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 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 Units: years			
median	35		
full range (min-max)	18 to 65		
Gender categorical 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: 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: 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. Well days were defined as days with no rescue medication and a symptom score of no larger than 2. 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. 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 subjects affected / exposed occurrences (all)	6 / 169 (3.55%) 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