Clinical trial results:
Efficacy and safety of the SQ tree sublingual immunotherapy tablet in children and adolescents (5 through 17 years of age) with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch and trees belonging to the birch homologous group.
P/0030/2018; P/0434/2020

Summary

EudraCT number	2020-004372-17
Trial protocol	DE LT HU SK PL AT DK BE NL
Global end of trial date	31 July 2023

Results information

Result version number	v1 (current)
This version publication date	15 February 2024
First version publication date	15 February 2024

Trial information

Trial identification

Sponsor protocol code	TT-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04878354
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ALK-Abelló A/S
Sponsor organisation address	Bøge Allé 6-8, Hørsholm, Denmark, 2970
Public contact	Head of Clinical Operations Strategy, ALK-Abelló A/S, clinicaltrials@alk.net
Scientific contact	Head of Clinical Operations Strategy, ALK-Abelló A/S, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2023
Global end of trial reached?	Yes
Global end of trial date	31 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of the SQ tree sublingual immunotherapy (SLIT)-tablet to placebo in the treatment of moderate to severe allergic rhinitis and/or conjunctivitis (AR/C) induced by pollen from birch and trees belonging to the birch homologous group in children and adolescents (5 through 17 years of age) based on the average allergic rhinoconjunctivitis daily total combined score (TCS*) during the birch pollen season (BPS).
*TCS = daily symptoms score (DSS) + daily medication score (DMS)

Protection of trial subjects:

Safety surveillance.
Access to rescue/reliever medication.

Background therapy:

AR/C rescue medication: Subjects were provided with rescue medication (antihistamine/nasal corticosteroid) to relieve AR/C symptoms. The rescue medication was provided before the start of the tree pollen season and could be used as needed in accordance with the label. The subjects were instructed to start with antihistamine and continue with nasal corticosteroids only if antihistamine could not alleviate the symptoms.

Asthma rescue medication: Prior to start of tree pollen season, subjects with a diagnosis of asthma were provided with short-acting β2-agonist (SABA), which was to be used when necessary and in accordance with the label. Subjects who were taking low or medium daily dose inhaled corticosteriods (ICS) alone or in combination with long-acting β2-agonist (LABA) for asthma management were allowed to continue with the same medications during the trial. Subjects had to be on a stable regimen (daily dose unchanged) for at least 4 weeks before randomisation.

Evidence for comparator: -

Actual start date of recruitment	08 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 446
Country: Number of subjects enrolled	Slovakia: 79
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Germany: 89
Country: Number of subjects enrolled	Hungary: 45
Country: Number of subjects enrolled	Lithuania: 92

Country: Number of subjects enrolled	Canada: 87
Country: Number of subjects enrolled	Russian Federation: 77
Worldwide total number of subjects	952
EEA total number of subjects	788

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)	597
Adolescents (12-17 years)	355
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 80 sites in 11 countries (Austria, Belgium, Canada, Denmark, Germany, Hungary, Lithuania, Netherlands, Poland, Russia and Slovakia).
First subject first visit: 08-Apr-2021
Last subject last visit/contact: 31-Jul-2023

Pre-assignment

Screening details:

*Male or female aged ≥5 to <18 years
*Documented, clinically relevant history of moderate to severe AR/C induced by birch pollen (with or without asthma) despite treatment with symptom-relieving medication
*Positive SPT and IgE against Betula verrucosa
*Presence of at least 1 ARIA quality of life item due to AR/C during the previous BPS

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo

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:

Subjects were instructed that IMP should preferably be taken in the morning and that food and beverages should not be taken for 5 minutes after intake of IMP. The tablet should be placed under the tongue and swallowing should be avoided for approximately 1 minute. When the first dose was administered at site, the subject was under medical supervision for 30 minutes after the tablet intake.

Arm title	SQ tree SLIT-tablet

Arm description:

SQ tree SLIT-tablet

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

Dosage and administration details:

Subjects were instructed that IMP should preferably be taken in the morning and that food and beverages should not be taken for 5 minutes after intake of IMP. The tablet should be placed under the tongue and swallowing should be avoided for approximately 1 minute. When the first dose was administered at site, the subject was under medical supervision for 30 minutes after the tablet intake.

Number of subjects in period 1	Placebo	SQ tree SLIT-tablet
Started	479	473
Completed	458	456
Not completed	21	17
Consent withdrawn by subject	15	13
Reason stated as "other" in CRF	2	-
Adverse event, non-fatal	-	3
Lost to follow-up	4	1

Baseline characteristics

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

Reporting group values	Placebo	SQ tree SLIT-tablet	Total
Number of subjects	479	473	952
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)	300	297	597
Adolescents (12-17 years)	179	176	355
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	194	185	379
Male	285	288	573

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. Subjects were analysed as randomised i.e., according to their randomised assignment of treatment.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set definded as all randomised subjects who received at least one dose of IMP. Subjects were analysed as treated i.e., according to treatment they actually received.	

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	952	952	
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)	597	597	
Adolescents (12-17 years)	355	355	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	379	379	
Male	573	573	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	SQ tree SLIT-tablet
Reporting group description:	
SQ tree SLIT-tablet	
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. Subjects were analysed as randomised i.e., according to their randomised assignment of treatment.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set definded as all randomised subjects who received at least one dose of IMP. Subjects were analysed as treated i.e., according to treatment they actually received.	

Primary: Average total combined score (TCS) during the birch pollen season (BPS)

End point title	Average total combined score (TCS) during the birch pollen season (BPS)
End point description:	
The primary endpoint of the trial was the average total combined rhinoconjunctivitis symptoms and medication score (TCS) during the birch pollen season (BPS). The average TCS evaluates the treatment effect based on reduction in daily rhinoconjunctivitis symptoms and medication use (on a scale of 0-38). Higher scores indicate more severe symptoms and/or more medication use. The primary estimand for the endpoint was the trial product estimand. The trial product estimand assesses the anticipated effect of the SQ tree SLIT-tablet if it is taken as instructed.	
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	479	473		
Units: Adjusted mean				
least squares mean (standard error)	5.88 (± 0.33)	4.60 (± 0.29)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

Multiple imputation was used to impute missing data under the hypothetical strategy. The square root transformed endpoint was analysed in an LME model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for

each treatment group. Back-transformation was used to estimate the absolute difference.

Adjusted p-value.

Comparison groups	Placebo v SQ tree SLIT-tablet
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Linear mixed effect (LME)
Parameter estimate	Absolute difference
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2

Secondary: Average total combined score (TCS) during the tree pollen season (TPS)

End point title	Average total combined score (TCS) during the tree pollen season (TPS)

End point description:

Average total combined score (TCS) measured in the tree pollen season (TPS). TPS includes hazel, alder, birch and oak pollen seasons. The average TCS evaluates the treatment effect based on reduction in daily rhinoconjunctivitis symptoms and medication use (on a scale of 0-38). Higher scores indicate more severe symptoms and/or more medication use.

The primary estimand for the endpoint was the trial product estimand. The trial product estimand assesses the anticipated effect of the SQ tree SLIT-tablet if it is taken as instructed.

End point type	Secondary

End point timeframe:

During the tree pollen season (TPS)

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	479	473		
Units: Adjusted mean				
least squares mean (standard error)	4.51 (± 0.25)	3.66 (± 0.22)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

Multiple imputation was used to impute missing data under the hypothetical strategy. The square root transformed endpoint was analysed in an LME model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.

Adjusted p-value.

Comparison groups	SQ tree SLIT-tablet v Placebo
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Linear mixed effect (LME)
Parameter estimate	Absolute difference
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.35

Secondary: Average daily symptoms score (DSS) during the birch pollen season (BPS)

End point title	Average daily symptoms score (DSS) during the birch pollen season (BPS)

End point description:

Average rhinoconjunctivitis daily symptoms score (DSS) during the birch pollen season (BPS) evaluates the treatment effect based on the reduction in daily rhinoconjunctivitis symptoms (on a scale of 0 to 18). Higher scores indicate more severe symptoms.

The primary estimand for the endpoint was the trial product estimand. The trial product estimand assesses the anticipated effect of the SQ tree SLIT-tablet if it is taken as instructed.

End point type	Secondary

End point timeframe:

During the birch pollen season (BPS)

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	479	473		
Units: Adjusted mean				
least squares mean (standard error)	2.75 (± 0.16)	2.39 (± 0.15)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

Multiple imputation was used to impute missing data under the hypothetical strategy. The square root transformed endpoint was analysed in an LME model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.

Adjusted p-value.

Comparison groups	Placebo v SQ tree SLIT-tablet
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0354
Method	Linear mixed effect (LME)
Parameter estimate	Absolute difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.71

Secondary: Average daily symptoms score (DSS) during the tree pollen season (TPS)

End point title	Average daily symptoms score (DSS) during the tree pollen season (TPS)

End point description:

Average rhinoconjunctivitis daily symptoms score (DSS) during the tree pollen season (TPS) evaluates the treatment effect based on the reduction in daily rhinoconjunctivitis symptoms (on a scale of 0 to 18). TPS includes hazel, alder, birch and oak pollen seasons. Higher scores indicate more severe symptoms.

The primary estimand for the endpoint was the trial product estimand. The trial product estimand assesses the anticipated effect of the SQ tree SLIT-tablet if it is taken as instructed.

End point type	Secondary

End point timeframe:

During the tree pollen season (TPS)

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	479	473		
Units: Adjusted mean				
least squares mean (standard error)	2.28 (± 0.14)	2.04 (± 0.13)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

Multiple imputation was used to impute missing data under the hypothetical strategy. The square root transformed endpoint was analysed in an LME model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.

Adjusted p-value.

Comparison groups	Placebo v SQ tree SLIT-tablet

Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0734
Method	Linear mixed effect
Parameter estimate	Absolute difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.5

Secondary: Average daily medication score (DMS) during the birch pollen season (BPS)

End point title	Average daily medication score (DMS) during the birch pollen season (BPS)

End point description:

Average rhinoconjunctivitis daily medication score (DMS) during the birch pollen season (BPS) evaluates the treatment effect based on the reduction in daily rhinoconjunctivitis medication use (on a scale of 0 to 20). Higher scores indicate more medication use.

The primary estimand for the endpoint was the trial product estimand. The trial product estimand assesses the anticipated effect of the SQ tree SLIT-tablet if it is taken as instructed.

End point type	Secondary

End point timeframe:

During the birch pollen season (BPS)

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	479	473		
Units: Adjusted mean				
least squares mean (standard error)	2.42 (± 0.23)	1.55 (± 0.18)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

Multiple imputation was used to impute missing data under the hypothetical strategy. The square root transformed endpoint was analysed in an LME model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.

Observed p-value.

Comparison groups	Placebo v SQ tree SLIT-tablet

Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effect (LME)
Parameter estimate	Absolute difference
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.28

Secondary: Average daily medication score (DMS) during the tree pollen season (TPS)

End point title	Average daily medication score (DMS) during the tree pollen season (TPS)

End point description:

Average rhinoconjunctivitis daily medication score (DMS) during the tree pollen season (TPS) evaluates the treatment effect based on the reduction in daily rhinoconjunctivitis medication use (on a scale of 0 to 20). TPS includes hazel, alder, birch and oak pollen seasons. Higher scores indicate more medication use.

The primary estimand for the endpoint was the trial product estimand. The trial product estimand assesses the anticipated effect of the SQ tree SLIT-tablet if it is taken as instructed.

End point type	Secondary

End point timeframe:

During the tree pollen season (TPS)

End point values	Placebo	SQ tree SLIT-tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	479	473		
Units: Adjusted mean				
least squares mean (standard error)	1.72 (± 0.16)	1.18 (± 0.13)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

Multiple imputation was used to impute missing data under the hypothetical strategy. The square root transformed endpoint was analysed in an LME model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.

Observed p-value.

Comparison groups	Placebo v SQ tree SLIT-tablet

Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Linear mixed effect (LME)
Parameter estimate	Absolute difference
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.82

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from informed consent to last contact with subject. Only treatment-emergent AEs are presented, i.e. AEs with start date/time on/after time of first IMP administration and no later than 7 days after IMP administration.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	SQ tree SLIT-tablet

Reporting group description:

SQ tree SLIT-tablet

Serious adverse events	Placebo	SQ tree SLIT-tablet	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 479 (1.25%)	5 / 473 (1.06%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 479 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Foot operation			
subjects affected / exposed	0 / 479 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 479 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	0 / 479 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	1 / 479 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 479 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 473 (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	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	194 / 479 (40.50%)	315 / 473 (66.60%)	
Gastrointestinal disorders			
Oral pruritus			
subjects affected / exposed	17 / 479 (3.55%)	114 / 473 (24.10%)	
occurrences (all)	19	136	
Tongue pruritus			
subjects affected / exposed	6 / 479 (1.25%)	60 / 473 (12.68%)	
occurrences (all)	6	76	
Paraesthesia oral			
subjects affected / exposed	8 / 479 (1.67%)	28 / 473 (5.92%)	
occurrences (all)	8	34	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	18 / 479 (3.76%)	112 / 473 (23.68%)	
occurrences (all)	19	140	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	82 / 479 (17.12%)	81 / 473 (17.12%)	
occurrences (all)	124	109	
Upper respiratory tract infection			
subjects affected / exposed	43 / 479 (8.98%)	42 / 473 (8.88%)	
occurrences (all)	55	53	
Pharyngitis			
subjects affected / exposed	21 / 479 (4.38%)	32 / 473 (6.77%)	
occurrences (all)	23	35	
COVID-19			
subjects affected / exposed	43 / 479 (8.98%)	27 / 473 (5.71%)	
occurrences (all)	44	28	
Influenza			

subjects affected / exposed occurrences (all)	25 / 479 (5.22%) 27	17 / 473 (3.59%) 18	

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