Clinical trial results:
Efficacy and safety of the SQ tree SLIT-tablet in subjects with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch group

Summary

EudraCT number	2015-004821-15
Trial protocol	DK SE CZ FI DE PL FR
Global end of trial date	20 June 2017

Results information

Result version number	v1
This version publication date	05 January 2018
First version publication date	05 January 2018

Trial information

Trial identification

Sponsor protocol code	TT-04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ALK- Abello A/S
Sponsor organisation address	Bøge alle 1, Hørsholm, Denmark, 2970
Public contact	Global pharmacovigilance & clinical development, ALK Abello A/S, +45 45747576, clinicaltrials@alk.net
Scientific contact	Global pharmacovigilance & clinical development, ALK Abello A/S, +45 45747576, clinicaltrials@alk.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001879-PIP01-15
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	01 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2017
Global end of trial reached?	Yes
Global end of trial date	20 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate superiority of the SQ tree SLIT-tablet given once daily compared to placebo in the treatment of allergic rhinoconjunctivitis induced by birch pollen.

Protection of trial subjects:

Safety surveillance
Access to rescue medication

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	15 April 2016
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: 232
Country: Number of subjects enrolled	Sweden: 35
Country: Number of subjects enrolled	Czech Republic: 71
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Finland: 24
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 198
Country: Number of subjects enrolled	Russian Federation: 36
Worldwide total number of subjects	634
EEA total number of subjects	598

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)	60
Adults (18-64 years)	571
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 57 trial sites in EU (Sweden, Finland, Denmark, Poland, Germany, the Czech Republic, France) and Russia
First subject first visit: 15 april 2016
Last subject last visit: 20 June 2017

Pre-assignment

Screening details:

Main selection criteria:
- Adults and adolescents (12-65 years)
- History of moderate to severe allergic rhinitis and or conjunctivitis caused by pollen from the birch homologous group
- Positive SPT and IgE against betula verrucosa

Period 1

Period 1 title	treatment period (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

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	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Subjects were instructed to take 1 tablet every day in the morning

Arm title	SQ tree SLIT-tablet

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SQ tree SLIT-tablet 12 DU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Subjects were instructed to take 1 tablet every day in the morning

Number of subjects in period 1	Placebo	SQ tree SLIT-tablet
Started	314	320
Completed	292	280
Not completed	22	40
Consent withdrawn by subject	4	9
Adverse event, non-fatal	8	26
Pregnancy	3	-
-	4	5
Lost to follow-up	1	-
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	SQ tree SLIT-tablet
Reporting group description: -	

Reporting group values	Placebo	SQ tree SLIT-tablet	Total
Number of subjects	314	320	634
Age categorical Units: Subjects			
Adolescents (12-17 years)	32	28	60
Adults (18-64 years)	281	290	571
From 65-84 years	1	2	3
Gender categorical Units: Subjects			
Female	168	168	336
Male	146	152	298

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set, defined as all randomised subjects	

Reporting group values	Full analysis set		
Number of subjects	634		
Age categorical Units: Subjects			
Adolescents (12-17 years)	60		
Adults (18-64 years)	571		
From 65-84 years	3		
Gender categorical Units: Subjects			
Female	336		
Male	298		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	SQ tree SLIT-tablet
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set, defined as all randomised subjects	

Primary: Average TCS in the birch pollen season (BPS)

End point title	Average TCS in the birch pollen season (BPS)
End point description:	
The primary endpoint of the trial was the average daily allergic rhinoconjunctivitis total combined score (TCS) during the BPS. The TCS is the sum of the rhinoconjunctivitis symptom score (DSS) and mediction score (DMS). For the DSS a total of 6 rhinoconjunctivitis symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty/red/itchy eyes and watery eyes) were measured on a scale from no symptoms (0) to severe symptoms (3) (range 0-12) For the DMS subjects recorded the use of open label rhinitis and conjunctivitis medication as needed for treatment of their rhinitis and/or conjunctivitis symptoms not controlled by the IMP. - Desloradine tablets: score per tablet 6, max daily score 6 (1 tablet) - Olopatadine eye drops: score per dose 1.5 per eye, max daily score 6 (4 doses) - Momethasone nasa spray; score per dose 2, maximum daily score 8 (4 doses) Range 0-20	
End point type	Primary
End point timeframe:	
During the birch pollen season	

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	283		
Units: 0-32				
least squares mean (confidence interval 95%)	7.62 (6.55 to 8.78)	4.61 (3.77 to 5.52)		

Statistical analyses

Statistical analysis title	Analysis of average TCS in the BPS
Statistical analysis description:	
The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on a linear mixed effect (lme) model with treatment as fixed class effect and pollen region as a random class variable.	
Comparison groups	Placebo v SQ tree SLIT-tablet

Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.99
upper limit	4.05

Secondary: Average TCS in the tree pollen season (TPS)

End point title	Average TCS in the tree pollen season (TPS)

End point description:

Average TCS measured in the alder, hazel and birch pollen seasons combined (days in-between seasons excluded)
TCS is a combination of the DSS and DMS (range 0-32)

End point type	Secondary

End point timeframe:

Tree pollen season (TPS)

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	283		
Units: 0-32				
least squares mean (confidence interval 95%)	6.22 (5.35 to 7.16)	3.95 (3.26 to 4.71)		

Statistical analyses

Statistical analysis title	Analysis of average TCS in the TPS

Statistical analysis description:

The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on a linear mixed effect (lme) model with treatment as fixed class effect and pollen region as a random class variable.

Comparison groups	SQ tree SLIT-tablet v Placebo
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.44
upper limit	3.11

Secondary: Average DSS in the BPS

End point title	Average DSS in the BPS

End point description:

The rhiniconjunctivitis daily symptom score (DSS) consisted of 6 symptoms (rynny nose, blocked nose, sneezing, itchy nose, gritty/red/itchy eyes, and watery eyes) scored from no symptoms (0) to severe symptoms (3)
Range 0-12

End point type	Secondary

End point timeframe:

Birch pollen season

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	283		
Units: 0-12				
least squares mean (confidence interval 95%)	3.60 (3.15 to 4.09)	2.28 (1.92 to 2.67)		

Statistical analyses

Statistical analysis title	Analysis of DSS in the BPS

Statistical analysis description:

The response variable in the analysis is: the square root of the average DSS (results were back-transformed to original scale). The analysis is based on a linear mixed effect (lme) model with treatment as fixed class effect and pollen region as a random class variable

Comparison groups	Placebo v SQ tree SLIT-tablet
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.81

Secondary: Average DSS in the TPS

End point title	Average DSS in the TPS

End point description:

The rhinoconjunctivitis daily symptom score (DSS) consists of 6 symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty/red/itchy eyes and watery eyes) scored from no symptoms (0) to severe symptoms (3). Range 0-12

End point type	Secondary

End point timeframe:

Tree pollen season defined as the alder, hazel and birch pollen seasons combined (days in-between seasons excluded)

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	283		
Units: 0-12				
least squares mean (confidence interval 95%)	3.02 (2.66 to 3.40)	2.03 (1.74 to 2.34)		

Statistical analyses

Statistical analysis title	Analysis of DSS in the TPS

Statistical analysis description:

The response variable in the analysis is: the square root of the average DSS (results were back-transformed to original scale). The analysis is based on a linear mixed effect (lme) model with treatment as fixed class effect and pollen region as a random class variable

Comparison groups	Placebo v SQ tree SLIT-tablet
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.38

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from consent to 7 days after end-of-trial or discontinuation.
Only treatment-emergent AEs are presented (from first IMP intake to 7 days 7 days after end-of-trial or discontinuation)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	SQ tree SLIT-tablet 12 DU
Reporting group description: -	

Serious adverse events	Placebo	SQ tree SLIT-tablet 12 DU	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 314 (1.91%)	4 / 320 (1.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accidental exposure to product by child	Additional description: child of subject ingested IMP. Subjects did not experience any AEs related to the ingestion		
subjects affected / exposed	1 / 314 (0.32%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 314 (0.32%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	SQ tree SLIT-tablet 12 DU	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	174 / 314 (55.41%)	262 / 320 (81.88%)	
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 314 (0.00%)	21 / 320 (6.56%)	
occurrences (all)	0	25	
Gastrointestinal disorders			
Lip swelling			
subjects affected / exposed	1 / 314 (0.32%)	23 / 320 (7.19%)	
occurrences (all)	2	28	
Mouth swelling			
subjects affected / exposed	2 / 314 (0.64%)	33 / 320 (10.31%)	
occurrences (all)	2	38	
Oral pruritus			
subjects affected / exposed	15 / 314 (4.78%)	116 / 320 (36.25%)	
occurrences (all)	16	161	
Paraesthesia oral			
subjects affected / exposed	12 / 314 (3.82%)	34 / 320 (10.63%)	
occurrences (all)	12	42	
Swollen tongue			
subjects affected / exposed	0 / 314 (0.00%)	19 / 320 (5.94%)	
occurrences (all)	0	19	
Tongue pruritus			
subjects affected / exposed	6 / 314 (1.91%)	33 / 320 (10.31%)	
occurrences (all)	7	35	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 314 (1.59%)	24 / 320 (7.50%)	
occurrences (all)	6	33	
Pharyngeal oedema			
subjects affected / exposed	1 / 314 (0.32%)	25 / 320 (7.81%)	
occurrences (all)	1	32	
Throat irritation			
subjects affected / exposed	8 / 314 (2.55%)	74 / 320 (23.13%)	
occurrences (all)	8	96	

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	58 / 314 (18.47%) 84	47 / 320 (14.69%) 59	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported