Clinical trial results:
A randomised, parallel-group, double-blind, placebo-controlled phase III trial assessing the efficacy and safety of 5-grass mix SLIT-drops in adults with grass pollen-induced rhinoconjunctivitis

Summary

EudraCT number	2020-000455-12
Trial protocol	EE LT LV CZ PL FR
Global end of trial date	26 September 2023

Results information

Result version number	v1 (current)
This version publication date	12 October 2024
First version publication date	12 October 2024

Trial information

Trial identification

Sponsor protocol code	SU-G-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04881461
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	Senior Director, Clinical Data Science, Global Clinical Development, ALK-Abelló A/S, +45 45747576, clinicaltrials@alk.net
Scientific contact	Senior Director, Clinical Data Science, 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	30 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2023
Global end of trial reached?	Yes
Global end of trial date	26 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of 5-grass mix SLIT-drops (sublingual immunotherapy) to placebo in relieving grass rhinoconjunctivitis symptoms and in use of symptom-relief medication during the 2nd Peak Grass Pollen Season (PGPS)

Protection of trial subjects:

Safety surveillance.
Access to rescue/reliever medication.

Background therapy:

Rhinoconjunctivitis rescue medication: Subjects were provided with rescue medication (antihistamine/nasal corticosteroid) to relieve rhinoconjunctivitis symptoms. The rescue medication was provided before the start of the grass 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.

Evidence for comparator: -

Actual start date of recruitment	10 May 2021
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: 233
Country: Number of subjects enrolled	Czechia: 113
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Latvia: 33
Country: Number of subjects enrolled	Lithuania: 51
Worldwide total number of subjects	445
EEA total number of subjects	445

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)	445
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 45 sites in 6 countries (Poland, Czechia, Estonia, France, Latvia and Lithuania).
First subject first visit: 10-May-2021
Last subject last visit/contact: 26-Sep-2023

Pre-assignment

Screening details:

*Male or female aged ≥18 years
*Clinical history of grass pollen-induced allergic rhinoconjunctivitis for ≥2 years (with or without asthma), which was severe and remained troublesome despite treatment with symptom-relieving medication during the previous grass pollen season.
*Positive SPT and specific IgE against Phleum pratense

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, 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 solution in single-dose container
Routes of administration	Sublingual use

Dosage and administration details:

Subjects were instructed to take IMP once daily and that eating and drinking should be avoided for the next 5 minutes. The entire content of the single-dose container should be placed under the tongue (sublingual) and swallowing should be avoided for 2 minutes.
The first administration of IMP was done at the clinic under medical supervision with a subsequent 30-minute observation period.

Arm title	5-grass mix SLIT-drops

Arm description:

5-grass mix SLIT-drops

Arm type	Experimental
Investigational medicinal product name	5-grass mix SLIT-drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Sublingual use

Dosage and administration details:

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(sublingual) and swallowing should be avoided for 2 minutes.
The first administration of IMP was done at the clinic under medical supervision with a subsequent 30-minute observation period.

Number of subjects in period 1	Placebo	5-grass mix SLIT-drops
Started	223	222
Completed	196	193
Not completed	27	29
Consent withdrawn by subject	19	19
Reason stated as "other" in CRF	1	2
Adverse event, non-fatal	2	4
Lost to follow-up	4	4
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	5-grass mix SLIT-drops
Reporting group description: 5-grass mix SLIT-drops	

Reporting group values	Placebo	5-grass mix SLIT-drops	Total
Number of subjects	223	222	445
Age categorical Units: Subjects			
Adults (18-64 years)	223	222	445
Gender categorical Units: Subjects			
Female	105	95	200
Male	118	127	245

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	445	445	
Age categorical Units: Subjects			
Adults (18-64 years)	445	445	
Gender categorical Units: Subjects			
Female	200	200	
Male	245	245	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	5-grass mix SLIT-drops
Reporting group description:	
5-grass mix SLIT-drops	
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 daily allergic rhinoconjunctivitis total combined score (TCS) during the 2nd peak grass pollen season (PGPS)

End point title	Average daily allergic rhinoconjunctivitis total combined score (TCS) during the 2nd peak grass pollen season (PGPS)
End point description:	
The average daily TCS evaluates the treatment effect based on reduction in daily rhinoconjunctivitis symptoms and in use of symptom-relieving medication (on a scale from 0 to 38). Higher scores indicate more severe symptoms and/or more medication use. The endpoint is calculated as the average score of all reported daily values during the 2nd PGPS.	
End point type	Primary
End point timeframe:	
During the 2nd PGPS (14 days)	

End point values	Placebo	5-grass mix SLIT-drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	187		
Units: Adjusted mean				
least squares mean (standard error)	7.10 (± 0.51)	5.22 (± 0.42)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator
Statistical analysis description:	
The endpoint was analysed using primary (trial product) estimand. The null hypothesis was defined as "no differences in means between treatment arms". The endpoint analysis was based on a 5% significance level. The endpoint was analysed using a linear mixed effects model with the following	

covariates: treatment, season and their interaction, ongoing asthma status, and country and season interaction.

Comparison groups	Placebo v 5-grass mix SLIT-drops
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036 [1]
Method	Mixed models analysis
Parameter estimate	Absolute difference
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	3.17

Notes:

[1] - Adjusted p-value

Secondary: Average weekly overall rhinoconjunctivitis quality of life questionnaire (RQLQ) score during the 2nd peak grass pollen season (PGPS)

End point title	Average weekly overall rhinoconjunctivitis quality of life questionnaire (RQLQ) score during the 2nd peak grass pollen season (PGPS)

End point description:

The RQLQ measures the rhinoconjunctivitis quality of life. The RQLQ contains 28 questions, each scored on a 7-point scale (0 = not impaired at all; 6 = severely impaired). The overall RQLQ score is a mean of the 28 questions. Higher scores indicate worse quality of life. The endpoint is calculated as the average score of all reported weekly values during the 2nd PGPS.

End point type	Secondary

End point timeframe:

During the 2nd PGPS (14 days)

End point values	Placebo	5-grass mix SLIT-drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	182		
Units: Adjusted mean				
least squares mean (standard error)	1.04 (± 0.08)	0.86 (± 0.08)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

The endpoint was analysed using primary (trial product) estimand. The null hypothesis was defined as "no differences in means between treatment arms". The endpoint analysis was based on a 5% significance level. The endpoint was analysed using a linear mixed effects model with the following covariates: treatment, season and their interaction, ongoing asthma status, and country and season interaction.

Comparison groups	Placebo v 5-grass mix SLIT-drops
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1111 [2]
Method	Mixed models analysis
Parameter estimate	Absolute difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.39

Notes:

[2] - Adjusted p-value

Secondary: Average daily allergic rhinoconjunctivitis total combined score (TCS) during the 1st peak grass pollen season (PGPS)

End point title	Average daily allergic rhinoconjunctivitis total combined score (TCS) during the 1st peak grass pollen season (PGPS)

End point description:

The average daily TCS evaluates the treatment effect based on reduction in daily rhinoconjunctivitis symptoms and in use of symptom-relieving medication (on a scale from 0 to 38). Higher scores indicate more severe symptoms and/or more medication use. The endpoint is calculated as the average score of all reported daily values during the 1st PGPS.

End point type	Secondary

End point timeframe:

During the 1st PGPS (14 days)

End point values	Placebo	5-grass mix SLIT-drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: Adjusted mean				
least squares mean (standard error)	8.10 (± 0.54)	6.76 (± 0.42)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

The endpoint was analysed using primary (trial product) estimand. The null hypothesis was defined as "no differences in means between treatment arms". The endpoint analysis was based on a 5% significance level. The endpoint was analysed using a linear mixed effects model with the following covariates: treatment, season and their interaction, ongoing asthma status, and country and season interaction.

Comparison groups	Placebo v 5-grass mix SLIT-drops

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0417 [3]
Method	Mixed models analysis
Parameter estimate	Absolute difference
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	2.67

Notes:

[3] - Observed p-value

Secondary: Average weekly overall rhinoconjunctivitis quality of life questionnaire (RQLQ) score during the 1st peak grass pollen season (PGPS)

End point title	Average weekly overall rhinoconjunctivitis quality of life questionnaire (RQLQ) score during the 1st peak grass pollen season (PGPS)

End point description:

The RQLQ measures the rhinoconjunctivitis quality of life. The RQLQ contains 28 questions, each scored on a 7-point scale (0 = not impaired at all; 6 = severely impaired). The overall RQLQ score is a mean of the 28 questions. Higher scores indicate worse quality of life. The endpoint is calculated as the average score of all reported weekly values during the 1st PGPS.

End point type	Secondary

End point timeframe:

During the 1st PGPS (14 days)

End point values	Placebo	5-grass mix SLIT-drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	197		
Units: Adjusted mean				
least squares mean (standard error)	1.26 (± 0.09)	1.19 (± 0.08)		

Statistical analyses

Statistical analysis title	Trial product estimand - Main estimator

Statistical analysis description:

The endpoint was analysed using primary (trial product) estimand. The null hypothesis was defined as "no differences in means between treatment arms". The endpoint analysis was based on a 5% significance level. The endpoint was analysed using a linear mixed effects model with the following covariates: treatment, season and their interaction, ongoing asthma status, and country and season interaction.

Comparison groups	Placebo v 5-grass mix SLIT-drops

Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4984 [4]
Method	Mixed models analysis
Parameter estimate	Absolute difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.3

Notes:

[4] - Observed p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from informed consent to last follow-up contact with subject. Only treatment-emergent AEs are presented, i.e. AEs starting on/after time of first IMP administration and no later than 7 days after last 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	5-grass mix SLIT-drops

Reporting group description:

5-grass mix SLIT-drops

Serious adverse events	Placebo	5-grass mix SLIT-drops	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 223 (2.69%)	4 / 222 (1.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal procedural complication			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Varicose vein			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
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	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Choking			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Appendicitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	5-grass mix SLIT-drops	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 223 (64.57%)	167 / 222 (75.23%)	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 223 (8.52%)	11 / 222 (4.95%)	
occurrences (all)	30	11	
Gastrointestinal disorders			
Oral pruritus			
subjects affected / exposed	11 / 223 (4.93%)	40 / 222 (18.02%)	
occurrences (all)	12	49	
Oral discomfort			
subjects affected / exposed	1 / 223 (0.45%)	15 / 222 (6.76%)	
occurrences (all)	1	18	
Mouth swelling			
subjects affected / exposed	0 / 223 (0.00%)	13 / 222 (5.86%)	
occurrences (all)	0	15	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	4 / 223 (1.79%)	16 / 222 (7.21%)	
occurrences (all)	4	16	
Infections and infestations			
COVID-19			
subjects affected / exposed	43 / 223 (19.28%)	41 / 222 (18.47%)	
occurrences (all)	50	44	
Nasopharyngitis			
subjects affected / exposed	43 / 223 (19.28%)	38 / 222 (17.12%)	
occurrences (all)	75	67	
Viral infection			

subjects affected / exposed	7 / 223 (3.14%)	14 / 222 (6.31%)	
occurrences (all)	8	15	
Influenza			
subjects affected / exposed	11 / 223 (4.93%)	12 / 222 (5.41%)	
occurrences (all)	13	12	
Upper respiratory tract infection			
subjects affected / exposed	15 / 223 (6.73%)	10 / 222 (4.50%)	
occurrences (all)	20	19	
Bronchitis			
subjects affected / exposed	14 / 223 (6.28%)	7 / 222 (3.15%)	
occurrences (all)	15	9	
Pharyngitis			
subjects affected / exposed	20 / 223 (8.97%)	4 / 222 (1.80%)	
occurrences (all)	25	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2021	The amendment was issued after first subject first visit and prior to unblinding. The main changes were: 1. Visit windows changed from 7 to 14 days for the pre-EGPS visits (V4 and V7). 2. A telephone contact between randomisation (V2) and 1st off-season visit (V3) was changed to optional. 3. The definition of end of trial changed from the last subject last physical visit to the last subject follow-up telephone contact. 4. Restricted and prohibited concomitant medication was updated to only include those medications that would impact the safety of the subject and significantly impact the endpoints. 5. Medical history re. asthma: it was clarified that only subjects diagnosed/treated in adulthood should be stratified as asthmatic. 6. Additional specification of events of special interest form and procedure (administrative). 7. Updated contact info on laboratory due to change of vendor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported