



## 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)                          | EMA-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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                        |
|--------------------------------------|------------------------|
| 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:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| 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  $\geq 2$ ) 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                                     |
| <b>Arm title</b>             | 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.

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | 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.

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | 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.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | 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                                     |
| <b>Arm title</b>             | 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.

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | 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                                |

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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<br>Units: Subjects                                |   |                                       |                                  |
| Adolescents (12-17 years)   | 11                                      | 24                                    | 3                                |
| Adults (18-70 years)  | 163                                     | 236                                   | 82                               |
| Age continuous<br>Units: years                                    |   |                                       |                                  |
| arithmetic mean   | 38.8                                    | 37.3                                  | 41.0                             |
| standard deviation  | ± 12.96                                 | ± 13.60                               | ± 12.84                          |
| Gender categorical<br>Units: Subjects                             |   |                                       |                                  |
| Female  | 98                                      | 138                                   | 48                               |
| Male  | 76                                      | 122                                   | 37                               |
| Race<br>Units: Subjects   |   |                                       |                                  |
| White   | 174                                     | 259                                   | 84                               |
| Other   | 0                                       | 1                                     | 1                                |
| Asthmatic reaction to birch pollen in the past<br>Units: Subjects |   |                                       |                                  |
| Yes   | 50                                      | 69                                    | 28                               |
| No  | 124                                     | 191                                   | 57                               |
| Asthmatic status at baseline<br>Units: Subjects                   |   |                                       |                                  |

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

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

|   |                 |     |  |
|---|-----------------|-----|--|
| Patients with nasal/ocular symptoms with at least moderate intensity<br>Units: Subjects                                 |                 |     |  |
| Yes   | 130             | 649 |  |
| No  | 0               | 0   |  |
| Weight<br>Units: kilogram(s)<br>arithmetic mean<br>standard deviation   | 73.3<br>± 15.91 | -   |  |
| Height<br>Units: centimeter(s)<br>arithmetic mean<br>standard deviation   | 171.8<br>± 9.91 | -   |  |
| BMI<br>Units: kilogram(s)/square meter<br>arithmetic mean<br>standard deviation   | 24.6<br>± 3.99  | -   |  |
| Time (years) since the first allergic reaction to birch pollen<br>Units: Years<br>arithmetic mean<br>standard deviation | 13.7<br>± 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)<sub>3</sub> 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)<sub>3</sub> 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 AI 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 (AI PK) set/Placebo contained randomized mono-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH)<sub>3</sub> 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 AI 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 (AI PK) set/Placebo contained all randomized co-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH)<sub>3</sub> plasma and/or urine measurements.

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

Subject analysis set description:

The Mono- and Co-sensitized Aluminium Pharmacokinetic (AI 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)<sub>3</sub> plasma and/or urine measurements.

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

Subject analysis set description:

The Mono- and Co-sensitized Aluminium Pharmacokinetic (AI 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)<sub>3</sub> 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  | ±   |
| <b>Reporting group values</b>  | Mono-sensitized PP<br>Year 5/Depigoid<br>Birch 5000 | Mono-sensitized AI<br>PK set/Depigoid<br>Birch 5000 | Co-sensitized<br>FAS/Depigoid Birch<br>5000 |
| Number of subjects   | 116   | 18  | 245   |

|   |                                       |   |   |
|---|---------------------------------------|---|---|
| Age categorical<br>Units: Subjects  |                                       |   |   |
| Adolescents (12-17 years)   | 7                                     | 0   | 24  |
| Adults (18-70 years)  | 109                                   | 18  | 221   |
| Age continuous<br>Units: years  |                                       |   |   |
| arithmetic mean   | 38.6                                  | 41.6  | 37.1  |
| standard deviation  | ± 12.08                               | ± 10.48                                     | ± 13.85                                     |
| Gender categorical<br>Units: Subjects   |                                       |   |   |
| Female  | 67                                    | 9   | 128   |
| Male  | 49                                    | 9   | 117   |
| Race<br>Units: Subjects   |                                       |   |   |
| White   | 116                                   | 18  | 244   |
| Other   | 0                                     | 0   | 1   |
| Asthmatic reaction to birch pollen in the past<br>Units: Subjects                       |                                       |   |   |
| Yes   |                                       |   | 65  |
| No  |                                       |   | 180   |
| Asthmatic status at baseline<br>Units: Subjects   |                                       |   |   |
| Yes   |                                       |   | 84  |
| No  |                                       |   | 161   |
| Patients with nasal/ocular symptoms with at least moderate intensity<br>Units: Subjects |                                       |   |   |
| Yes   |                                       |   | 245   |
| No  |                                       |   | 0   |
| Weight<br>Units: kilogram(s)  |                                       |   |   |
| arithmetic mean   | 73.3                                  | 76.3  | 74.8  |
| standard deviation  | ± 16.53                               | ± 17.84                                     | ± 16.21                                     |
| Height<br>Units: centimeter(s)  |                                       |   |   |
| arithmetic mean   | 171.7                                 | 172.8                                       | 172.4                                       |
| standard deviation  | ± 9.41                                | ± 10.60                                     | ± 10.34                                     |
| BMI<br>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<br>Units: Years          |                                       |   |   |
| arithmetic mean   |                                       |   | 12.8  |
| standard deviation  | ±                                     | ±   | ± 9.60                                      |
| <b>Reporting group values</b>   | Co-sensitized SAF/Depigoid Birch 5000 | Co-sensitized PP Year 3/Depigoid Birch 5000 | Co-sensitized AI 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                             | ±                                  | ±  |
| <b>Reporting group values</b>  | <b>Mono-sensitized FAS/Placebo</b> | <b>Mono-sensitized SAF/Placebo</b> | <b>Mono-sensitized PP Year 3/Placebo</b> |
| Number of subjects   | 79                                 | 85                                 | 66                                       |



|   |                                      |                                      |                              |
|---|--------------------------------------|--------------------------------------|------------------------------|
| Age categorical<br>Units: Subjects  |                                      |                                      |                              |
| Adolescents (12-17 years)   | 3                                    | 3                                    | 2                            |
| Adults (18-70 years)  | 76                                   | 82                                   | 64                           |
| Age continuous<br>Units: years  |                                      |                                      |                              |
| arithmetic mean   | 40.8                                 | 41.0                                 | 40.6                         |
| standard deviation  | ± 12.99                              | ± 12.84                              | ± 12.67                      |
| Gender categorical<br>Units: Subjects   |                                      |                                      |                              |
| Female  | 45                                   | 48                                   | 37                           |
| Male  | 34                                   | 37                                   | 29                           |
| Race<br>Units: Subjects   |                                      |                                      |                              |
| White   | 78                                   | 84                                   | 65                           |
| Other   | 1                                    | 1                                    | 1                            |
| Asthmatic reaction to birch pollen in the past<br>Units: Subjects                       |                                      |                                      |                              |
| Yes   | 27                                   | 28                                   |                              |
| No  | 52                                   | 57                                   |                              |
| Asthmatic status at baseline<br>Units: Subjects   |                                      |                                      |                              |
| Yes   | 30                                   | 31                                   |                              |
| No  | 49                                   | 54                                   |                              |
| Patients with nasal/ocular symptoms with at least moderate intensity<br>Units: Subjects |                                      |                                      |                              |
| Yes   | 79                                   | 85                                   |                              |
| No  | 0                                    | 0                                    |                              |
| Weight<br>Units: kilogram(s)  |                                      |                                      |                              |
| arithmetic mean   | 72.7                                 | 73.1                                 | 71.6                         |
| standard deviation  | ± 13.75                              | ± 13.99                              | ± 13.24                      |
| Height<br>Units: centimeter(s)  |                                      |                                      |                              |
| arithmetic mean   | 169.2                                | 169.2                                | 168.8                        |
| standard deviation  | ± 8.80                               | ± 8.75                               | ± 8.86                       |
| BMI<br>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<br>Units: Years          |                                      |                                      |                              |
| arithmetic mean   | 10.7                                 | 10.8                                 |                              |
| standard deviation  | ± 7.58                               | ± 8.02                               | ±                            |
| <b>Reporting group values</b>   | Mono-sensitized PP<br>Year 5/Placebo | Mono-sensitized AI<br>PK set/Placebo | Co-sensitized<br>FAS/Placebo |
| Number of subjects  | 63                                   | 5                                    | 123                          |

|   |                           |                                 |                                 |
|---|---------------------------|---------------------------------|---------------------------------|
| Age categorical<br>Units: Subjects  |                           |                                 |                                 |
| Adolescents (12-17 years)   | 2                         | 0                               | 11                              |
| Adults (18-70 years)  | 61                        | 5                               | 112                             |
| Age continuous<br>Units: years  |                           |                                 |                                 |
| arithmetic mean   | 40.9                      | 48.8                            | 35.6                            |
| standard deviation  | ± 12.76                   | ± 10.66                         | ± 13.06                         |
| Gender categorical<br>Units: Subjects   |                           |                                 |                                 |
| Female  | 34                        | 3                               | 68                              |
| Male  | 29                        | 2                               | 55                              |
| Race<br>Units: Subjects   |                           |                                 |                                 |
| White   | 62                        | 5                               | 122                             |
| Other   | 1                         | 0                               | 1                               |
| Asthmatic reaction to birch pollen in the past<br>Units: Subjects                       |                           |                                 |                                 |
| Yes   |                           |                                 | 36                              |
| No  |                           |                                 | 87                              |
| Asthmatic status at baseline<br>Units: Subjects   |                           |                                 |                                 |
| Yes   |                           |                                 | 44                              |
| No  |                           |                                 | 79                              |
| Patients with nasal/ocular symptoms with at least moderate intensity<br>Units: Subjects |                           |                                 |                                 |
| Yes   |                           |                                 | 123                             |
| No  |                           |                                 | 0                               |
| Weight<br>Units: kilogram(s)  |                           |                                 |                                 |
| arithmetic mean   | 71.7                      | 75.0                            | 73.0                            |
| standard deviation  | ± 13.54                   | ± 11.66                         | ± 15.97                         |
| Height<br>Units: centimeter(s)  |                           |                                 |                                 |
| arithmetic mean   | 168.9                     | 167.4                           | 171.5                           |
| standard deviation  | ± 9.05                    | ± 10.81                         | ± 9.85                          |
| BMI<br>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<br>Units: Years          |                           |                                 |                                 |
| arithmetic mean   |                           |                                 | 13.7                            |
| standard deviation  | ±                         | ±                               | ± 10.64                         |
| <b>Reporting group values</b>   | 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  | ±   | ±       |
| <b>Reporting group values</b>  | 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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 (AI 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)<sub>3</sub> 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 AI 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 (AI 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)<sub>3</sub> 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:<br>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:<br>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 AI PK set/Placebo                |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>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 (AI PK) set/Placebo contained randomized mono-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH) <sub>3</sub> plasma and/or urine measurements.  |  |
| Subject analysis set title   | Co-sensitized FAS/Placebo                        |
| Subject analysis set type  | Full analysis                                    |
| Subject analysis set description:<br>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:<br>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:<br>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 AI PK set/Placebo                  |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Co-sensitized patients were those who were with co-allergies through a positive skin prick test (SPT) at screening. The Co-sensitized Aluminium Pharmacokinetic (AI PK) set/Placebo contained all randomized co-sensitized patients who received placebo and enrolled in the PK sub-study with post-baseline Al(OH) <sub>3</sub> plasma and/or urine measurements.  |  |
| Subject analysis set title   | Mono- and Co-sensitized AI PK set/Depigoid Birch |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>The Mono- and Co-sensitized Aluminium Pharmacokinetic (AI 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) <sub>3</sub> plasma and/or urine measurements.  |  |
| Subject analysis set title   | Mono- and Co-sensitized AI 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)<sub>3</sub> 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 <sup>[1]</sup>                      | 235 <sup>[2]</sup>                    | 77 <sup>[3]</sup>           | 116 <sup>[4]</sup>        |
| 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 <sup>[5]</sup>       |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[6]</sup>  |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[7]</sup>       |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[8]</sup>  |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[9]</sup>       |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[10]</sup>                                       |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[11]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[12]</sup>                                       |
| 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 <sup>[13]</sup>                     | 235 <sup>[14]</sup>                   | 77 <sup>[15]</sup>          | 116 <sup>[16]</sup>       |
| 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 <sup>[17]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 2)                    |
| Statistical analysis description:<br>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 <sup>[18]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 3)                    |
| Statistical analysis description:<br>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 <sup>[19]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 4)                    |
| Statistical analysis description:<br>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 <sup>[20]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 5)                    |
| Statistical analysis description:<br>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 <sup>[21]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Co-sensitized Year 1)      |
| Statistical analysis description:<br>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 <sup>[22]</sup>      |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[23]</sup>                                       |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[24]</sup>      |
| 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 <sup>[25]</sup>                     | 235 <sup>[26]</sup>                   | 77 <sup>[27]</sup>          | 116 <sup>[28]</sup>       |
| 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:<br>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 <sup>[29]</sup>   |
| 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:<br>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 <sup>[30]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 3)                    |
| Statistical analysis description:<br>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 <sup>[31]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 4)                    |
| Statistical analysis description:<br>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 <sup>[32]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 5)                    |
| Statistical analysis description:<br>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 <sup>[33]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Co-sensitized Year 1)                  |
| Statistical analysis description:<br>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 <sup>[34]</sup>                                       |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Co-sensitized Year 2)      |
| Statistical analysis description:<br>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 <sup>[35]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[36]</sup>                                       |
| 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 <sup>[37]</sup>                     | 235 <sup>[38]</sup>                   | 77 <sup>[39]</sup>          | 116 <sup>[40]</sup>       |
| 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 <sup>[41]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 2)                    |
| Statistical analysis description:<br>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 <sup>[42]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 3)                    |
| Statistical analysis description:<br>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 <sup>[43]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 4)        |
| Statistical analysis description:<br>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 <sup>[44]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[45]</sup>   |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[46]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[47]</sup>                                       |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[48]</sup>      |
| 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 <sup>[49]</sup>                     | 235 <sup>[50]</sup>                   | 77 <sup>[51]</sup>          | 116 <sup>[52]</sup>       |
| 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 <sup>[53]</sup>   |
| 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 <sup>[54]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 3)                    |
| Statistical analysis description:<br>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 <sup>[55]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 4)                    |
| Statistical analysis description:<br>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 <sup>[56]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Mono-sensitized Year 5)                    |
| Statistical analysis description:<br>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 <sup>[57]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Co-sensitized Year 1)                  |
| Statistical analysis description:<br>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 <sup>[58]</sup>                                       |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo(Co-sensitized Year 2)      |
| Statistical analysis description:<br>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 <sup>[59]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[60]</sup>                                       |
| 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 <sup>[61]</sup>                      | 87 <sup>[62]</sup>                    | 33 <sup>[63]</sup>          | 46 <sup>[64]</sup>        |
| 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 <sup>[65]</sup>   |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Depigoid Birch vs. placebo(Mono-sensitized Year 2)                    |
| Statistical analysis description:<br>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 <sup>[66]</sup>   |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Depigoid Birch vs. placebo(Mono-sensitized Year 3)                    |
| Statistical analysis description:<br>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 <sup>[67]</sup>   |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Depigoid Birch vs. placebo(Mono-sensitized Year 4)        |
| Statistical analysis description:<br>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 <sup>[68]</sup>      |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | 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 <sup>[69]</sup>   |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[70]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[71]</sup>                                       |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[72]</sup>      |
| 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  $\leq 2$  and no RM. Hell days were defined as days with a SS  $\geq 10$  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 <sup>[73]</sup>                     | 235 <sup>[74]</sup>                   | 77 <sup>[75]</sup>          | 116 <sup>[76]</sup>       |
| Units: days                          |   |                                       |                             |                           |
| arithmetic mean (standard deviation) |   |                                       |                             |                           |
| Year 1 - Well days                   | 4.24 ( $\pm$ 6.866)                     | 3.35 ( $\pm$ 5.529)                   | 3.65 ( $\pm$ 6.458)         | 4.68 ( $\pm$ 6.720)       |
| Year 1 - Hell days                   | 3.29 ( $\pm$ 5.097)                     | 4.06 ( $\pm$ 5.646)                   | 4.61 ( $\pm$ 6.090)         | 4.03 ( $\pm$ 5.826)       |
| Year 2 - Well days                   | 4.61 ( $\pm$ 6.989)                     | 4.60 ( $\pm$ 6.770)                   | 3.83 ( $\pm$ 6.616)         | 5.95 ( $\pm$ 8.345)       |
| Year 2 - Hell days                   | 3.56 ( $\pm$ 5.925)                     | 3.86 ( $\pm$ 5.615)                   | 5.25 ( $\pm$ 6.507)         | 3.86 ( $\pm$ 5.891)       |
| Year 3 - Well days                   | 5.64 ( $\pm$ 7.866)                     | 5.17 ( $\pm$ 6.856)                   | 3.71 ( $\pm$ 6.952)         | 5.40 ( $\pm$ 7.750)       |
| Year 3 - Hell days                   | 2.42 ( $\pm$ 4.818)                     | 3.01 ( $\pm$ 5.027)                   | 4.86 ( $\pm$ 6.442)         | 3.16 ( $\pm$ 5.395)       |
| Year 4 - Well days                   | 9.64 ( $\pm$ 11.363)                    | 0 ( $\pm$ 0)                          | 7.10 ( $\pm$ 10.140)        | 0 ( $\pm$ 0)              |
| Year 4 - Hell days                   | 2.29 ( $\pm$ 4.998)                     | 0 ( $\pm$ 0)                          | 4.25 ( $\pm$ 7.383)         | 0 ( $\pm$ 0)              |
| Year 5 - Well days                   | 7.00 ( $\pm$ 8.869)                     | 0 ( $\pm$ 0)                          | 5.98 ( $\pm$ 9.508)         | 0 ( $\pm$ 0)              |
| Year 5 - Hell days                   | 2.44 ( $\pm$ 4.445)                     | 0 ( $\pm$ 0)                          | 4.43 ( $\pm$ 6.674)         | 0 ( $\pm$ 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[77]</sup>   |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[78]</sup>   |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[79]</sup>   |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[80]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo (MO Year 3)/Well days                      |
| Statistical analysis description:<br>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 <sup>[81]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo (MO Year 3)/Hell days                      |
| Statistical analysis description:<br>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 <sup>[82]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo (MO Year 4)/Well days                      |
| Statistical analysis description:<br>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 <sup>[83]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo (MO Year 4)/Hell days                      |
| Statistical analysis description:<br>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 <sup>[84]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Depigoid Birch vs. placebo (MO Year 5)/Well days          |
| Statistical analysis description:<br>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 <sup>[85]</sup>      |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[86]</sup>   |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[87]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[88]</sup>                                       |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[89]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[90]</sup>                                       |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[91]</sup>      |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[92]</sup>                                       |
| 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 <sup>[93]</sup>                     | 150 <sup>[94]</sup>                   | 56 <sup>[95]</sup>          | 63 <sup>[96]</sup>        |
| 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 <sup>[97]</sup>                      | 73 <sup>[98]</sup>                    | 18 <sup>[99]</sup>          | 34 <sup>[100]</sup>       |
| 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 <sup>[101]</sup>                     | 82 <sup>[102]</sup>                   | 22 <sup>[103]</sup>         | 39 <sup>[104]</sup>       |
| 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):

**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**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[105]</sup>  |
| 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) |
|--|--|

|   |   |
|---|---|
| <b>Statistical analysis title</b>       |   |
| 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 <sup>[106]</sup>  |
| 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 <sup>[107]</sup>                    | 234                                   | 74 <sup>[108]</sup>         | 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 <sup>[109]</sup>                    | 234                                   | 74 <sup>[110]</sup>         | 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



## 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)<sub>3</sub>, 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 <sup>[111]</sup>                              | 15 <sup>[112]</sup>                       |  |  |
| 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: AI PK - Plasma Concentration/Change from baseline

|                 |   |
|-----------------|---|
| End point title | AI 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 AI 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 AI PK set/Depigoid Birch | Mono- and Co-sensitized AI PK set/Placebo |  |  |
|--|--|---|--|--|
| Subject group type                     | Subject analysis set                             | Subject analysis set                      |  |  |
| Number of subjects analysed            | 29 <sup>[113]</sup>                              | 15 <sup>[114]</sup>                       |  |  |
| 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)<sub>3</sub>, 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 <sup>[115]</sup>                              | 15 <sup>[116]</sup>                       |  |  |
| 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 AI PK set/Depigoid Birch | Mono- and Co-sensitized AI PK set/Placebo |  |  |
|--|--|---|--|--|
| Subject group type                     | Subject analysis set                             | Subject analysis set                      |  |  |
| Number of subjects analysed            | 26 <sup>[117]</sup>                              | 15 <sup>[118]</sup>                       |  |  |
| 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: AI PK - Plasma Concentration/Cmax

|  |                                   |
|--|-----------------------------------|
| End point title  | AI 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 WinNonlin™ 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 AI 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 AI PK set/Depigoid Birch | Mono- and Co-sensitized AI PK set/Placebo |  |  |
|--|--|---|--|--|
| Subject group type                     | Subject analysis set                             | Subject analysis set                      |  |  |
| Number of subjects analysed            | 29 <sup>[119]</sup>                              | 16 <sup>[120]</sup>                       |  |  |
| 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: AI PK - Plasma Concentration/Tmax

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | AI 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 WinNonlin™ 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 AI 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 AI PK set/Depigoid Birch | Mono- and Co-sensitized AI PK set/Placebo |  |  |
|--|--|---|--|--|
| Subject group type                     | Subject analysis set                             | Subject analysis set                      |  |  |
| Number of subjects analysed            | 29 <sup>[121]</sup>                              | 16 <sup>[122]</sup>                       |  |  |
| 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: AI PK - Plasma Concentration/AUC[0-8h]

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

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**End point description:**

PK parameters (C<sub>max</sub>, T<sub>max</sub>, AUC[0-8h]) were derived by non-compartmental analysis at V1-2 and V1-10 using Phoenix WinNonlin™ 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 AI PK set.

---

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

---

**End point timeframe:**

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

---

| <b>End point values</b>                | Mono- and Co-sensitized AI PK set/Depigoid Birch | Mono- and Co-sensitized AI PK set/Placebo |  |  |
|--|--|---|--|--|
| Subject group type                     | Subject analysis set                             | Subject analysis set                      |  |  |
| Number of subjects analysed            | 9 <sup>[123]</sup>                               | 7 <sup>[124]</sup>                        |  |  |
| 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

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**Statistical analyses**

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No statistical analyses for this end point

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## Adverse events

### 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           |
| <b>Diverticulitis</b>                           |                 |                |                 |
| 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           |
| <b>Infectious mononucleosis</b>                 |                 |                |                 |
| 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           |
| <b>Pneumonia</b>                                |                 |                |                 |
| 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           |
| <b>Tonsillitis</b>                              |                 |                |                 |
| 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           |
| <b>Urinary tract infection</b>                  |                 |                |                 |
| 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           |
| <b>Wound infection</b>                          |                 |                |                 |
| 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           |

| <b>Serious adverse events</b>                     | 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 %

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

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



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

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

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

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

|  |                        |                      |                        |
|--|------------------------|----------------------|------------------------|
| Hypoacusis<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 260 (0.00%)<br>0   | 2 / 130 (1.54%)<br>2 | 2 / 390 (0.51%)<br>2   |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)  | 1 / 260 (0.38%)<br>1   | 1 / 130 (0.77%)<br>2 | 2 / 390 (0.51%)<br>3   |
| Eye disorders<br>Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all)       | 19 / 260 (7.31%)<br>19 | 6 / 130 (4.62%)<br>6 | 25 / 390 (6.41%)<br>25 |
| Eye pruritus<br>subjects affected / exposed<br>occurrences (all)                                   | 12 / 260 (4.62%)<br>21 | 4 / 130 (3.08%)<br>7 | 16 / 390 (4.10%)<br>28 |
| Gastrointestinal disorders<br>Dyspepsia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 260 (0.38%)<br>1   | 0 / 130 (0.00%)<br>0 | 1 / 390 (0.26%)<br>1   |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)                                      | 4 / 260 (1.54%)<br>4   | 4 / 130 (3.08%)<br>4 | 8 / 390 (2.05%)<br>8   |
| Gastroesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                | 5 / 260 (1.92%)<br>5   | 2 / 130 (1.54%)<br>2 | 7 / 390 (1.79%)<br>7   |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all) | 1 / 260 (0.38%)<br>1   | 4 / 130 (3.08%)<br>4 | 5 / 390 (1.28%)<br>5   |
| Eczema<br>subjects affected / exposed<br>occurrences (all)   | 14 / 260 (5.38%)<br>16 | 1 / 130 (0.77%)<br>1 | 15 / 390 (3.85%)<br>17 |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)                                      | 7 / 260 (2.69%)<br>7   | 2 / 130 (1.54%)<br>2 | 9 / 390 (2.31%)<br>9   |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)          | 2 / 260 (0.77%)<br>2   | 1 / 130 (0.77%)<br>1 | 3 / 390 (0.77%)<br>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 | <p>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:</p> <ol style="list-style-type: none"><li>1. Modification of a few inclusion/exclusion criteria for precise formulation and thereby enhanced patient's safety.</li><li>2. Further clarifications and/or modifications of some study procedures, including:<ol style="list-style-type: none"><li>a. Added requirement for venous access prior to administration of IMP in the rush build-up phase</li><li>b. Adaptations in the escalation scheme for RM</li><li>c. Added instructions to investigators for recording data in eCRF</li><li>d. Added assessments of patients' asthma status, vitamin D in blood, SPT at EoS</li><li>e. Modified definitions of AE causality categories</li><li>f. Modifications in the schedule of PK blood sampling</li><li>g. Added definition for futility analysis population</li><li>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)</li></ol></li></ol> |
| 30 November 2012  | <p>This global amendment No. 2 was implemented in the protocol at the request of the sponsor. The main changes include:</p> <ol style="list-style-type: none"><li>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).</li><li>2. Extension of the SCR period (from up to 4 weeks to up to 8 weeks).</li><li>3. Added clarifications of inclusion criteria No. 9 and 10, and modification of exclusion criterion No. 20 regarding prior use of psychoactive drugs</li><li>4. Further specifications on mid-season visit scheduling with respect to birch pollen season</li><li>5. Clarifications on the use of permitted RMs and procedures for recording information about RMs</li><li>6. Minor modification to type of psychoactive drugs considered prohibited concomitant medication.</li><li>7. The PK sub-study was not any longer specified to German sites only.</li><li>8. The statistical analysis for futility was further specified.</li></ol>  |
| 11 July 2013      | <p>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:</p> <ol style="list-style-type: none"><li>1. Adding the number of screened patients needed to attain the required number of randomized patients for statistical analyses.</li><li>2. Further specifications/modifications of two exclusion criteria (No. 10 - SCORAD cut off was increased from 30 to 40; No. 19 - "parenthesis" was added)</li><li>3. Correction of a typo in the escalation scheme for inhaled corticosteroids</li><li>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</li><li>5. Adding clarifications for handling of AdoIRQLQ</li></ol>   |

|                  |  |
|------------------|--|
| 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:<br>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.<br>2. Cancellation of the planned 3rd- year futility analysis<br>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<br>4. Immunoblotting analysis of Alnus and Corylus was added for patients who had blood samples still available on storage in the central laboratory<br>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:<br>1. Scheduling of a post-study visit for all co-sensitized patients that had to be withdrawn from the study (requested by the PEI)<br>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: