# Clinical trial results:
# A randomized, double-blind, placebo-controlled (DBPC), parallel group study to assess the clinical efficacy and safety of SUBLIVAC FIX Birch immunotherapy in patients suffering from allergic rhinitis/rhinoconjunctivitis caused by birch pollen.

## Summary

| | |
|---|---|
| EudraCT number | 2013-005550-30 |
| Trial protocol | CZ DE SK BE PL |
| Global end of trial date | 01 February 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 17 August 2017 |
| First version publication date | 17 August 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | SB/0042 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | HAL Allergy |
| Sponsor organisation address | J.H. Oortweg 15-17, Leiden, Netherlands, NL-2333 CH |
| Public contact | Head Department of Clinical Development & Pharmacovigilance, HAL Allergy, + 31 881959000, pjdkam@hal-allergy.com |
| Scientific contact | Head Department of Clinical Development & Pharmacovigilance, HAL Allergy, + 31 881959000, pjdkam@hal-allergy.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 23 March 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 February 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 February 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess clinical efficacy of sublingual immunotherapy with SUBLIVAC FIX Birch (40.000 AUN/ml), compared to placebo, in patients suffering from birch pollen induced rhinitis/rhinoconjunctivitis, measured by a combined rhinoconjunctivitis symptoms score and medication score during the birch pollen season.

Protection of trial subjects:

The trial is performed in accordance with GCP and with all applicable governmental regulations. Independent approval for the study conduct was obtained from the IECs. Informed consent was obtained from each subject participating in the trial after explanation of the aims, design, methods, benefits and potential hazards of the trial before any trial-specific procedures were performed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 September 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 158 |
| Country: Number of subjects enrolled | Slovakia: 42 |
| Country: Number of subjects enrolled | Belgium: 50 |
| Country: Number of subjects enrolled | Czech Republic: 83 |
| Country: Number of subjects enrolled | Germany: 73 |
| Worldwide total number of subjects | 406 |
| EEA total number of subjects | 406 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |

| | |
|---|---|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 404 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The actual recruitment period was from September until end October 2014. Patients fulfilling all the inclusion criteria and none of the exclusion criteria have been recruited at outpatient clinics, private practices or site management organization/research clinics from regular patient visits, database screening and advertisement.

### Pre-assignment

Screening details:

501 patients were screened, 95 were not randomized. The three main reasons for screen failure were the absence of a sufficiently high serum specific anti-birch IgE response (n=46), a positive SPT to allergens other than birch pollen (may aggravate clinical symptoms during birch pollen season (n=30)) and a negative SPT for birch allergen (n=8).

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | SUBLIVAC Placebo |

Arm description:

Subjects treated with Placebo during the double blind study period.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Sublingual use |

Dosage and administration details:

Start with 1 drop daily of SUBLIVAC Placebo (0 AUN/mL) and increase by 1 drop daily, until the maintenance dose of 5 drops is reached.
Mode of administration: Sublingual administration.

| | |
|---|---|
| **Arm title** | SUBLIVAC FIX Birch |

Arm description:

Subjects treated with SUBLIVAC FIX during the double blind study period.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | SUBLIVAC FIX Birch |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Sublingual use |

Dosage and administration details:

Start with 1 drop daily of SUBLIVAC FIX Birch (40,000 AUN/ml) and increase by 1 drop daily, until the maintenance dose of 5 drops is reached.
Mode of administration: Sublingual administration.

| Number of subjects in period 1 | SUBLIVAC Placebo | SUBLIVAC FIX Birch |
|---|---|---|
| Started | 198 | 208 |
| Completed | 186 | 188 |
| Not completed | 12 | 20 |
| Consent withdrawn by subject | 3 | 4 |
| Physician decision | 1 | - |
| Adverse event, non-fatal | 5 | 10 |
| Other | - | 2 |
| Protocol violation, <75% treatment compliance | 1 | - |
| Lost to follow-up | 2 | 2 |
| Not able to reach maintenance dose within 14 days | - | 2 |

## Period 2

| | |
|---|---|
| Period 2 title | open-label extension period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | SUBLIVAC Placebo origin |

Arm description:

Subjects participating in the safety extension period who were previously randomized to the Placebo treatment arm during the double blind study period.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | SUBLIVAC FIX Birch |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Sublingual use |

Dosage and administration details:

Start with 1 drop daily of SUBLIVAC FIX Birch (40,000 AUN/ml) and increase by 1 drop daily, until the maintenance dose of 5 drops is reached.
Mode of administration: Sublingual administration.

| | |
|---|---|
| **Arm title** | SUBLIVAC FIX Birch origin |

Arm description:

Subjects participating in the safety extension period who were previously randomized to the SUBLIVAX FIX active treatment arm during the double blind study period.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Sublivac FIX Birch |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Sublingual use |

Dosage and administration details:

Dose: Start with 1 drop daily of SUBLIVAC FIX Birch and increase by 1 drop daily, until the maintenance dose of 5 drops is reached.
Mode of administration: Sublingual administration.

| **Number of subjects in period 2[1]** | SUBLIVAC Placebo origin | SUBLIVAC FIX Birch origin |
|---|---|---|
| Started | 174 | 169 |
| Completed | 174 | 169 |

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: Subjects who completed the double-blind part of the study and were willing to proceed were included in the open-label safety extension period and treated with SB . In total 343 subjects participated in this extension period; 174 subjects originally randomized to placebo group and 169 subjects originally randomized to the SUBLIVAC FIX Birch group.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | SUBLIVAC Placebo |
| Reporting group description: | |
| Subjects treated with Placebo during the double blind study period. | |
| Reporting group title | SUBLIVAC FIX Birch |
| Reporting group description: | |
| Subjects treated with SUBLIVAC FIX during the double blind study period. | |

| Reporting group values | SUBLIVAC Placebo | SUBLIVAC FIX Birch | Total |
|---|---|---|---|
| Number of subjects | 198 | 208 | 406 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 198 | 206 | 404 |
| From 65-84 years | 0 | 2 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 36 | 37 | |
| full range (min-max) | 18 to 61 | 18 to 65 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 118 | 106 | 224 |
| Male | 80 | 102 | 182 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | ITT SUBLIVAC FIX Birch |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Intention-to-Treat population (ITT): all patients who were randomized and received at least one dose of study medication and for whom at least one post-baseline (post-screening) measurement for the primary efficacy parameter was available. | |
| Subject analysis set title | ITT Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Intention-to-Treat population (ITT): all patients who were randomized and received at least one dose of study medication and for whom at least one post-baseline (post-screening) measurement for the primary efficacy parameter was available. | |

| **Reporting group values** | ITT SUBLIVAC FIX Birch | ITT Placebo | |
|---|---|---|---|
| Number of subjects | 179 | 178 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 177 | 178 | |
| From 65-84 years | 2 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| median | 35 | | |
| full range (min-max) | 18 to 65 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 89 | | |
| Male | 90 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | SUBLIVAC Placebo |
| Reporting group description: | |
| Subjects treated with Placebo during the double blind study period. | |
| Reporting group title | SUBLIVAC FIX Birch |
| Reporting group description: | |
| Subjects treated with SUBLIVAC FIX during the double blind study period. | |
| Reporting group title | SUBLIVAC Placebo origin |
| Reporting group description: | |
| Subjects participating in the safety extension period who were previously randomized to the Placebo treatment arm during the double blind study period. | |
| Reporting group title | SUBLIVAC FIX Birch origin |
| Reporting group description: | |
| Subjects participating in the safety extension period who were previously randomized to the SUBLIVAX FIX active treatment arm during the double blind study period. | |
| Subject analysis set title | ITT SUBLIVAC FIX Birch |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Intention-to-Treat population (ITT): all patients who were randomized and received at least one dose of study medication and for whom at least one post-baseline (post-screening) measurement for the primary efficacy parameter was available. | |
| Subject analysis set title | ITT Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Intention-to-Treat population (ITT): all patients who were randomized and received at least one dose of study medication and for whom at least one post-baseline (post-screening) measurement for the primary efficacy parameter was available. | |

### Primary: Mean CSMS during the pollen season

| | |
|---|---|
| End point title | Mean CSMS during the pollen season |
| End point description: | |
| Difference in mean Combined Symptom Medication Score (CSMS) between the SUBLIVAC FIX and placebo treatment group, assessed during birch pollen season in ITT population. | |
| End point type | Primary |
| End point timeframe: | |
| Assessed during birch pollen season. | |

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: CSMS | | | | |
| least squares mean (standard error) | 1 (± 0.08) | 1.45 (± 0.08) | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of mean CSMS during the pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.66 |
| upper limit | -0.26 |

## Secondary: Mean CSMS during the Peak Pollen Season

| End point title | Mean CSMS during the Peak Pollen Season |
|---|---|
| End point description: | |
| Difference in mean Combined Symptom and Medication Score (CSMS) between the SUBLIVAC FIX and placebo treatment group, assessed during the peak pollen season in the ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed during the peak pollen season. | |

| **End point values** | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: CSMS | | | | |
| least squares mean (standard error) | 0.96 (± 0.1) | 1.56 (± 0.1) | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of mean CSMS during peak pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.6 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.87 |
| upper limit | -0.33 |

## Secondary: Mean Symptom Score during the Pollen Season

| | |
|---|---|
| End point title | Mean Symptom Score during the Pollen Season |

End point description:

Difference In mean Symptom Scores between the SUBLIVAC FIX and placebo treatment group, assessed during the pollen season in the ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Assessed during the pollen season.

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: Symptom score | | | | |
| least squares mean (standard error) | 0.55 (± 0.04) | 0.82 (± 0.04) | | |

### Statistical analyses

| Statistical analysis title | Analysis of mean symptom score: pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | -0.16 |

## Secondary: Mean Medication Score during the Pollen Season

| | |
|---|---|
| End point title | Mean Medication Score during the Pollen Season |

End point description:

Difference in mean Medication Scores between the SUBLIVAC FIX and placebo treatment group, assessed during birch pollen season in the ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Assessed during the pollen season.

| **End point values** | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: Medication score | | | | |
| least squares mean (standard error) | 0.45 (± 0.05) | 0.64 (± 0.05) | | |

**Statistical analyses**

| **Statistical analysis title** | Analysis of mean medication score: pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | -0.06 |

**Secondary: Mean Symptom score during the Peak Pollen Season**

| End point title | Mean Symptom score during the Peak Pollen Season |
|---|---|

End point description:

Difference in mean Symptom Scores between the active vs. placebo treatment group, assessed during the peak pollen season in the ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

Assessed during the peak pollen season.

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: Symptom score | | | | |
| least squares mean (standard error) | 0.55 (± 0.04) | 0.82 (± 0.04) | | |

**Statistical analyses**

| Statistical analysis title | Analysis of mean symptom score: peak pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | -0.23 |

**Secondary: Mean Medication Score during the Peak Pollen Season**

| End point title | Mean Medication Score during the Peak Pollen Season |
|---|---|
| End point description: | |
| Mean Symptom scores during the Peak Pollen Season for ITT population, comparing Placebo and Sublivac Birch group. | |
| End point type | Secondary |
| End point timeframe: | |
| During the peak pollen season | |

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: Medication score | | | | |
| least squares mean (standard error) | 0.43 (± 0.06) | 0.66 (± 0.06) | | |

**Statistical analyses**

| Statistical analysis title | Analysis mean medication score: peak pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.008 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | -0.06 |

## Secondary: RQLQ-S during the pollen season and at EOT/ET visit

| End point title | RQLQ-S during the pollen season and at EOT/ET visit |
|---|---|
| End point description: | |
| Rhinoconjunctivitis Quality of Life Questionnaire Score (RQLQ-S) during the pollen-season and at end of trial (EOT)/ early termination (ET) visit in the ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed at baseline, at pollen-season visit and at end of trial/ early termination visit. | |

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: RQLQ-S | | | | |
| least squares mean (standard error) | | | | |
| during the pollen season | 0.53 (± 0.09) | 1.06 (± 0.09) | | |
| at EOT/ET | 0.41 (± 0.08) | 0.49 (± 0.08) | | |

### Statistical analyses

| Statistical analysis title | Analysis of RQLQ during the pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.53 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.75 |
| upper limit | -0.32 |

| **Statistical analysis title** | Analysis of RQLQ at EOT/ET |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | 0.11 |

| **Secondary: EQ-5D during the pollen season and at EOT/ET** | |
|---|---|
| End point title | EQ-5D during the pollen season and at EOT/ET |
| End point description: | |
| Quality of life Questionnaire Score (EQ-5D) during the pollen season and at the end of trial (EOT)/ early termination (ET) in ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed at baseline and at pollen season visit and at the end of trial (EOT)/ early termination (ET) | |

| **End point values** | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: EQ-5D | | | | |
| least squares mean (standard error) | | | | |
| during the pollen season | -0.59 (± 0.2) | -1.3 (± 0.2) | | |
| at EOT/ET | -0.26 (± 0.17) | -0.13 (± 0.17) | | |

**Statistical analyses**

| **Statistical analysis title** | Analysis of EQ-5D during pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 1.2 |

| **Statistical analysis title** | Analysis of EQ-5D at EOT/ET |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.49 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 0.25 |

| **Secondary: ACQ during the pollen season and EOT/ET visit** | |
|---|---|
| End point title | ACQ during the pollen season and EOT/ET visit |
| End point description: | |
| Asthma Control Questionnaire (ACQ) during the pollen-season (mid-season visit) and at end of the trial (EOT)/ early termination (ET) visit in ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed during the pollen season (mid-season visit) and at end of the trial (EOT)/ early termination (ET) visit | |

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 44 | 38 | | |
| Units: ACQ | | | | |
| least squares mean (standard error) | | | | |
| Mid-season visit | 0.21 (± 0.1) | 0.21 (± 0.11) | | |
| EOT/ET visit | 0.06 (± 0.09) | 0.19 (± 0.09) | | |

## Statistical analyses

| Statistical analysis title | Analysis of ACQ at mid-season visit |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.99 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.29 |

| Statistical analysis title | Analysis of ACQ at EOT/ET visit |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.39 |
| upper limit | 0.13 |

## Secondary: Specific Bet v1 IgE at 12 weeks and at EOT/ET visit

| End point title | Specific Bet v1 IgE at 12 weeks and at EOT/ET visit |
|---|---|

End point description:

Change from baseline in logarithmic scale of Bet v1 (t215) specific IgE at 12 weeks and at end of trial (EOT)/ early termination (ET) visit in ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

After 12 weeks treatment and at end of trial/ early termination.

| **End point values** | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| 12 weeks after treatment start | 2.5 (2.23 to 2.79) | 1.08 (0.97 to 1.21) | | |
| EOT/ ET visit | 1.85 (1.62 to 2.11) | 1.35 (1.18 to 1.54) | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of Specific Bet v1 IgE at 12 weeks |
|---|---|

Statistical analysis description:

Presented in SB/ placebo ratio.

| Comparison groups | ITT Placebo v ITT SUBLIVAC FIX Birch |
|---|---|
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 2.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.99 |
| upper limit | 2.68 |

| **Statistical analysis title** | Analysis of Specific Bet v1 IgE at EOT/ET |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0007 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 1.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 1.64 |

## Secondary: Specific Birch pollen IgE at 12 weeks and EOT/ET visit

| | |
|---|---|
| End point title | Specific Birch pollen IgE at 12 weeks and EOT/ET visit |

End point description:

Change from baseline in logarithmic scale of Birch pollen (t3) specific IgE at 12 weeks and at end of trial (EOT)/ early termination (ET) visit in ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Assessed after 12 weeks of treatment and at end of trial/ early termination.

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| 12 weeks after treatment start | 2.34 (2.11 to 2.59) | 1.02 (0.92 to 1.12) | | |
| EOT/ET visit | 1.31 (1.1 to 1.55) | 0.99 (0.83 to 1.17) | | |

### Statistical analyses

| Statistical analysis title | Analysis of Specific Birch pollen IgE at 12 weeks |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 2.3 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.02 |
| upper limit | 2.62 |

| | |
|---|---|
| **Statistical analysis title** | Analysis of Specific Birch pollen IgE at EOT/ET |
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.05 |
| upper limit | 1.67 |

| **Secondary: Specific Bet v1 IgG at 12 weeks and at EOT/ET visit** | |
|---|---|
| End point title | Specific Bet v1 IgG at 12 weeks and at EOT/ET visit |
| End point description: | |
| Change from baseline in logarithmic scale of Bet v1 (t215) specific IgG at 12 weeks and at end of trial (EOT)/ early termination (ET) visit in ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed after 12 weeks of treatment and at end of trial/early termination visit | |

| **End point values** | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| 12 weeks after treatment start | 1.9 (1.77 to 2.04) | 1.01 (0.94 to 1.08) | | |
| EOT/ET visit | 2.32 (2.11 to 2.54) | 0.94 (0.86 to 1.03) | | |

**Statistical analyses**

| **Statistical analysis title** | Analysis of Specific Bet v1 IgG at 12 weeks |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 1.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.71 |
| upper limit | 2.08 |

| **Statistical analysis title** | Analysis of Specific Bet v1 IgG at EOT/ET |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 2.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.17 |
| upper limit | 2.8 |

| **Secondary: Specific Birch pollen IgG at 12 weeks and EOT/ET visit** | |
|---|---|
| End point title | Specific Birch pollen IgG at 12 weeks and EOT/ET visit |
| End point description: | |
| Change from baseline in logarithmic scale of Birch pollen (t3) specific IgG at 12 weeks and at end of trial (EOT)/ early termination (ET) visit in ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed after 12 weeks of treatment and at end of trial/early termination visit | |

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| 12 weeks after treatment start | 1.93 (1.78 to 2.08) | 1.09 (1.01 to 1.18) | | |
| EOT/ET visit | 2.46 (2.25 to 2.68) | 1.03 (0.94 to 1.12) | | |

**Statistical analyses**

| Statistical analysis title | Analysis of Specific Birch pollen IgG at 12 weeks |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 1.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.6 |
| upper limit | 1.95 |

| Statistical analysis title | Analysis of Specific Birch pollen IgG at EOT/ET |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 2.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.13 |
| upper limit | 2.67 |

**Secondary: Specific Bet v1 IgG4 at 12 weeks and at EOT/ET visit**

| End point title | Specific Bet v1 IgG4 at 12 weeks and at EOT/ET visit |
|---|---|
| End point description:<br>Change from baseline in logarithmic scale of Bet v1 (t215) specific IgG4 at 12 weeks and at end of trial (EOT)/ early termination (ET) visit in ITT population. | |
| End point type | Secondary |
| End point timeframe:<br>Assessed after 12 weeks of treatment and at end of trial/early termination visit | |

| **End point values** | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: ratio | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| 12 weeks after treatment start | 3.73 (3.3 to 4.23) | 1.03 (0.91 to 1.17) | | |
| EOT / ET visit | 6.71 (5.81 to 7.75) | 1.03 (0.89 to 1.19) | | |

**Statistical analyses**

| **Statistical analysis title** | Analysis of Specific Bet v1 IgG4 at 12 weeks |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 3.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.1 |
| upper limit | 4.2 |

| **Statistical analysis title** | Analysis of Specific Bet v1 IgG4 at EOT/ET |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 6.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.42 |
| upper limit | 7.81 |

## Secondary: Specific Birch pollen IgG4 at 12 weeks and EOT/ET visit

| | |
|---|---|
| End point title | Specific Birch pollen IgG4 at 12 weeks and EOT/ET visit |

End point description:

Change from baseline in logarithmic scale of Birch pollen (t3) specific IgG4 at 12 weeks and at end of trial (EOT)/ early termination (ET) visit in ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Assessed after 12 weeks of treatment and at end of study/early termination visit

| End point values | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| 12 weeks after treatment start | 2.73 (2.45 to 3.05) | 0.91 (0.81 to 1.01) | | |
| EOT/ET visit | 4.86 (4.27 to 5.53) | 0.99 (0.87 to 1.13) | | |

### Statistical analyses

| Statistical analysis title | Analysis of Specific Birch pollen IgG4 at 12 weeks |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 3.01 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.63 |
| upper limit | 3.44 |

| **Statistical analysis title** | Analysis of Specific Birch pollen IgG4 at EOT/ET |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | SB / Placebo Geometric mean ratio |
| Point estimate | 4.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.15 |
| upper limit | 5.78 |

| **Secondary: Percentage well days during the pollen season** | |
|---|---|
| End point title | Percentage well days during the pollen season |
| End point description: | |
| Percentage of well days days during the pollen season in ITT population.<br>Well days were defined as days with no rescue medication and a symptom score of no larger than 2.<br>The percentage of well days has been calculated as the number of well days divided by the number of days the patient completed e-diary during the birch pollen season, times 100, respectively. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed during the pollen season. | |

| **End point values** | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: percentage | | | | |
| arithmetic mean (standard error) | 67.53 (± 3.31) | 52.26 (± 3.32) | | |

**Statistical analyses**

| **Statistical analysis title** | Aanalysis of well days during the pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 15.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.64 |
| upper limit | 22.89 |

## Secondary: Percentage severe days during the pollen season

| End point title | Percentage severe days during the pollen season |
|---|---|
| End point description: | |
| Percentage of severe days during the pollen season in ITT population.<br>Severe days were defined as days with a symptom score of 3 in any of the six rhinoconjunctivitis symptoms. The percentage of severe days has been calculated as the number of severe days divided by the number of days the patient completed e-diary during the birch pollen season, times 100, respectively. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed during the pollen season | |

| **End point values** | ITT SUBLIVAC FIX Birch | ITT Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 178 | | |
| Units: precentage | | | | |
| arithmetic mean (standard error) | 4.04 (± 1.32) | 9.47 (± 1.32) | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of severe days during the pollen season |
|---|---|
| Comparison groups | ITT SUBLIVAC FIX Birch v ITT Placebo |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -5.43 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.89 |
| upper limit | -1.97 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event monitoring was done during the double-blind period as well as during the safety-extension period.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo (Double-blind period) |

Reporting group description:

Safety population during the double-blind study period allocated to Placebo treatment.

| | |
|---|---|
| Reporting group title | SUBLIVAC FIX Birch (Double-blind period) |

Reporting group description:

Safety population during the double-blind study period allocated to SUBLIVAC FIX Birch active treatment.

| | |
|---|---|
| Reporting group title | Former Placebo (Open label extension period) |

Reporting group description:

Subjects participating in the safety extension period who were previously randomized to the Placebo treatment arm during the double blind study period.

| | |
|---|---|
| Reporting group title | Former SUBLIVAC FIX Birch (Open label extension period) |

Reporting group description:

Subjects participating in the safety extension period who were previously randomized to the SUBLIVAC FIX treatment arm during the double blind study period.

| Serious adverse events | Placebo (Double-blind period) | SUBLIVAC FIX Birch (Double-blind period) | Former Placebo (Open label extension period) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 198 (2.02%) | 5 / 208 (2.40%) | 2 / 174 (1.15%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 208 (0.48%) | 1 / 174 (0.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 0 / 208 (0.00%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Surgical and medical procedures | | | |
| Tonsillectomy | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 208 (0.00%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 208 (0.48%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Uterine prolapse | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 0 / 208 (0.00%) | 1 / 174 (0.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Menstrual disorder | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 0 / 208 (0.00%) | 0 / 174 (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 | | | |
| Throat oedema | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 208 (0.48%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 208 (0.48%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary sarcoidosis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 0 / 208 (0.00%) | 0 / 174 (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 | | | |
| Atopic dermatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 208 (0.00%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angioedema | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 208 (0.48%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 208 (0.00%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pilonidal sinus | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 208 (0.00%) | 0 / 174 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Former SUBLIVAC FIX Birch (Open label extension period) | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 169 (1.78%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |

| | | | |
|---|---|---|---|
| Tonsillectomy | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Uterine prolapse | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menstrual disorder | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Throat oedema | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary sarcoidosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Atopic dermatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pilonidal sinus | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Placebo (Double-blind period) | SUBLIVAC FIX Birch (Double-blind period) | Former Placebo (Open label extension period) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 112 / 198 (56.57%) | 159 / 208 (76.44%) | 99 / 174 (56.90%) |
| Ear and labyrinth disorders | | | |
| Ear pruritus | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 18 / 208 (8.65%) | 11 / 174 (6.32%) |
| occurrences (all) | 2 | 19 | 11 |
| Gastrointestinal disorders | | | |
| Oedema mouth | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 20 / 208 (9.62%) | 10 / 174 (5.75%) |
| occurrences (all) | 1 | 21 | 10 |
| Oral discomfort | | | |
| subjects affected / exposed | 5 / 198 (2.53%) | 11 / 208 (5.29%) | 11 / 174 (6.32%) |
| occurrences (all) | 5 | 14 | 14 |
| Oral pruritus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 198 (7.07%) | 54 / 208 (25.96%) | 39 / 174 (22.41%) |
| occurrences (all) | 15 | 59 | 44 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 5 / 198 (2.53%) | 13 / 208 (6.25%) | 4 / 174 (2.30%) |
| occurrences (all) | 5 | 15 | 4 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 13 / 208 (6.25%) | 9 / 174 (5.17%) |
| occurrences (all) | 1 | 14 | 11 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 11 / 198 (5.56%) | 7 / 208 (3.37%) | 3 / 174 (1.72%) |
| occurrences (all) | 13 | 8 | 3 |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 13 / 208 (6.25%) | 5 / 174 (2.87%) |
| occurrences (all) | 3 | 13 | 6 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 10 / 198 (5.05%) | 6 / 208 (2.88%) | 2 / 174 (1.15%) |
| occurrences (all) | 12 | 6 | 2 |
| Sneezing | | | |
| subjects affected / exposed | 10 / 198 (5.05%) | 8 / 208 (3.85%) | 2 / 174 (1.15%) |
| occurrences (all) | 11 | 10 | 2 |
| Throat irritation | | | |
| subjects affected / exposed | 6 / 198 (3.03%) | 22 / 208 (10.58%) | 21 / 174 (12.07%) |
| occurrences (all) | 7 | 24 | 23 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 42 / 198 (21.21%) | 36 / 208 (17.31%) | 6 / 174 (3.45%) |
| occurrences (all) | 62 | 53 | 6 |

| **Non-serious adverse events** | Former SUBLIVAC FIX Birch (Open label extension period) | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 169 (32.54%) | | |
| Ear and labyrinth disorders | | | |
| Ear pruritus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences (all) | 3 | | |
| Gastrointestinal disorders | | | |
| Oedema mouth | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences (all) | 1 | | |
| Oral discomfort | | | |
| subjects affected / exposed | 4 / 169 (2.37%) | | |
| occurrences (all) | 4 | | |
| Oral pruritus | | | |
| subjects affected / exposed | 21 / 169 (12.43%) | | |
| occurrences (all) | 24 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences (all) | 1 | | |
| Paraesthesia oral | | | |
| subjects affected / exposed | 3 / 169 (1.78%) | | |
| occurrences (all) | 4 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sneezing | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | | |
| occurrences (all) | 0 | | |
| Throat irritation | | | |
| subjects affected / exposed | 6 / 169 (3.55%) | | |
| occurrences (all) | 8 | | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 6 / 169 (3.55%)<br>7 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 30 January 2015 | In version 4 of the protocol, the study was amended with a safety extension period. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported