Clinical trial results:
A dose-response evaluation of ALK tree AIT

Summary

EudraCT number	2012-000031-59
Trial protocol	LT FI NO SE NL PL DK
Global end of trial date	05 July 2013

Results information

Result version number	v1 (current)
This version publication date	16 February 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	TT-02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ALK-Abelló
Sponsor organisation address	Bøge Allé 1, Hørsholm, Denmark, 2970
Public contact	Global Clinical Development, ALK-Abelló A/S, +45 45747576, ClinicalTrials@alk.net
Scientific contact	Global Clinical Development, ALK-Abelló A/S, +45 45747576, ClinicalTrials@alk.net

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	05 July 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2013
Global end of trial reached?	Yes
Global end of trial date	05 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify an optimal dose interval with respect to efficacy and safety for the ALK tree AIT in adults and adolescents with moderate to severe birch pollen induced allergic rhinoconjunctivitis.

Protection of trial subjects:

Rescue medication for residual sypmtoms allowed
Ongoing safety surveillance

Background therapy:

Subjects received open-labelled pharmacotherapy for rhinoconjunctivitis symptoms. In case of asthma symptoms, subjects were free to use their regular controller and reliever medications.

Evidence for comparator:

Placebo comparator

Actual start date of recruitment	20 August 2012
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	Norway: 24
Country: Number of subjects enrolled	Netherlands: 60
Country: Number of subjects enrolled	Poland: 100
Country: Number of subjects enrolled	Sweden: 120
Country: Number of subjects enrolled	Denmark: 100
Country: Number of subjects enrolled	Finland: 100
Country: Number of subjects enrolled	Lithuania: 133
Worldwide total number of subjects	637
EEA total number of subjects	637

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	57
Adults (18-64 years)	577
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial included 65 sites in 7 European countries: Denmark, Finland, Lithuania, The Netherlands, Norway, Poland, Sweden. 773 subjects were screened and 637 subjects were randomised.

Pre-assignment

Screening details:

136 subjects were screening failures. Common reasons for screening failures were negative SPT to Betula verrucosa, specific IgE <class 2, or clinically relevant perennial allergic rhinitis or asthma.

Period 1

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

Blinding implementation details:

The placebo tablets were similar to the active IMP in appearance, smell and taste.

The randomisation code was not broken for any subject during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP in this trial was 1 tablet, which should be taken at the same time each day; preferably in the morning. Instructions were to carefully remove the foil from the back of tablet blister card, to take out the tablet with dry fingers and to place the tablet under the tongue. Swallowing was to be avoided for 1 minute and eating and drinking was not allowed within 5 minutes after intake of the tablet.

Arm title	Tree SLIT-tablet 0.5 DU

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tree SLIT-tablet 0.5 DU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP in this trial was 1 tablet, which should be taken at the same time each day; preferably in the morning. Instructions were to carefully remove the foil from the back of tablet blister card, to take out the tablet with dry fingers and to place the tablet under the tongue. Swallowing was to be avoided for 1 minute and eating and drinking was not allowed within 5 minutes after intake of the tablet.

Arm title	Tree SLIT-tablet 1 DU

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tree SLIT-tablet 1 DU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP in this trial was 1 tablet, which should be taken at the same time each day; preferably in the morning. Instructions were to carefully remove the foil from the back of tablet blister card, to take out the tablet with dry fingers and to place the tablet under the tongue. Swallowing was to be avoided for 1 minute and eating and drinking was not allowed within 5 minutes after intake of the tablet.

Arm title	Tree SLIT tablet 2 DU

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tree SLIT-tablet 2 DU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP in this trial was 1 tablet, which should be taken at the same time each day; preferably in the morning. Instructions were to carefully remove the foil from the back of tablet blister card, to take out the tablet with dry fingers and to place the tablet under the tongue. Swallowing was to be avoided for 1 minute and eating and drinking was not allowed within 5 minutes after intake of the tablet.

Arm title	Tree SLIT-tablet 4 DU

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tree SLIT-tablet 4 DU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP in this trial was 1 tablet, which should be taken at the same time each day; preferably in the morning. Instructions were to carefully remove the foil from the back of tablet blister card, to take out the tablet with dry fingers and to place the tablet under the tongue. Swallowing was to be avoided for 1 minute and eating and drinking was not allowed within 5 minutes after intake of the tablet.

Arm title	Tree SLIT-tablet 7 DU

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tree SLIT-tablet 7 DU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP in this trial was 1 tablet, which should be taken at the same time each day; preferably in the morning. Instructions were to carefully remove the foil from the back of tablet blister card, to take out the tablet with dry fingers and to place the tablet under the tongue. Swallowing was to be avoided for 1 minute and eating and drinking was not allowed within 5 minutes after intake of the tablet.

Arm title	Tree SLIT-tablet 12 DU
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tree SLIT-tablet 12 DU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP in this trial was 1 tablet, which should be taken at the same time each day; preferably in the morning. Instructions were to carefully remove the foil from the back of tablet blister card, to take out the tablet with dry fingers and to place the tablet under the tongue. Swallowing was to be avoided for 1 minute and eating and drinking was not allowed within 5 minutes after intake of the tablet.

Number of subjects in period 1	Placebo	Tree SLIT-tablet 0.5 DU	Tree SLIT-tablet 1 DU
Started	88	93	90
Completed	76	83	82
Not completed	12	10	8
Consent withdrawn by subject	5	-	1
Adverse event, non-fatal	3	7	7
Not specified	1	2	-
Lost to follow-up	2	-	-
Lack of efficacy	1	-	-
Protocol deviation	-	1	-

Number of subjects in period 1	Tree SLIT tablet 2 DU	Tree SLIT-tablet 4 DU	Tree SLIT-tablet 7 DU
Started	89	92	88
Completed	83	83	77
Not completed	6	9	11
Consent withdrawn by subject	-	2	1
Adverse event, non-fatal	3	4	9
Not specified	1	1	-
Lost to follow-up	-	-	1
Lack of efficacy	-	-	-
Protocol deviation	2	2	-

Number of subjects in period 1	Tree SLIT-tablet 12 DU
Started	97
Completed	84
Not completed	13
Consent withdrawn by subject	3
Adverse event, non-fatal	7

Not specified	2
Lost to follow-up	-
Lack of efficacy	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 0.5 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 1 DU
Reporting group description: -	
Reporting group title	Tree SLIT tablet 2 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 4 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 7 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 12 DU
Reporting group description: -	

Reporting group values	Placebo	Tree SLIT-tablet 0.5 DU	Tree SLIT-tablet 1 DU
Number of subjects	88	93	90
Age categorical Units: Subjects			
Adolescents (12-17 years)	5	7	8
Adults (18-64 years)	83	86	81
From 65-84 years	0	0	1
Age continuous Units: years			
arithmetic mean	37.6	34.7	35.4
standard deviation	± 12.6	± 13.1	± 13.3
Gender categorical Units: Subjects			
Female	40	44	45
Male	48	49	45

Reporting group values	Tree SLIT tablet 2 DU	Tree SLIT-tablet 4 DU	Tree SLIT-tablet 7 DU
Number of subjects	89	92	88
Age categorical Units: Subjects			
Adolescents (12-17 years)	12	9	9
Adults (18-64 years)	76	83	78
From 65-84 years	1	0	1
Age continuous Units: years			
arithmetic mean	36.2	35.5	36.6
standard deviation	± 13.5	± 13.4	± 13.5
Gender categorical Units: Subjects			
Female	48	46	38

Male	41	46	50

Reporting group values	Tree SLIT-tablet 12 DU	Total	
Number of subjects	97	637	
Age categorical Units: Subjects			
Adolescents (12-17 years)	7	57	
Adults (18-64 years)	90	577	
From 65-84 years	0	3	
Age continuous Units: years			
arithmetic mean	37.5		
standard deviation	± 12.7	-	
Gender categorical Units: Subjects			
Female	48	309	
Male	49	328	

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 0.5 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 1 DU
Reporting group description: -	
Reporting group title	Tree SLIT tablet 2 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 4 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 7 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 12 DU
Reporting group description: -	

Primary: average rhinoconjunctivitis daily symptom score	
End point title	average rhinoconjunctivitis daily symptom score
End point description:	
The average rhinoconjunctivitis daily symptom score during the birch pollen season (calculated for each subject as the sum of the rhinoconjunctivitis individual daily symptom score during the birch pollen season divided by the number of days with diary records in the birch pollen season)	
End point type	Primary
End point timeframe:	
During the birch pollen season (defined by limits of 10 grains/m3)	

End point values	Placebo	Tree SLIT-tablet 0.5 DU	Tree SLIT-tablet 1 DU	Tree SLIT tablet 2 DU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[1]	71[2]	68[3]	71[4]
Units: symptom score units				
arithmetic mean (confidence interval 95%)	3.4 (2.7 to 4.3)	3.1 (2.4 to 3.9)	3.8 (3 to 4.6)	3.5 (2.7 to 4.4)

Notes:

[1] - subjects with no major protocol deviations that might influence the primary endpoint

[2] - subjects with no major protocol deviations that might influence the primary endpoint

[3] - subjects with no major protocol deviations that might influence the primary endpoint

[4] - subjects with no major protocol deviations that might influence the primary endpoint

End point values	Tree SLIT-tablet 4 DU	Tree SLIT-tablet 7 DU	Tree SLIT-tablet 12 DU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65[5]	62[6]	58[7]	
Units: symptom score units				
arithmetic mean (confidence interval	3.4 (2.7 to 4.2)	2.3 (1.7 to 3)	2.9 (2.2 to 3.7)	

95%)

Notes:

[5] - subjects with no major protocol deviations that might influence the primary endpoint

[6] - subjects with no major protocol deviations that might influence the primary endpoint

[7] - subjects with no major protocol deviations that might influence the primary endpoint

Statistical analyses

Statistical analysis title	daily symptom score, 12 DU vs placebo
Comparison groups	Tree SLIT-tablet 12 DU v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.2992
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.6

Notes:

[8] - The primary endpoint, the average rhinoconjunctivitis daily symptom score, was planned to be analysed by fitting appropriate dose response curves. However, as the daily symptom score did not display a dose response relationship (due to modest pollen exposure), none of the planned models for fitting the data were appropriate to execute and the data was instead presented as pairwise comparisons.

Statistical analysis title	daily symptom score, 7 DU vs placebo
Comparison groups	Placebo v Tree SLIT-tablet 7 DU
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0189
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.1

Notes:

[9] - The primary endpoint, the average rhinoconjunctivitis daily symptom score, was planned to be analysed by fitting appropriate dose response curves. However, as the daily symptom score did not display a dose response relationship (due to modest pollen exposure), none of the planned models for fitting the data were appropriate to execute and the data was instead presented as pairwise comparisons.

Statistical analysis title	daily symptom score, 4 DU vs placebo
Comparison groups	Placebo v Tree SLIT-tablet 4 DU

Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.907
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1

Notes:

[10] - The primary endpoint, the average rhinoconjunctivitis daily symptom score, was planned to be analysed by fitting appropriate dose response curves. However, as the daily symptom score did not display a dose response relationship (due to modest pollen exposure), none of the planned models for fitting the data were appropriate to execute and the data was instead presented as pairwise comparisons.

Statistical analysis title	daily symptom score, 2 DU vs placebo
Comparison groups	Placebo v Tree SLIT tablet 2 DU
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.9571
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	1

Notes:

[11] - The primary endpoint, the average rhinoconjunctivitis daily symptom score, was planned to be analysed by fitting appropriate dose response curves. However, as the daily symptom score did not display a dose response relationship (due to modest pollen exposure), none of the planned models for fitting the data were appropriate to execute and the data was instead presented as pairwise comparisons.

Statistical analysis title	daily symptom score, 1 DU vs placebo
Comparison groups	Placebo v Tree SLIT-tablet 1 DU
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.5132
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.7

Notes:

[12] - The primary endpoint, the average rhinoconjunctivitis daily symptom score, was planned to be analysed by fitting appropriate dose response curves. However, as the daily symptom score did not display a dose response relationship (due to modest pollen exposure), none of the planned models for fitting the data were appropriate to execute and the data was instead presented as pairwise comparisons.

Statistical analysis title	daily symptom score, 0.5 DU vs placebo
Comparison groups	Placebo v Tree SLIT-tablet 0.5 DU
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.5277
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.3

Notes:

[13] - The primary endpoint, the average rhinoconjunctivitis daily symptom score, was planned to be analysed by fitting appropriate dose response curves. However, as the daily symptom score did not display a dose response relationship (due to modest pollen exposure), none of the planned models for fitting the data were appropriate to execute and the data was instead presented as pairwise comparisons.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from signing the informed consent form until end of trial

Adverse event reporting additional description:

Pre-planned procedures and pre-existing conditions found as a result of screening procedures were not considered adverse events. Common signs and symptoms of rhinoconjunctivitis should also not be recorded as adverse events unless there was a clear temporal relationship to IMP administration or the event meet the definition of a serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 0.5 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 1 DU
Reporting group description: -	
Reporting group title	Tree SLIT tablet 2 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 4 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 7 DU
Reporting group description: -	
Reporting group title	Tree SLIT-tablet 12 DU

Reporting group description: -

Serious adverse events	Placebo	Tree SLIT-tablet 0.5 DU	Tree SLIT-tablet 1 DU
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	1 / 90 (1.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid adenoma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Foetal growth restriction			
subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 93 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tree SLIT tablet 2	Tree SLIT-tablet 4	Tree SLIT-tablet 7

	DU	DU	DU
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 89 (2.25%)	1 / 92 (1.09%)	0 / 88 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid adenoma			
subjects affected / exposed	0 / 89 (0.00%)	0 / 92 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 89 (0.00%)	0 / 92 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 89 (0.00%)	0 / 92 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Foetal growth restriction			
subjects affected / exposed	1 / 89 (1.12%)	0 / 92 (0.00%)	0 / 88 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 89 (0.00%)	0 / 92 (0.00%)	0 / 88 (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			
Angioedema			
subjects affected / exposed	0 / 89 (0.00%)	0 / 92 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 92 (0.00%)	0 / 88 (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			
Appendicitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 92 (1.09%)	0 / 88 (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

Serious adverse events	Tree SLIT-tablet 12 DU		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 97 (5.15%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid adenoma			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Foetal growth restriction			

subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 97 (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	Tree SLIT-tablet 0.5 DU	Tree SLIT-tablet 1 DU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 88 (80.68%)	85 / 93 (91.40%)	78 / 90 (86.67%)
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 88 (15.91%)	14 / 93 (15.05%)	12 / 90 (13.33%)
occurrences (all)	22	25	19
Gastrointestinal disorders			

Oedema mouth			
subjects affected / exposed	0 / 88 (0.00%)	8 / 93 (8.60%)	14 / 90 (15.56%)
occurrences (all)	0	11	21
Oral pruritus			
subjects affected / exposed	13 / 88 (14.77%)	48 / 93 (51.61%)	46 / 90 (51.11%)
occurrences (all)	16	71	73
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	6 / 88 (6.82%)	21 / 93 (22.58%)	14 / 90 (15.56%)
occurrences (all)	6	27	15
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 88 (20.45%)	17 / 93 (18.28%)	15 / 90 (16.67%)
occurrences (all)	31	27	19

Non-serious adverse events	Tree SLIT tablet 2 DU	Tree SLIT-tablet 4 DU	Tree SLIT-tablet 7 DU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 89 (93.26%)	86 / 92 (93.48%)	82 / 88 (93.18%)
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 89 (14.61%)	14 / 92 (15.22%)	11 / 88 (12.50%)
occurrences (all)	22	16	27
Gastrointestinal disorders			
Oedema mouth			
subjects affected / exposed	12 / 89 (13.48%)	20 / 92 (21.74%)	21 / 88 (23.86%)
occurrences (all)	12	30	31
Oral pruritus			
subjects affected / exposed	47 / 89 (52.81%)	57 / 92 (61.96%)	56 / 88 (63.64%)
occurrences (all)	79	116	75
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	27 / 89 (30.34%)	31 / 92 (33.70%)	28 / 88 (31.82%)
occurrences (all)	34	42	33
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 89 (19.10%)	20 / 92 (21.74%)	12 / 88 (13.64%)
occurrences (all)	23	37	20

Non-serious adverse events	Tree SLIT-tablet 12 DU		
Total subjects affected by non-serious adverse events subjects affected / exposed	89 / 97 (91.75%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 19		
Gastrointestinal disorders Oedema mouth subjects affected / exposed occurrences (all) Oral pruritus subjects affected / exposed occurrences (all)	14 / 97 (14.43%) 29 60 / 97 (61.86%) 104		
Respiratory, thoracic and mediastinal disorders Throat irritation subjects affected / exposed occurrences (all)	28 / 97 (28.87%) 39		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	17 / 97 (17.53%) 23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2012	Before FSFV - minor general corrections and change of inclusion criterion i8.d (relating to breast-feeding) to an exclusion criterion (e24)
06 March 2013	An error in the protocol was corrected regarding the use of other antihistamines than those provided as pharmacotherapy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial was carried out in a pollen season that was unusually low for birch as well as alder and hazel pollen counts. The low pollen exposure is a likely explanation for the inability to identify a dose response for the primary efficacy endpoint.

Notes: