. The RMS was defined as the mean of daily RMS during a pollen season. The RMS calculation was based on score points allocated per application of each single RM product to treat the characteristic allergy related symptoms.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1-5 in the Mono-sensitized patients and Year 1-3 in the Co-sensitized patients.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	148[37]	235[38]	77[39]	116[40]
Units: score				
arithmetic mean (standard deviation)				
Year 1	2.02 (± 2.197)	1.91 (± 2.083)	2.50 (± 2.399)	1.94 (± 1.895)
Year 2	1.64 (± 1.803)	1.54 (± 1.790)	2.42 (± 2.299)	1.70 (± 1.964)
Year 3	1.31 (± 1.819)	1.45 (± 1.911)	2.15 (± 2.152)	1.45 (± 1.827)
Year 4	1.18 (± 1.783)	0 (± 0)	1.74 (± 2.100)	0 (± 0)
Year 5	1.25 (± 1.758)	0 (± 0)	2.00 (± 2.010)	0 (± 0)

Notes:

[37] - No. of subjects analyzed:
Year 1-2: 148; Year 3: 137; Year 4: 123; Year 5: 124
[38] - No. of subjects analyzed:
Year 1: 235; Year 2: 218; Year 3: 214
[39] - No. of subjects analyzed:
Year 1: 77, Year 2: 71, Year 3: 66, Year 4-5: 63
[40] - No. of subjects analyzed:
Year 1: 116; Year 2: 111; Year 3: 108

Statistical analyses

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.1184
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[41] - The mean integrated RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[42] - The mean integrated RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.0006
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[43] - The mean integrated RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 4)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized

	FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.0114
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.179

Notes:

[44] - The mean integrated RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 5)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.0012
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[45] - The mean integrated RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.632
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.153

Notes:

[46] - The mean integrated RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.4787
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.102

Notes:

[47] - The mean integrated RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.3999
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.102

Notes:

[48] - The mean integrated RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Secondary: Mean Integrated Combined Symptom Medication Score (SMS)

End point title	Mean Integrated Combined Symptom Medication Score (SMS)

End point description:

Only the Mono-sensitized patients continued with the follow-up phase. Therefore, full results (Year 1-5) are presented for the Mono-sensitized patients, while only results in the treatment phase (Year 1-3) are presented for the Co-sensitized patients. The mean combined SMS includes pulmonary symptoms, in addition to nasal and ocular symptoms. The mean integrated combined SMS (i.e. SMS-pul) was calculated as the sum of daily scores for nasal, eye, and pulmonary symptoms and their RM per pollen season.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1-5 in the Mono-sensitized patients and Year 1-3 in the Co-sensitized patients.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	148[49]	235[50]	77[51]	116[52]
Units: score				
arithmetic mean (standard deviation)				
Year 1	9.18 (± 6.037)	9.80 (± 5.279)	10.71 (± 6.294)	9.38 (± 5.682)
Year 2	8.78 (± 5.434)	9.17 (± 5.226)	10.66 (± 6.696)	8.78 (± 5.856)
Year 3	7.68 (± 5.629)	8.63 (± 5.704)	9.64 (± 5.520)	8.36 (± 5.462)
Year 4	6.99 (± 5.162)	0 (± 0)	8.67 (± 6.678)	0 (± 0)
Year 5	7.22 (± 5.063)	0 (± 0)	9.13 (± 6.346)	0 (± 0)

Notes:

[49] - No. of subjects analyzed:
Year 1-2: 148; Year 3: 137; Year 4: 123; Year 5: 124

[50] - No. of subjects analyzed:
Year 1: 235; Year 2: 218; Year 3: 214

[51] - No. of subjects analyzed:
Year 1: 77; Year 2: 71; Year 3: 66; Year 4-5: 63
[52] - No. of subjects analyzed:
Year 1: 116; Year 2: 111; Year 3: 108

Statistical analyses

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 1)
Statistical analysis description:	
The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.	
Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.0565
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	0.867

Notes:

[53] - The mean integrated combined SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 2)
Statistical analysis description:	
The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.	
Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.058
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.4
Variability estimate	Standard error of the mean
Dispersion value	0.867

Notes:

[54] - The mean integrated combined SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.0057
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	0.791

Notes:

[55] - The mean integrated combined SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 4)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.1739
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	0.765

Notes:

[56] - The mean integrated combined SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 5)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.0489
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.2
Variability estimate	Standard error of the mean
Dispersion value	0.816

Notes:

[57] - The mean integrated combined SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.3507
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.612

Notes:

[58] - The mean integrated combined SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized

	FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.3949
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.587

Notes:

[59] - The mean integrated combined SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.9001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.612

Notes:

[60] - The mean integrated combined SMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Secondary: Mean Integrated Asthmatic Rescue Medication Score (RMS)

End point title	Mean Integrated Asthmatic Rescue Medication Score (RMS)

End point description:

Only the Mono-sensitized patients continued with the follow-up phase. Therefore, full results (Year 1-5) are presented for the Mono-sensitized patients, while only results in the treatment phase (Year 1-3) are presented for the Co-sensitized patients. The scores of RMS for asthmatic patients only were not considered for the calculation of the primary endpoint but were evaluated separately as a secondary efficacy endpoint, i.e. the asthmatic RMS. The RMS, defined as the mean of daily RMS during a pollen season, was calculated from score points allocated per application of each single RM product to treat the characteristic allergy related symptoms.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1-5 in the Mono-sensitized patients and Year 1-3 in the Co-sensitized patients.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56[61]	87[62]	33[63]	46[64]
Units: score				
arithmetic mean (standard deviation)				
Year 1	3.97 (± 3.677)	3.45 (± 3.217)	4.23 (± 3.201)	3.52 (± 4.284)
Year 2	3.24 (± 3.237)	2.97 (± 2.907)	4.38 (± 3.567)	3.64 (± 4.299)
Year 3	2.78 (± 3.346)	2.62 (± 2.905)	3.86 (± 2.904)	3.68 (± 4.283)
Year 4	2.77 (± 3.392)	0 (± 0)	3.32 (± 2.792)	0 (± 0)
Year 5	2.50 (± 3.315)	0 (± 0)	3.27 (± 2.602)	0 (± 0)

Notes:

[61] - No. of subjects analyzed:
Year 1-3: 56; Year 4-5: 53
[62] - No. of subjects analyzed:
Year 1-2: 87; Year 3: 82
[63] - No. of subjects analyzed:
Year 1: 33; Year 2: 31; Year 3: 28; Year 4: 28; Year 5: 29
[64] - No. of subjects analyzed:
Year 1: 46; Year 2-3: 44

Statistical analyses

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 89 in Year 1, 87 in Year 2, 84 in Year 3, 81 in Year 4, and 82 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[65]
P-value	= 0.4571
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.74

Notes:

[65] - The mean integrated asthmatic RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 89 in Year 1, 87 in Year 2, 84 in Year 3, 81 in Year 4, and 82 in Year 5.

Comparison groups	Mono-sensitized FAS/Placebo v Mono-sensitized FAS/Depigoid Birch 5000
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.0532
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	0.612

Notes:

[66] - The mean integrated asthmatic RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 89 in Year 1, 87 in Year 2, 84 in Year 3, 81 in Year 4, and 82 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	= 0.0254
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	0.561

Notes:

[67] - The mean integrated asthmatic RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 4)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 89 in Year 1, 87 in Year 2, 84 in Year 3, 81 in Year 4, and 82 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized

	FAS/Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 0.1033
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	0.485

Notes:

[68] - The mean integrated asthmatic RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Mono-sensitized Year 5)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 89 in Year 1, 87 in Year 2, 84 in Year 3, 81 in Year 4, and 82 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.0321
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	0.561

Notes:

[69] - The mean integrated asthmatic RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 1)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 133 in Year 1, 131 in Year 2, and 126 in Year 3.

Comparison groups	Co-sensitized FAS/Placebo v Co-sensitized FAS/Depigoid Birch 5000

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	= 0.712
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.459

Notes:

[70] - The mean integrated asthmatic RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 2)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 133 in Year 1, 131 in Year 2, and 126 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[71]
P-value	= 0.6259
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.434

Notes:

[71] - The mean integrated asthmatic RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo(Co-sensitized Year 3)

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 133 in Year 1, 131 in Year 2, and 126 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.1783
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	0.383

Notes:

[72] - The mean integrated asthmatic RMS between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Secondary: Number of Well Days and Hell Days

End point title	Number of Well Days and Hell Days

End point description:

Only the Mono-sensitized patients continued with the follow-up phase. Therefore, full results (Year 1-5) are presented for the Mono-sensitized patients, while only results in the treatment phase (Year 1-3) are presented for the Co-sensitized patients. Well days were defined as days with a SS ≤ 2 and no RM. Hell days were defined as days with a SS ≥ 10 and additional use of RM.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1-5 in the Mono-sensitized patients and Year 1-3 in the Co-sensitized patients.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	148[73]	235[74]	77[75]	116[76]
Units: days				
arithmetic mean (standard deviation)				
Year 1 - Well days	4.24 (± 6.866)	3.35 (± 5.529)	3.65 (± 6.458)	4.68 (± 6.720)
Year 1 - Hell days	3.29 (± 5.097)	4.06 (± 5.646)	4.61 (± 6.090)	4.03 (± 5.826)
Year 2 - Well days	4.61 (± 6.989)	4.60 (± 6.770)	3.83 (± 6.616)	5.95 (± 8.345)
Year 2 - Hell days	3.56 (± 5.925)	3.86 (± 5.615)	5.25 (± 6.507)	3.86 (± 5.891)
Year 3 - Well days	5.64 (± 7.866)	5.17 (± 6.856)	3.71 (± 6.952)	5.40 (± 7.750)
Year 3 - Hell days	2.42 (± 4.818)	3.01 (± 5.027)	4.86 (± 6.442)	3.16 (± 5.395)
Year 4 - Well days	9.64 (± 11.363)	0 (± 0)	7.10 (± 10.140)	0 (± 0)
Year 4 - Hell days	2.29 (± 4.998)	0 (± 0)	4.25 (± 7.383)	0 (± 0)
Year 5 - Well days	7.00 (± 8.869)	0 (± 0)	5.98 (± 9.508)	0 (± 0)
Year 5 - Hell days	2.44 (± 4.445)	0 (± 0)	4.43 (± 6.674)	0 (± 0)

Notes:

[73] - No. of subjects analyzed:
Year 1-2: 148; Year 3: 137: Year 4: 123; Year 5: 124
[74] - No. of subjects analyzed:
Year 1: 235; Year 2: 218; Year 3: 214
[75] - No. of subjects analyzed:
Year 1: 77; Year 2: 71; Year 3: 66; Year 4-5: 63
[76] - No. of subjects analyzed:
Year 1: 116; Year 2: 111; Year 3: 108

Statistical analyses

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 1)/Well days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Placebo v Mono-sensitized FAS/Depigoid Birch 5000
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[77]
P-value	= 0.3793
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:

[77] - The mean number of well days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 1)/Hell days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	= 0.0658
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2

Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[78] - The mean number of hell days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 2)/Well days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[79]
P-value	= 0.2977
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:

[79] - The mean number of well days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 2)/Hell days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	= 0.0254
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[80] - The mean number of hell days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 3)/Well days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[81]
P-value	= 0.0649
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.255

Notes:

[81] - The mean number of well days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 3)/Hell days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[82]
P-value	= 0.0019
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[82] - The mean number of hell days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 4)/Well days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[83]
P-value	= 0.109
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.765

Notes:

[83] - The mean number of well days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 4)/Hell days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	= 0.0267
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.255

Notes:

[84] - The mean number of hell days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 5)/Well days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized

	FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[85]
P-value	= 0.2132
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.255

Notes:

[85] - The mean number of well days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (MO Year 5)/Hell days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 225 in Year 1, 219 in Year 2, 203 in Year 3, 186 in Year 4, and 187 in Year 5.

Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority[86]
P-value	= 0.0836
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.255

Notes:

[86] - The mean number of hell days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (CO Year 1)/Well days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Placebo v Co-sensitized FAS/Depigoid Birch 5000

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[87]
P-value	= 0.0732
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.255

Notes:

[87] - The mean number of well days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (CO Year 1)/Hell days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[88]
P-value	= 0.6451
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:

[88] - The mean number of hell days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (CO Year 2)/Well days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[89]
P-value	= 0.2719
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.255

Notes:

[89] - The mean number of well days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (CO Year 2)/Hell days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[90]
P-value	= 0.8606
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:

[90] - The mean number of hell days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (CO Year 3)/Well days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[91]
P-value	= 0.7638
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:

[91] - The mean number of well days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Statistical analysis title	Depigoid Birch vs. placebo (CO Year 3)/Hell days

Statistical analysis description:

The number of subjects analyzed for both Depigoid Birch and placebo started with total 351 in Year 1, 329 in Year 2, and 322 in Year 3.

Comparison groups	Co-sensitized FAS/Depigoid Birch 5000 v Co-sensitized FAS/Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[92]
P-value	= 0.6366
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:

[92] - The mean number of hell days between treatments were compared using Wilcoxon-Mann-Whitney test (two-sided). Median differences between treatment groups were compared using Hodges-Lehmann estimator with two-sided 95% CI.

Secondary: Immunology - Specific IgE

End point title	Immunology - Specific IgE

End point description:

Only the Mono-sensitized patients continued with the follow-up phase. Therefore, Year 5 (EoS) results are only presented for the Mono-sensitized patients. Serum levels of specific IgE against birch and all co-allergens were evaluated for all patients, with the value at screening as the baseline.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1 (baseline), Year 2 (V2-10), and Year 3 (V3-10) in both Mono- and Co-sensitized patients; and Year 5 (end of study/EoS) in the Mono-sensitized patients only.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	118[93]	150[94]	56[95]	63[96]
Units: kU/L				
median (full range (min-max))				
Baseline	38.20 (0.7 to 97.3)	45.40 (1.4 to 100.0)	29.45 (0.8 to 99.9)	36.80 (2.3 to 95.6)
Year 2 (V2-10)	35.80 (1.0 to 98.3)	40.00 (3.1 to 99.7)	34.40 (0.6 to 94.3)	45.00 (1.1 to 98.9)
Year 3 (V3-10)	20.30 (0.4 to 100.0)	25.95 (1.3 to 98.8)	22.20 (0.6 to 99.9)	28.00 (0.9 to 99.8)
EoS	11.30 (0.5 to 88.8)	0 (0 to 0)	12.70 (0.5 to 75.9)	0 (0 to 0)

Notes:

[93] - No. of subjects analyzed:
Baseline: 118; Year 2: 117; Year 3: 120; EoS: 121
[94] - No. of subjects analyzed:
Baseline: 150; Year 2: 147; Year 3: 176
[95] - No. of subjects analyzed:
Baseline: 56; Year 2: 49; Year 3: 54; EoS: 59
[96] - No. of subjects analyzed:
Baseline: 63; Year 2: 63; Year 3: 77

Statistical analyses

No statistical analyses for this end point

Secondary: Immunology - Specific IgG1

End point title	Immunology - Specific IgG1

End point description:

Only the Mono-sensitized patients continued with the follow-up phase. Therefore, Year 5 (EoS) results are only presented for the Mono-sensitized patients. The samples for analysis were collected in selected sites in Germany. Serum levels of specific IgG1 were evaluated, with the value at V1-1 as the baseline.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1 (baseline), Year 2 (V2-10), and Year 3 (V3-10) in both Mono- and Co-sensitized patients; and Year 5 (end of study/EoS) in the Mono-sensitized patients only.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[97]	73[98]	18[99]	34[100]
Units: U/mL				
median (full range (min-max))				
Baseline	6.10 (1.1 to 418.5)	6.90 (0.5 to 667.1)	25.55 (0.8 to 804.6)	5.60 (1.2 to 278.5)

Year 2 (V2-10)	30.40 (2.0 to 430.4)	21.00 (3.7 to 395.2)	5.95 (2.1 to 235.5)	7.40 (1.5 to 105.6)
Year 3 (V3-10)	7.80 (1.4 to 293.7)	14.80 (2.2 to 533.0)	4.30 (1.6 to 145.9)	4.60 (0.9 to 261.5)
EoS	2.80 (0 to 195.5)	0 (0 to 0)	2.55 (0.4 to 119.8)	0 (0 to 0)

Notes:

[97] - No. of subjects analyzed (selected German sites only):
Baseline: 39; Year 2: 44; Year 3: 43; EoS:42
[98] - No. of subjects analyzed (selected German sites only):
Baseline, Year 2, and Year 3:73
[99] - No. of subjects analyzed (selected German sites only):
Baseline, Year 2, Year 3, EoS: 18
[100] - No. of subjects analyzed (selected German sites only):
Baseline: 34; Year 2: 35; Year 3: 33

Statistical analyses

No statistical analyses for this end point

Secondary: Immunology - Specific IgG4

End point title	Immunology - Specific IgG4

End point description:

Only the Mono-sensitized patients continued with the follow-up phase. Therefore, Year 5 (EoS) results are only presented for the Mono-sensitized patients. The samples for analysis were collected in selected sites in Germany. Serum levels of specific IgG4 were evaluated, with the value at V1-1 as the baseline.

End point type	Secondary

End point timeframe:

The results for FAS are presented and summarized by year, i.e. Year 1 (baseline), Year 2 (V2-10), and Year 3 (V3-10) in both Mono- and Co-sensitized patients; and Year 5 (end of study/EoS) in the Mono-sensitized patients only.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Co-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo	Co-sensitized FAS/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46[101]	82[102]	22[103]	39[104]
Units: ng/mL				
median (full range (min-max))				
Baseline	13.50 (0.8 to 49.4)	16.25 (0.6 to 236.9)	9.55 (0.8 to 103.8)	19.40 (1.2 to 81.0)
Year 2 (V2-10)	72.70 (2.4 to 890.3)	105.60 (2.9 to 698.1)	12.80 (2.0 to 151.2)	26.10 (4.3 to 156.5)
Year 3 (V3-10)	70.90 (7.5 to 455.7)	112.70 (2.8 to 759.7)	9.85 (1.9 to 181.7)	13.60 (3.3 to 127.8)
EoS	19.00 (2.2 to 372.9)	0 (0 to 0)	9.60 (3.1 to 148.7)	0 (0 to 0)

Notes:

[101] - No. of subjects analyzed (selected German sites only):
Baseline: 46, Year 2: 43; Year 3: 42; EoS:42
[102] - No. of subjects analyzed (selected German sites only):
Baseline: 82; Year 2: 73; Year 3: 73
[103] - No. of subjects analyzed (selected German sites only):
Baseline: 22; Year 2: 18; Year 3: 18; EoS:18
[104] - No. of subjects analyzed (selected German sites only):

Baseline: 39; Year 2: 35; Year 3: 33

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-modifying effect After 5 Years

End point title	Disease-modifying effect After 5 Years

End point description:

Only the Mono-sensitized patients continued and completed all 5 years of study duration. Numbers of Mono-sensitized patients who became allergic to other than birch pollen allergen during the study as well as patients who developed asthma or allergic symptoms during the study were evaluated after the 5th pollen season (Year 5). Comparisons between the groups with respect to these disease-modifying effects were performed by means of Fisher's exact test.

End point type	Secondary

End point timeframe:

The results of FAS in Year 5 for the Mono-sensitized patients are presented.

End point values	Mono-sensitized FAS/Depigoid Birch 5000	Mono-sensitized FAS/Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	161	79		
Units: subject				
Asthmatic - Yes	35	16		
Asthmatic - No	126	63		
Allergens - Yes	58	24		
Allergens - No	103	55		

Statistical analyses

Statistical analysis title	Depigoid Birch vs. placebo (Asthmatic)
Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other[105]
P-value	= 0.8675
Method	Fisher exact

Notes:

[105] - Comparisons between the groups with respect to these disease-modifying effects were performed by means of Fisher's exact test.

	Depigoid Birch vs. placebo (Allergens)

Statistical analysis title	
Comparison groups	Mono-sensitized FAS/Depigoid Birch 5000 v Mono-sensitized FAS/Placebo
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other[106]
P-value	= 0.4692
Method	Fisher exact

Notes:

[106] - Comparisons between the groups with respect to these disease-modifying effects were performed by means of Fisher’s exact test.

Secondary: Investigator's Global Evaluation

End point title	Investigator's Global Evaluation

End point description:

Both the investigator's global evaluation of efficacy and safety & tolerability were recorded in Year 2, while only the global evaluation of efficacy was recorded at EoS.

End point type	Secondary

End point timeframe:

Global evaluation of efficacy and/or safety & tolerability were assessed by the investigator at the end of the 2nd pollen season (Year 2 [V2-10]) for both Mono- and Co-sensitized patients; and at EoS visit (Year 5) for the Mono-sensitized patients

End point values	Mono-sensitized SAF/Depigoid Birch 5000	Co-sensitized SAF/Depigoid Birch 5000	Mono-sensitized SAF/Placebo	Co-sensitized SAF/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	156[107]	234	74[108]	116
Units: subject				
Year 2 - Efficacy/Excellent	28	41	9	22
Year 2 - Efficacy/Good	79	133	28	59
Year 2 - Efficacy/Moderate	29	39	18	21
Year 2 - Efficacy/Insufficient	7	7	8	7
Year 2 - Efficacy/None	1	3	3	0
Year 2 - Efficacy/Missing	12	11	8	7
Year 2 - Safety&Tolerability/Excellent	74	131	29	57
Year 2 - Safety&Tolerability/Good	65	87	35	44
Year 2 - Safety&Tolerability/Moderate	5	3	2	8
Year 2 - Safety&Tolerability/Poor	0	0	0	0
Year 2 - Safety&Tolerability/Unacceptable	0	0	0	0
Year 2 - Safety&Tolerability/Missing	12	13	8	7
EoS - Efficacy/Excellent	29	0	2	0
EoS - Efficacy/Good	65	0	42	0
EoS - Efficacy/Moderate	30	0	15	0
EoS - Efficacy/Insufficient	10	0	13	0
EoS - Efficacy/None	13	0	6	0
EoS - Efficacy/Missing	2	0	0	0

Notes:

[107] - No. of subjects analyzed:
Year 2: 156; EoS: 174
[108] - No. of subjects analyzed:
Year 2: 74; EoS: 85

Statistical analyses

No statistical analyses for this end point

Secondary: Patient's Global Evaluation

End point title	Patient's Global Evaluation

End point description:

Both the patient's global evaluation of efficacy and safety & tolerability were recorded in Year 2, while only the global evaluation of efficacy was recorded at EoS.

End point type	Secondary

End point timeframe:

Global evaluation of efficacy and/or safety & tolerability were assessed by the patient at the end of the 2nd pollen season (Year 2 [V2-10]) for both Mono-sensitized and Co-sensitized patients; and at EoS visit (Year 5) for the Mono-sensitized patients.

End point values	Mono-sensitized SAF/Depigoid Birch 5000	Co-sensitized SAF/Depigoid Birch 5000	Mono-sensitized SAF/Placebo	Co-sensitized SAF/Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	156[109]	234	74[110]	116
Units: subject				
Year 2 - Efficacy/Excellent	24	131	29	57
Year 2 - Efficacy/Good	77	87	35	44
Year 2 - Efficacy/Moderate	31	3	2	8
Year 2 - Efficacy/Insufficient	6	0	0	0
Year 2 - Efficacy/None	6	0	0	0
Year 2 - Efficacy/Missing	12	13	8	7
Year 2 - Safety&Tolerability/Excellent	73	110	27	54
Year 2 - Safety&Tolerability/Good	64	99	38	48
Year 2 - Safety&Tolerability/Moderate	7	11	1	7
Year 2 - Safety&Tolerability/Poor	0	1	0	0
Year 2 - Safety&Tolerability/Unacceptable	0	0	0	0
Year 2 - Safety&Tolerability/Missing	12	13	8	7
EoS - Efficacy/Excellent	28	0	8	0
EoS - Efficacy/Good	58	0	32	0
EoS - Efficacy/Moderate	36	0	19	0
EoS - Efficacy/Insufficient	15	0	9	0
EoS - Efficacy/None	10	0	10	0
EoS - Efficacy/Missing	2	0	0	0

Notes:

[109] - No. of subjects analyzed:
Year 2: 156; EoS: 174

[110] - No. of subjects analyzed:
Year 2: 74; EoS: 85

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Al PK - Plasma concentration

End point title	Al PK - Plasma concentration

End point description:

Because the IMP contains Al(OH)3, the Pediatric Committee has required PK analyses of aluminum. Thus, a PK sub-study was performed to assess the levels of aluminum in plasma and in urine in a subgroup of adult patients. Plasma concentration measurement below the limit of quantification was set to half of the respective value. The results for Year 1-3 were presented for the Al PK set.

End point type	Other pre-specified

End point timeframe:

Before the start of treatment (V1-1, within 1h pre-dose), after the first maintenance dose (V1-2) and 1 year of treatment (V1-10). Blood collection for V1-2 and V1-10 was done within 1h pre-dose (0h) and at 1h, 2h, 4h, 8h post-dose.

End point values	Mono- and Co-sensitized Al PK set/Depigoid Birch	Mono- and Co-sensitized Al PK set/Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32[111]	15[112]		
Units: µg/L				
arithmetic mean (full range (min-max))				
V1-1	2.097 (1.617 to 7.547)	1.725 (1.617 to 3.235)		
V1-2 (0h)	1.887 (1.617 to 5.930)	2.224 (1.617 to 5.391)		
V1-2 (1h)	1.775 (1.617 to 6.199)	2.241 (1.617 to 5.121)		
V1-2 (2h)	1.989 (1.617 to 8.356)	2.089 (1.617 to 5.930)		
V1-2 (4h)	11.284 (1.617 to 278.437)	2.055 (1.617 to 5.660)		
V1-2 (8h)	2.045 (1.617 to 7.817)	3.319 (1.617 to 24.259)		
V1-10 (0h)	2.408 (1.617 to 7.547)	2.041 (1.617 to 5.391)		
V1-10 (1h)	1.991 (1.617 to 5.930)	1.868 (1.617 to 5.121)		
V1-10 (2h)	2.278 (1.617 to 7.547)	2.156 (1.617 to 4.852)		
V1-10 (4h)	2.191 (1.617 to 7.008)	2.041 (1.617 to 3.774)		
V1-10 (8h)	2.617 (1.617 to 9.164)	2.176 (1.617 to 6.739)		

Notes:

[111] - No. of subjects analyzed:
V1-1: 32; V1-2: 29; V1-10: 31
[112] - No. of subjects analyzed:
V1-1: 15; V1-2: 16; V1-10: 14

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Al PK - Plasma Concentration/Change from baseline

End point title	Al PK - Plasma Concentration/Change from baseline

End point description:

The absolute changes were calculated as the difference between the baseline value and the value reported at the corresponding visit and time point. The measurement at V1-1 was the baseline. The results for Year 1 to 3 were presented for the Al PK set.

End point type	Other pre-specified

End point timeframe:

The absolute changes from baseline at each visit (V1-2 and V1-10) and time point (pre-dose [0h], then 1h, 2h, 4h, and 8h post-dose).

End point values	Mono- and Co-sensitized Al PK set/Depigoid Birch	Mono- and Co-sensitized Al PK set/Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29[113]	15[114]		
Units: µg/L				
arithmetic mean (full range (min-max))				
V1-2 (0h)	-0.260 (-4.313 to 3.504)	0.539 (-1.617 to 3.774)		
V1-2 (1h)	-0.372 (-5.930 to 4.582)	0.557 (-1.617 to 3.504)		
V1-2 (2h)	-0.158 (-5.930 to 6.739)	0.395 (-1.617 to 4.313)		
V1-2 (4h)	9.137 (-4.313 to 276.820)	0.359 (-1.617 to 4.043)		
V1-2 (8h)	-0.102 (-4.313 to 1.887)	1.707 (-1.617 to 22.642)		
V1-10 (0h)	0.296 (-4.313 to 5.930)	0.166 (0 to 2.156)		
V1-10 (1h)	-0.122 (-4.313 to 4.313)	0 (0 to 0)		
V1-10 (2h)	0.165 (-4.313 to 4.043)	0.332 (0 to 2.156)		
V1-10 (4h)	0.078 (-2.156 to 2.695)	0.290 (0 to 1.887)		
V1-10 (8h)	0.504 (-4.313 to 7.547)	0.394 (0 to 5.121)		

Notes:

[113] - No. of subjects analyzed:
V1-2: 29; V1-10: 31

[114] - No. of subjects analyzed:
V1-2: 15; V1-10: 13

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Al PK - Urine Concentration

End point title	Al PK - Urine Concentration

End point description:

Because the IMP contains Al(OH)3, the Pediatric Committee has required PK analyses of aluminum. Thus, a PK sub-study was performed to assess the levels of aluminum in plasma and in urine in a subgroup of adult patients. The results for Year 1 to 3 were presented for the Al PK set. Data of analysis for samples collected post-dose only (excluding cases in which urine sampling was performed before IMP administration at a visit) are presented here.

End point type	Other pre-specified

End point timeframe:

Before the start of treatment (V1-1, over 24 hours before administration of IMP), V1-2 and V1-10 (both over 24 hours beginning from administration of IMP).

End point values	Mono- and Co-sensitized Al PK set/Depigoid Birch	Mono- and Co-sensitized Al PK set/Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27[115]	15[116]		
Units: µg/L				
arithmetic mean (full range (min-max))				
V1-2	10.542 (2.16 to 58.76)	9.775 (2.43 to 32.61)		
V1-10	13.333 (5.93 to 28.84)	15.402 (7.28 to 46.63)		

Notes:

[115] - No. of subjects analyzed:
V1-2: 27; V1-10: 28

[116] - No. of subjects analyzed:
V1-2: 15; V1-10: 14

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Al PK - Urine Concentration/Change from baseline

End point title	Al PK - Urine Concentration/Change from baseline

End point description:

At V1-2 and V1-10, assessments for urine samples from sampling started prior to IMP administration were excluded and were analyzed as missing values. The absolute changes were calculated as the difference between the baseline value and the value reported at the corresponding visit. The measurement at V1-1 was the baseline. The results for Year 1 to 3 were presented for the Al PK set.

End point type	Other pre-specified

End point timeframe:

The absolute changes from baseline at each post-dose visit (V1-2 and V1-10).

End point values	Mono- and Co-sensitized Al PK set/Depigoid Birch	Mono- and Co-sensitized Al PK set/Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[117]	15[118]		
Units: µg/L				
arithmetic mean (full range (min-max))				
V1-2	1.825 (-23.18 to 56.33)	-1.707 (-37.20 to 24.53)		
V1-10	4.813 (-13.21 to 22.64)	3.292 (-27.76 to 37.47)		

Notes:

[117] - No. of subjects analyzed:
V1-2: 26; V1-10: 28
[118] - No. of subjects analyzed:
V1-2: 15; V1-10: 14

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Al PK - Plasma Concentration/Cmax

End point title	Al PK - Plasma Concentration/Cmax

End point description:

PK parameters (Cmax, Tmax, AUC[0-8h]) were derived by non-compartmental analysis at V1-2 and V1-10 using Phoenix WinNonlinTM Software Version 6.3 (Pharsight Corporation, Mountain View, CA 94041-1530, USA). AUC was derived using the (linear) trapezoidal rule. If all aluminum concentration data obtained for a patient were below the limit of quantification at V1-2 or visit V1-10, the AUC was presented as "not determined". The PK parameters were derived using actual time points (i.e. calculated actual time of sample collection relative to administration time of IMP). Samples that were taken prior to administration of IMP were considered as to be collected at time zero. The results for Year 1 to 3 were presented for the Al PK set.

End point type	Other pre-specified

End point timeframe:

The PK parameters were calculated for V1-2 and V1-10.

End point values	Mono- and Co-sensitized Al PK set/Depigoid Birch	Mono- and Co-sensitized Al PK set/Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29[119]	16[120]		
Units: µg/L				
arithmetic mean (full range (min-max))				

V1-2	12.120 (1.617 to 278.437)	4.279 (1.617 to 24.259)		
V1-10	3.165 (1.617 to 9.164)	2.407 (1.617 to 6.739)		

Notes:

[119] - No. of subjects analyzed:
V1-2: 29; V1-10: 31

[120] - No. of subjects analyzed:
V1-2: 16; V1-10: 14

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Al PK - Plasma Concentration/Tmax

End point title	Al PK - Plasma Concentration/Tmax

End point description:

PK parameters (Cmax, Tmax, AUC[0-8h]) were derived by non-compartmental analysis at V1-2 and V1-10 using Phoenix WinNonlinTM Software Version 6.3 (Pharsight Corporation, Mountain View, CA 94041-1530, USA). AUC was derived using the (linear) trapezoidal rule. If all aluminum concentration data obtained for a patient were below the limit of quantification at V1-2 or visit V1-10, the AUC was presented as "not determined". The PK parameters were derived using actual time points (i.e. calculated actual time of sample collection relative to administration time of IMP). Samples that were taken prior to administration of IMP were considered as to be collected at time zero. The results for Year 1 to 3 were presented for the Al PK set.

End point type	Other pre-specified

End point timeframe:

The PK parameters were calculated for V1-2 and V1-10.

End point values	Mono- and Co-sensitized Al PK set/Depigoid Birch	Mono- and Co-sensitized Al PK set/Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29[121]	16[122]		
Units: hour				
arithmetic mean (full range (min-max))				
V1-2	1.481 (0 to 8.02)	1.063 (0 to 8.00)		
V1-10	1.258 (0 to 8.00)	0.714 (0 to 8.00)		

Notes:

[121] - No. of subjects analyzed:
V1-2: 29; V1-10: 31

[122] - No. of subjects analyzed:
V1-2: 16; V1-10: 14

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Al PK - Plasma Concentration/AUC[0-8h]

End point title	Al PK - Plasma Concentration/AUC[0-8h]

End point description:

PK parameters (Cmax, Tmax, AUC[0-8h]) were derived by non-compartmental analysis at V1-2 and V1-10 using Phoenix WinNonlinTM Software Version 6.3 (Pharsight Corporation, Mountain View, CA 94041-1530, USA). AUC was derived using the (linear) trapezoidal rule. If all aluminum concentration data obtained for a patient were below the limit of quantification at V1-2 or visit V1-10, the AUC was presented as "not determined". The PK parameters were derived using actual time points (i.e. calculated actual time of sample collection relative to administration time of IMP). Samples that were taken prior to administration of IMP were considered as to be collected at time zero. The results for Year 1 to 3 were presented for the Al PK set.

End point type	Other pre-specified

End point timeframe:

The PK parameters were calculated for V1-2 and V1-10.

End point values	Mono- and Co-sensitized Al PK set/Depigoid Birch	Mono- and Co-sensitized Al PK set/Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[123]	7[124]		
Units: hour.µg/L				
arithmetic mean (full range (min-max))				
V1-2	111.875 (15.50 to 845.43)	27.455 (14.82 to 58.22)		
V1-10	27.129 (15.36 to 53.88)	30.009 (21.83 to 35.04)		

Notes:

[123] - No. of subjects analyzed:
V1-2: 9; V1-10: 12
[124] - No. of subjects analyzed:
V1-2: 7; V1-10: 3

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from signing of the informed consent until the end of the study (Year 5). Only treatment-emergent AEs (TEAEs) (AEs that started or worsened after first dose of the IMP) reported from V1 until the end-of-study (EoS) visit were analyzed.

Adverse event reporting additional description:

Systemic reactions (SR, according to the EAACI grading criteria) and local reactions (LR, according to induration [wheal] size as determined by the largest diameter of the wheal, itching, and pain) were additionally analyzed as separate categories, and are presented here as part of the TEAEs analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Mono-sensitized Year 1-5/Depigoid Birch

Reporting group description:

The Mono-sensitized SAF patients who received at least one dose of Depigoid Birch were analyzed for adverse events. Overall TEAEs over all 5 years of the study period are reported in this section.

Reporting group title	Mono-sensitized Year 1-5/Placebo

Reporting group description:

The Mono-sensitized SAF patients who received at least one dose of placebo were analyzed for adverse events. Overall TEAEs over all 5 years of the study period are reported in this section.

Reporting group title	Overall Mono-sensitized Year 1-5

Reporting group description:

All Mono-sensitized SAF patients who received at least one dose of Depigoid Birch or placebo were analyzed for adverse events. Overall TEAEs over all 5 years of the study period are reported in this section.

Reporting group title	Co-sensitized Year 1-3/Depigoid Birch

Reporting group description:

The Co-sensitized SAF patients who received at least one dose of Depigoid Birch were analyzed for adverse events. Overall TEAEs for 3 years (treatment phase only) of the study period are reported in this section.

Reporting group title	Co-sensitized Year 1-3/Placebo

Reporting group description:

The Co-sensitized SAF patients who received at least one dose of placebo were analyzed for adverse events. Overall TEAEs for 3 years (treatment phase only) of the study period are reported in this section.

Reporting group title	Overall Co-sensitized Year 1-3

Reporting group description:

All Co-sensitized SAF patients who received at least one dose of Depigoid Birch or placebo were analyzed for adverse events. Overall TEAEs for 3 years (treatment phase only) of the study period are reported in this section.

Serious adverse events	Mono-sensitized Year 1-5/Depigoid Birch	Mono-sensitized Year 1-5/Placebo	Overall Mono-sensitized Year 1-5
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 174 (8.05%)	7 / 85 (8.24%)	21 / 259 (8.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 174 (0.00%)	1 / 85 (1.18%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fallopian tube cancer stage III			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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			
Deep vein thrombosis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Hypertensive crisis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Ischaemia			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Thrombosis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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			
Atrial septal defect repair			

subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoid operation			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve repair			
subjects affected / exposed	0 / 174 (0.00%)	1 / 85 (1.18%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion induced			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Bunion operation			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Cholecystectomy			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Colporrhaphy			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Intervertebral disc operation			

subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Meniscus removal			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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 septal operation			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Removal of internal fixation			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Uterine dilation and curettage			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Uterine prolapse repair			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Pregnancy, puerperium and perinatal conditions			
Twin pregnancy			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal death			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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			

Chest pain			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Hernia			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Hyperthermia			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 174 (0.57%)	1 / 85 (1.18%)	2 / 259 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Testicular pain			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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			
Dyspnoea			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Psychiatric disorders			
Major depression			

subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Arteriogram coronary			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accident			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Ankle fracture			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Fibula fracture			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Hand fracture			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Ligament rupture			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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

Lower limb fracture			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Meniscus injury			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Splenic rupture			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Upper limb fracture			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 174 (0.00%)	1 / 85 (1.18%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Coronary artery disease			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 174 (0.00%)	1 / 85 (1.18%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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 adhesions			
subjects affected / exposed	0 / 174 (0.00%)	1 / 85 (1.18%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 174 (0.00%)	1 / 85 (1.18%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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 disorder			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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

Inguinal hernia			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Pancreatitis acute			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis of pregnancy			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Osteoarthritis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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			
Anal abscess			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic hepatitis C			
subjects affected / exposed	0 / 174 (0.00%)	1 / 85 (1.18%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Diverticulitis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Infectious mononucleosis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Pneumonia			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Tonsillitis			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Urinary tract infection			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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
Wound infection			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (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	Co-sensitized Year 1-3/Depigoid Birch	Co-sensitized Year 1-3/Placebo	Overall Co-sensitized Year 1-3
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 260 (11.54%)	14 / 130 (10.77%)	44 / 390 (11.28%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 260 (0.38%)	1 / 130 (0.77%)	2 / 390 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fallopian tube cancer stage III			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Hypertension			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	2 / 260 (0.77%)	0 / 130 (0.00%)	2 / 390 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Atrial septal defect repair			

subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Haemorrhoid operation			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Mitral valve repair			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Abortion induced			
subjects affected / exposed	2 / 260 (0.77%)	0 / 130 (0.00%)	2 / 390 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bunion operation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy			
subjects affected / exposed	2 / 260 (0.77%)	0 / 130 (0.00%)	2 / 390 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colporrhaphy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc operation			

subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus removal			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septal operation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Removal of internal fixation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine dilation and curettage			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse repair			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Twin pregnancy			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Foetal death			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 260 (0.38%)	1 / 130 (0.77%)	2 / 390 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Endometriosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular pain			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			

subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Investigations			
Arteriogram coronary			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Accident			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lower limb fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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			
Arrhythmia			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Atrial flutter			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Hemiparesis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Hypoaesthesia			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Loss of consciousness			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Speech disorder			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Sciatica			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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			
Visual impairment			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Abdominal pain upper			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Anal fissure			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Diarrhoea			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Colitis ulcerative			
subjects affected / exposed	2 / 260 (0.77%)	0 / 130 (0.00%)	2 / 390 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Inguinal hernia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Cholestasis of pregnancy			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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			
Drug eruption			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Spinal column stenosis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	3 / 260 (1.15%)	0 / 130 (0.00%)	3 / 390 (0.77%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	2 / 260 (0.77%)	0 / 130 (0.00%)	2 / 390 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Chronic hepatitis C			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Influenza			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (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
Appendicitis			

subjects affected / exposed	2 / 260 (0.77%)	1 / 130 (0.77%)	3 / 390 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 260 (0.38%)	1 / 130 (0.77%)	2 / 390 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 130 (0.77%)	1 / 390 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Mono-sensitized Year 1-5/Depigoid Birch	Mono-sensitized Year 1-5/Placebo	Overall Mono-sensitized Year 1-5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 174 (85.63%)	67 / 85 (78.82%)	216 / 259 (83.40%)
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 174 (0.00%)	2 / 85 (2.35%)	2 / 259 (0.77%)
occurrences (all)	0	2	2
Hypertension			
subjects affected / exposed	6 / 174 (3.45%)	5 / 85 (5.88%)	11 / 259 (4.25%)
occurrences (all)	7	5	12
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	28 / 174 (16.09%)	9 / 85 (10.59%)	37 / 259 (14.29%)
occurrences (all)	79	36	115
Injection site nodule			
subjects affected / exposed	4 / 174 (2.30%)	1 / 85 (1.18%)	5 / 259 (1.93%)
occurrences (all)	4	1	5
Injection site oedema			
subjects affected / exposed	6 / 174 (3.45%)	5 / 85 (5.88%)	11 / 259 (4.25%)
occurrences (all)	8	11	19
Injection site pain			
subjects affected / exposed	7 / 174 (4.02%)	3 / 85 (3.53%)	10 / 259 (3.86%)
occurrences (all)	9	18	27
Injection site papule			
subjects affected / exposed	2 / 174 (1.15%)	0 / 85 (0.00%)	2 / 259 (0.77%)
occurrences (all)	2	0	2
Injection site pruritus			
subjects affected / exposed	18 / 174 (10.34%)	2 / 85 (2.35%)	20 / 259 (7.72%)
occurrences (all)	71	2	73
Injection site reaction			
subjects affected / exposed	42 / 174 (24.14%)	11 / 85 (12.94%)	53 / 259 (20.46%)
occurrences (all)	145	72	217
Injection site swelling			
subjects affected / exposed	10 / 174 (5.75%)	4 / 85 (4.71%)	14 / 259 (5.41%)
occurrences (all)	37	7	44
Injection site urticaria			

subjects affected / exposed	2 / 174 (1.15%)	1 / 85 (1.18%)	3 / 259 (1.16%)
occurrences (all)	31	1	32
Pyrexia			
subjects affected / exposed	4 / 174 (2.30%)	1 / 85 (1.18%)	5 / 259 (1.93%)
occurrences (all)	4	1	5
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 174 (2.87%)	1 / 85 (1.18%)	6 / 259 (2.32%)
occurrences (all)	5	1	6
Respiratory, thoracic and mediastinal disorders			
Allergic cough			
subjects affected / exposed	0 / 174 (0.00%)	2 / 85 (2.35%)	2 / 259 (0.77%)
occurrences (all)	0	2	2
Asthma			
subjects affected / exposed	17 / 174 (9.77%)	11 / 85 (12.94%)	28 / 259 (10.81%)
occurrences (all)	19	12	31
Cough			
subjects affected / exposed	11 / 174 (6.32%)	7 / 85 (8.24%)	18 / 259 (6.95%)
occurrences (all)	12	9	21
Dyspnoea			
subjects affected / exposed	5 / 174 (2.87%)	5 / 85 (5.88%)	10 / 259 (3.86%)
occurrences (all)	8	7	15
Epistaxis			
subjects affected / exposed	4 / 174 (2.30%)	0 / 85 (0.00%)	4 / 259 (1.54%)
occurrences (all)	4	0	4
Nasal congestion			
subjects affected / exposed	1 / 174 (0.57%)	2 / 85 (2.35%)	3 / 259 (1.16%)
occurrences (all)	1	4	5
Oropharyngeal pain			
subjects affected / exposed	4 / 174 (2.30%)	0 / 85 (0.00%)	4 / 259 (1.54%)
occurrences (all)	4	0	4
Rhinitis allergic			
subjects affected / exposed	4 / 174 (2.30%)	3 / 85 (3.53%)	7 / 259 (2.70%)
occurrences (all)	6	4	10
Rhinorrhoea			

subjects affected / exposed	5 / 174 (2.87%)	2 / 85 (2.35%)	7 / 259 (2.70%)
occurrences (all)	6	2	8
Sneezing			
subjects affected / exposed	2 / 174 (1.15%)	3 / 85 (3.53%)	5 / 259 (1.93%)
occurrences (all)	2	3	5
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 174 (0.57%)	1 / 85 (1.18%)	2 / 259 (0.77%)
occurrences (all)	1	1	2
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	17 / 174 (9.77%)	8 / 85 (9.41%)	25 / 259 (9.65%)
occurrences (all)	53	32	85
Peak expiratory flow rate decreased			
subjects affected / exposed	20 / 174 (11.49%)	17 / 85 (20.00%)	37 / 259 (14.29%)
occurrences (all)	71	30	101
Pulmonary function test decreased			
subjects affected / exposed	2 / 174 (1.15%)	3 / 85 (3.53%)	5 / 259 (1.93%)
occurrences (all)	2	3	5
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences (all)	1	0	1
Hand fracture			
subjects affected / exposed	1 / 174 (0.57%)	1 / 85 (1.18%)	2 / 259 (0.77%)
occurrences (all)	1	1	2
Ligament sprain			
subjects affected / exposed	1 / 174 (0.57%)	0 / 85 (0.00%)	1 / 259 (0.39%)
occurrences (all)	1	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 174 (4.60%)	3 / 85 (3.53%)	11 / 259 (4.25%)
occurrences (all)	17	6	23
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 174 (0.00%)	2 / 85 (2.35%)	2 / 259 (0.77%)
occurrences (all)	0	2	2
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	4 / 174 (2.30%)	2 / 85 (2.35%)	6 / 259 (2.32%)
occurrences (all)	4	2	6
Vertigo			
subjects affected / exposed	4 / 174 (2.30%)	1 / 85 (1.18%)	5 / 259 (1.93%)
occurrences (all)	7	1	8
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	9 / 174 (5.17%)	6 / 85 (7.06%)	15 / 259 (5.79%)
occurrences (all)	12	6	18
Eye pruritus			
subjects affected / exposed	4 / 174 (2.30%)	4 / 85 (4.71%)	8 / 259 (3.09%)
occurrences (all)	6	7	13
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	5 / 174 (2.87%)	0 / 85 (0.00%)	5 / 259 (1.93%)
occurrences (all)	5	0	5
Gastritis			
subjects affected / exposed	4 / 174 (2.30%)	2 / 85 (2.35%)	6 / 259 (2.32%)
occurrences (all)	4	2	6
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 174 (2.30%)	2 / 85 (2.35%)	6 / 259 (2.32%)
occurrences (all)	4	2	6
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 174 (0.00%)	2 / 85 (2.35%)	2 / 259 (0.77%)
occurrences (all)	0	2	2
Eczema			
subjects affected / exposed	3 / 174 (1.72%)	1 / 85 (1.18%)	4 / 259 (1.54%)
occurrences (all)	5	1	6
Urticaria			
subjects affected / exposed	7 / 174 (4.02%)	2 / 85 (2.35%)	9 / 259 (3.47%)
occurrences (all)	11	2	13
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	4 / 174 (2.30%)	2 / 85 (2.35%)	6 / 259 (2.32%)
occurrences (all)	4	2	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 174 (4.02%)	1 / 85 (1.18%)	8 / 259 (3.09%)
occurrences (all)	7	1	8
Back pain			
subjects affected / exposed	13 / 174 (7.47%)	4 / 85 (4.71%)	17 / 259 (6.56%)
occurrences (all)	14	5	19
Intervertebral disc protrusion			
subjects affected / exposed	0 / 174 (0.00%)	2 / 85 (2.35%)	2 / 259 (0.77%)
occurrences (all)	0	2	2
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 174 (0.57%)	1 / 85 (1.18%)	2 / 259 (0.77%)
occurrences (all)	1	1	2
Bronchitis			
subjects affected / exposed	12 / 174 (6.90%)	9 / 85 (10.59%)	21 / 259 (8.11%)
occurrences (all)	12	12	24
Conjunctivitis			
subjects affected / exposed	8 / 174 (4.60%)	3 / 85 (3.53%)	11 / 259 (4.25%)
occurrences (all)	11	3	14
Gastroenteritis			
subjects affected / exposed	10 / 174 (5.75%)	3 / 85 (3.53%)	13 / 259 (5.02%)
occurrences (all)	13	3	16
Influenza			
subjects affected / exposed	9 / 174 (5.17%)	3 / 85 (3.53%)	12 / 259 (4.63%)
occurrences (all)	9	3	12
Laryngitis			
subjects affected / exposed	0 / 174 (0.00%)	3 / 85 (3.53%)	3 / 259 (1.16%)
occurrences (all)	0	3	3
Nasopharyngitis			
subjects affected / exposed	62 / 174 (35.63%)	15 / 85 (17.65%)	77 / 259 (29.73%)
occurrences (all)	129	26	155
Pharyngitis			

subjects affected / exposed	14 / 174 (8.05%)	5 / 85 (5.88%)	19 / 259 (7.34%)
occurrences (all)	19	8	27
Pneumonia			
subjects affected / exposed	0 / 174 (0.00%)	0 / 85 (0.00%)	0 / 259 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	6 / 174 (3.45%)	4 / 85 (4.71%)	10 / 259 (3.86%)
occurrences (all)	9	6	15
Respiratory tract infection viral			
subjects affected / exposed	3 / 174 (1.72%)	2 / 85 (2.35%)	5 / 259 (1.93%)
occurrences (all)	3	2	5
Rhinitis			
subjects affected / exposed	7 / 174 (4.02%)	5 / 85 (5.88%)	12 / 259 (4.63%)
occurrences (all)	8	7	15
Sinusitis			
subjects affected / exposed	8 / 174 (4.60%)	4 / 85 (4.71%)	12 / 259 (4.63%)
occurrences (all)	9	9	18
Tonsillitis			
subjects affected / exposed	10 / 174 (5.75%)	4 / 85 (4.71%)	14 / 259 (5.41%)
occurrences (all)	11	5	16
Upper respiratory tract infection			
subjects affected / exposed	6 / 174 (3.45%)	4 / 85 (4.71%)	10 / 259 (3.86%)
occurrences (all)	6	5	11
Urinary tract infection			
subjects affected / exposed	5 / 174 (2.87%)	0 / 85 (0.00%)	5 / 259 (1.93%)
occurrences (all)	7	0	7
Viral infection			
subjects affected / exposed	4 / 174 (2.30%)	0 / 85 (0.00%)	4 / 259 (1.54%)
occurrences (all)	4	0	4

Non-serious adverse events	Co-sensitized Year 1-3/Depigoid Birch	Co-sensitized Year 1-3/Placebo	Overall Co-sensitized Year 1-3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	216 / 260 (83.08%)	104 / 130 (80.00%)	320 / 390 (82.05%)
Vascular disorders			
Essential hypertension			

subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	15 / 260 (5.77%)	1 / 130 (0.77%)	16 / 390 (4.10%)
occurrences (all)	15	2	17
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	36 / 260 (13.85%)	14 / 130 (10.77%)	50 / 390 (12.82%)
occurrences (all)	106	33	139
Injection site nodule			
subjects affected / exposed	4 / 260 (1.54%)	3 / 130 (2.31%)	7 / 390 (1.79%)
occurrences (all)	5	4	9
Injection site oedema			
subjects affected / exposed	12 / 260 (4.62%)	4 / 130 (3.08%)	16 / 390 (4.10%)
occurrences (all)	19	4	23
Injection site pain			
subjects affected / exposed	4 / 260 (1.54%)	5 / 130 (3.85%)	9 / 390 (2.31%)
occurrences (all)	4	19	23
Injection site papule			
subjects affected / exposed	7 / 260 (2.69%)	1 / 130 (0.77%)	8 / 390 (2.05%)
occurrences (all)	9	1	10
Injection site pruritus			
subjects affected / exposed	16 / 260 (6.15%)	6 / 130 (4.62%)	22 / 390 (5.64%)
occurrences (all)	47	19	66
Injection site reaction			
subjects affected / exposed	63 / 260 (24.23%)	19 / 130 (14.62%)	82 / 390 (21.03%)
occurrences (all)	299	122	421
Injection site swelling			
subjects affected / exposed	13 / 260 (5.00%)	12 / 130 (9.23%)	25 / 390 (6.41%)
occurrences (all)	39	23	62
Injection site urticaria			
subjects affected / exposed	9 / 260 (3.46%)	3 / 130 (2.31%)	12 / 390 (3.08%)
occurrences (all)	41	19	60
Pyrexia			

subjects affected / exposed	3 / 260 (1.15%)	1 / 130 (0.77%)	4 / 390 (1.03%)
occurrences (all)	4	1	5
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 260 (1.54%)	1 / 130 (0.77%)	5 / 390 (1.28%)
occurrences (all)	4	1	5
Respiratory, thoracic and mediastinal disorders			
Allergic cough			
subjects affected / exposed	0 / 260 (0.00%)	0 / 130 (0.00%)	0 / 390 (0.00%)
occurrences (all)	0	0	0
Asthma			
subjects affected / exposed	27 / 260 (10.38%)	14 / 130 (10.77%)	41 / 390 (10.51%)
occurrences (all)	31	16	47
Cough			
subjects affected / exposed	10 / 260 (3.85%)	7 / 130 (5.38%)	17 / 390 (4.36%)
occurrences (all)	11	9	17
Dyspnoea			
subjects affected / exposed	4 / 260 (1.54%)	4 / 130 (3.08%)	8 / 390 (2.05%)
occurrences (all)	4	6	10
Epistaxis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences (all)	1	0	1
Nasal congestion			
subjects affected / exposed	4 / 260 (1.54%)	4 / 130 (3.08%)	8 / 390 (2.05%)
occurrences (all)	4	4	8
Oropharyngeal pain			
subjects affected / exposed	7 / 260 (2.69%)	4 / 130 (3.08%)	11 / 390 (2.82%)
occurrences (all)	7	4	11
Rhinitis allergic			
subjects affected / exposed	8 / 260 (3.08%)	5 / 130 (3.85%)	13 / 390 (3.33%)
occurrences (all)	9	7	16
Rhinorrhoea			
subjects affected / exposed	8 / 260 (3.08%)	5 / 130 (3.85%)	13 / 390 (3.33%)
occurrences (all)	12	6	18
Sneezing			

subjects affected / exposed	3 / 260 (1.15%)	1 / 130 (0.77%)	4 / 390 (1.03%)
occurrences (all)	4	1	5
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 260 (0.38%)	3 / 130 (2.31%)	4 / 390 (1.03%)
occurrences (all)	1	3	4
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	29 / 260 (11.15%)	9 / 130 (6.92%)	38 / 390 (9.74%)
occurrences (all)	51	22	73
Peak expiratory flow rate decreased			
subjects affected / exposed	24 / 260 (9.23%)	18 / 130 (13.85%)	42 / 390 (10.77%)
occurrences (all)	61	39	100
Pulmonary function test decreased			
subjects affected / exposed	9 / 260 (3.46%)	3 / 130 (2.31%)	12 / 390 (3.08%)
occurrences (all)	16	5	21
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 260 (1.15%)	3 / 130 (2.31%)	6 / 390 (1.54%)
occurrences (all)	3	3	6
Hand fracture			
subjects affected / exposed	3 / 260 (1.15%)	2 / 130 (1.54%)	5 / 390 (1.28%)
occurrences (all)	3	2	5
Ligament sprain			
subjects affected / exposed	6 / 260 (2.31%)	1 / 130 (0.77%)	7 / 390 (1.79%)
occurrences (all)	6	1	7
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 260 (1.92%)	9 / 130 (6.92%)	14 / 390 (3.59%)
occurrences (all)	9	13	22
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 260 (0.77%)	1 / 130 (0.77%)	3 / 390 (0.77%)
occurrences (all)	2	1	3
Ear and labyrinth disorders			

Hypoacusis			
subjects affected / exposed	0 / 260 (0.00%)	2 / 130 (1.54%)	2 / 390 (0.51%)
occurrences (all)	0	2	2
Vertigo			
subjects affected / exposed	1 / 260 (0.38%)	1 / 130 (0.77%)	2 / 390 (0.51%)
occurrences (all)	1	2	3
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	19 / 260 (7.31%)	6 / 130 (4.62%)	25 / 390 (6.41%)
occurrences (all)	19	6	25
Eye pruritus			
subjects affected / exposed	12 / 260 (4.62%)	4 / 130 (3.08%)	16 / 390 (4.10%)
occurrences (all)	21	7	28
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences (all)	1	0	1
Gastritis			
subjects affected / exposed	4 / 260 (1.54%)	4 / 130 (3.08%)	8 / 390 (2.05%)
occurrences (all)	4	4	8
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 260 (1.92%)	2 / 130 (1.54%)	7 / 390 (1.79%)
occurrences (all)	5	2	7
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 260 (0.38%)	4 / 130 (3.08%)	5 / 390 (1.28%)
occurrences (all)	1	4	5
Eczema			
subjects affected / exposed	14 / 260 (5.38%)	1 / 130 (0.77%)	15 / 390 (3.85%)
occurrences (all)	16	1	17
Urticaria			
subjects affected / exposed	7 / 260 (2.69%)	2 / 130 (1.54%)	9 / 390 (2.31%)
occurrences (all)	7	2	9
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 260 (0.77%)	1 / 130 (0.77%)	3 / 390 (0.77%)
occurrences (all)	2	1	3

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 260 (1.54%)	1 / 130 (0.77%)	5 / 390 (1.28%)
occurrences (all)	4	1	5
Back pain			
subjects affected / exposed	15 / 260 (5.77%)	4 / 130 (3.08%)	19 / 390 (4.87%)
occurrences (all)	27	6	33
Intervertebral disc protrusion			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences (all)	1	0	1
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	3 / 260 (1.15%)	3 / 130 (2.31%)	6 / 390 (1.54%)
occurrences (all)	5	3	8
Bronchitis			
subjects affected / exposed	22 / 260 (8.46%)	10 / 130 (7.69%)	32 / 390 (8.21%)
occurrences (all)	28	12	40
Conjunctivitis			
subjects affected / exposed	11 / 260 (4.23%)	9 / 130 (6.92%)	20 / 390 (5.13%)
occurrences (all)	12	11	23
Gastroenteritis			
subjects affected / exposed	9 / 260 (3.46%)	5 / 130 (3.85%)	14 / 390 (3.59%)
occurrences (all)	12	7	19
Influenza			
subjects affected / exposed	4 / 260 (1.54%)	3 / 130 (2.31%)	7 / 390 (1.79%)
occurrences (all)	4	5	9
Laryngitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 130 (0.00%)	1 / 390 (0.26%)
occurrences (all)	1	0	1
Nasopharyngitis			
subjects affected / exposed	56 / 260 (21.54%)	33 / 130 (25.38%)	89 / 390 (22.82%)
occurrences (all)	96	64	160
Pharyngitis			
subjects affected / exposed	17 / 260 (6.54%)	10 / 130 (7.69%)	27 / 390 (6.92%)
occurrences (all)	18	11	29
Pneumonia			

subjects affected / exposed	1 / 260 (0.38%)	3 / 130 (2.31%)	4 / 390 (1.03%)
occurrences (all)	1	3	4
Respiratory tract infection			
subjects affected / exposed	16 / 260 (6.15%)	7 / 130 (5.38%)	23 / 390 (5.90%)
occurrences (all)	28	11	39
Respiratory tract infection viral			
subjects affected / exposed	11 / 260 (4.23%)	3 / 130 (2.31%)	14 / 390 (3.59%)
occurrences (all)	16	4	20
Rhinitis			
subjects affected / exposed	8 / 260 (3.08%)	6 / 130 (4.62%)	14 / 390 (3.59%)
occurrences (all)	8	10	18
Sinusitis			
subjects affected / exposed	15 / 260 (5.77%)	6 / 130 (4.62%)	21 / 390 (5.38%)
occurrences (all)	18	7	25
Tonsillitis			
subjects affected / exposed	15 / 260 (5.77%)	3 / 130 (2.31%)	18 / 390 (4.62%)
occurrences (all)	17	3	20
Upper respiratory tract infection			
subjects affected / exposed	17 / 260 (6.54%)	8 / 130 (6.15%)	25 / 390 (6.41%)
occurrences (all)	22	9	31
Urinary tract infection			
subjects affected / exposed	6 / 260 (2.31%)	3 / 130 (2.31%)	9 / 390 (2.31%)
occurrences (all)	8	4	12
Viral infection			
subjects affected / exposed	5 / 260 (1.92%)	3 / 130 (2.31%)	8 / 390 (2.05%)
occurrences (all)	6	3	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2012	The global protocol amendment No. 1 was conducted in accordance with the changes requested by German Competent Authorities and the Central EC in Germany. The main changes include: 1. Modification of a few inclusion/exclusion criteria for precise formulation and thereby enhanced patient's safety. 2. Further clarifications and/or modifications of some study procedures, including: a. Added requirement for venous access prior to administration of IMP in the rush build-up phase b. Adaptations in the escalation scheme for RM c. Added instructions to investigators for recording data in eCRF d. Added assessments of patients' asthma status, vitamin D in blood, SPT at EoS e. Modified definitions of AE causality categories f. Modifications in the schedule of PK blood sampling g. Added definition for futility analysis population h. Clarifications for PFT scheduling, definition of topical corticosteroids as RM, time window for collection of medical history data, negative SPT control, timing of RQLQ assessments, observation period for AEs, and scoring of SMS (also including asthmatic patients)
30 November 2012	This global amendment No. 2 was implemented in the protocol at the request of the sponsor. The main changes include: 1. Extension of patients' recruitment period (the first recruitment period lasted 3 to 4 months starting September 2012 and the newly added recruitment period was planned to start after termination of birch pollen season 2013 and until December 2013). 2. Extension of the SCR period (from up to 4 weeks to up to 8 weeks). 3. Added clarifications of inclusion criteria No. 9 and 10, and modification of exclusion criterion No. 20 regarding prior use of psychoactive drugs 4. Further specifications on mid-season visit scheduling with respect to birch pollen season 5. Clarifications on the use of permitted RMs and procedures for recording information about RMs 6. Minor modification to type of psychoactive drugs considered prohibited concomitant medication. 7. The PK sub-study was not any longer specified to German sites only. 8. The statistical analysis for futility was further specified.
11 July 2013	This global amendment No. 3 was implemented at the request of the sponsor and partly requested by the Paul-Ehrlich-Institut (PEI, German Competent Authority) due to the extended recruitment period that had already been approved with the global amendment No. 2. The main changes include: 1. Adding the number of screened patients needed to attain the required number of randomized patients for statistical analyses. 2. Further specifications/modifications of two exclusion criteria (No. 10 - SCORAD cut off was increased from 30 to 40; No. 19 - "parenthesis" was added) 3. Correction of a typo in the escalation scheme for inhaled corticosteroids 4. The description of primary and futility analyses was adapted due to the addition of a second recruitment period as requested by the PEI, Germany 5. Adding clarifications for handling of AdolRQLQ

11 October 2016	This global protocol amendment No. 4 was prepared at the request of the sponsor and submitted to the ECs in Czech Republic, Germany, Latvia, Lithuania, and Poland. In Russia, the protocol amendment was implemented in protocol version 3.0 for Russia, dated 13-OCT-2016, and was submitted for approval as well. Before receiving response from any of the ECs, the sponsor decided to withdraw the global amendment. The reason for withdrawal was the need of additional changes to the protocol based on recommendations of the DMC to continue the study with Mono-sensitized patients only. Thus, all changes in the protocol included in global amendment No. 4 were included in the global amendment No. 5.
11 January 2017	This global protocol amendment No.5 was prepared to implement changes in the study conduct following from DMC recommendations based on results of the planned 2nd-year interim analysis and additional analyses of 3rd-year data and post-hoc analyses. The main changes include: 1. Only patients who turned out to be mono-sensitized to birch according to the SPT at SCR could continue participating in the study; the remaining, co-sensitized, patients had to be withdrawn from the study. This decision was supported by the results of the planned 2nd-year interim analysis, the additional analyses of 3rd-year data and the post-hoc analyses of 2nd and 3rd year data performed by the DMC. 2. Cancelation of the planned 3rd- year futility analysis 3. A new stopping rule for individual patients was added: Patients with any co-sensitization documented at SCR according to the SPT were to be withdrawn from the study 4. Immunoblotting analysis of Alnus and Corylus was added for patients who had blood samples still available on storage in the central laboratory 5. Addition of analysis of immediate and delayed SRs
28 February 2017	This global amendment No. 6 was prepared at the request of the German Authority PEI and the sponsor and aimed to introduce the following changes in the conduct of the study: 1. Scheduling of a post-study visit for all co-sensitized patients that had to be withdrawn from the study (requested by the PEI) 2. Clarification on additional laboratory evaluations for co-sensitized patients at EoS visit (including hematology, clinical chemistry investigations, serum pregnancy test, vitamin D, immunology parameters and immunoblotting. An immunoblot analysis of birch (Betula) was added to enable comparisons with results of Alnus and Corylus testing at EoS visit

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to withdrawal of the Co-sensitized patients from the study, only the complete data for Year 1-3 were available for analysis in this arm. Data analysis for Year 1-5 was only done for a subset of Co-sensitized patients who completed Year 4-5.

Notes: